Psychological trauma as a transdiagnostic risk factor for mental disorders, and results from a first multicentre randomised controlled trial into the efficacy of an adjunctive trauma-focused therapy in bipolar disorder

Bridget Hogg

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To Carlos, Benji, and Aidan

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Abbreviations

ADHD – Attention-Deficit Hyperactivity Disorder

ANOVA – Analysis of Variance

BD – Bipolar Disorder

BD-I – Bipolar Disorder Type 1

BD-II – Bipolar Disorder Type 2

BDRS – Bipolar Depression Rating Scale

BPD – Borderline Personality Disorder

CAPS – Clinician-Administered PTSD Scale

CGI-BP – Clinical Global Impressions Scale for use in Bipolar disorders

CBT – Cognitive Behavioural Therapy

CI – Confidence Interval

CPTSD - Complex Post-Traumatic Stress Disorder

CRF – Case Report Form

CTQ – Childhood Trauma Questionnaire

DES – Dissociative Experiences Scale

DMN – Default Mode Network

DSM-IV - Diagnostic and statistical manual of mental disorders, 4th edition

DSM-5 – Diagnostic and statistical manual of mental disorders, 5th edition.

DTD – Developmental Trauma Disorder

EMDR – Eye Movement Desensitisation and Reprocessing

FAST – Functioning Assessment Short Test

fMRI – functional Magnetic Resonance Imaging

ICD-11 – International Classification of Diseases, 11th Revision

IES-R – Impact of Event Scale-Revised

MA – Meta-Analysis

MDD – Major Depressive Disorder

MeSH – Medical Subject Headings

MOOSE – Meta-analysis Of Observational Studies in Epidemiology

OCD – Obsessive Compulsive Disorder

OR – Odds Ratio

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PTSD - Post-Traumatic Stress Disorder

RCT – Randomised Controlled Trial

RR – Risk Ratio

SCIP – Screening for Cognitive Impairment in Psychiatry

SCIP-S – Screening for Cognitive Impairment in Psychiatry – Spanish version

SR – Systematic Review

SSRIs – Selective Serotonin Reuptake Inhibitors

ST – Supportive Therapy

TAU – Treatment As Usual

TF-CBT – Trauma-Focused Cognitive Behavioural Therapy

TRANSD – TRANSD recommendations: improving transdiagnostic research in psychiatry

YMRS – Young Mania Rating Scale

Abstract

Psychological trauma has been associated with an increased risk for a range of mental disorders but its potential role as a transdiagnostic risk factor has not been systematically evaluated, and there is scant evidence of how to treat this comorbidity in patients with severe mental disorder. This thesis therefore has two main objectives. Firstly, to analyse the role of psychological trauma as a transdiagnostic risk factor across mental disorders through an umbrella review. Secondly, to examine the characteristics of people with a specific disorder, Bipolar Disorder (BD), and comorbid trauma, and to investigate the possibility of improving its clinical course with an adjunctive trauma-focused psychotherapy such as Eye Movement Desensitisation and Reprocessing (EMDR), adapted for BD.

The umbrella review synthesised evidence from existing published systematic reviews and meta-analyses regarding the association between psychological trauma and any mental disorder, to provide an overall odds ratio (OR). Evidence was graded for its quality using Ioannidis' criteria for umbrella reviews, and assessed against TRANSD transdiagnostic criteria. The results showed highly suggestive evidence that psychological trauma is associated with nearly triple the risk of experiencing a mental disorder (OR = 2.92), and meets criteria as a transdiagnostic risk factor.

For the second objective of the thesis, a randomised controlled trial (RCT) was carried out in a multicentre study comprising Hospital Benito Menni, Hospital Clínic, and Hospital del Mar Barcelona in the Barcelona area. Seventy-nine people with BD were recruited into the study. Inclusion criteria were: a) two to six affective relapses in the previous year, b) currently not in acute phase of BD (as determined by the Bipolar Depression Rating Scale and Young

Mania Rating Scale), c) a history of psychological trauma and current symptoms. Subjects were randomised to receive 20 weekly one-hour sessions of either EMDR Bipolar protocol, or a control non-trauma-focused therapy, Supportive Therapy (ST). Affective symptoms, affective relapses, psychosocial functioning, and cognition were assessed at baseline, post-treatment, and at 12 and 24 months post-treatment as follow-up visits. Of note, to further monitor patients' mood, affective symptoms were also assessed at two weeks and three months.

For this second part, two studies were carried out. In the first of these, a descriptive analysis was carried out with the baseline data, and the results showed no difference in trauma symptom profile between BD subtype, which concurs with previous evidence. There was also little difference in terms of clinical course depending on the type of trauma suffered or if there was a lifetime diagnosis of post-traumatic stress disorder, suggesting that in a traumatised sample with a high level of subsyndromal symptoms the impact of specific abuse types or a PTSD diagnosis is diminished.

Regarding the second study where the two interventions were compared, the results showed that EMDR therapy was superior to ST in reducing subsyndromal depressive, mixed and hypomanic symptoms and in improving psychosocial functioning at six months post-treatment. Hospitalisation, relapse, and dropout rates were similar across the two treatment arms. Trauma symptoms reduced in both treatment arms as compared to baseline but there was no significant difference between EMDR and ST. There was no significant change in cognition in either treatment arm.

In summary, the thesis shows for the first time through an umbrella review that psychological trauma is a transdiagnostic risk factor for mental disorder. Furthermore, it shows through a

multicentre RCT that EMDR therapy can be safely applied in BD patients and may alleviate affective symptoms.

Resumen

El trauma psicológico se ha asociado con un mayor riesgo de padecer diferentes trastornos mentales, pero su papel como factor de riesgo transdiagnóstico no se ha evaluado sistemáticamente, y hay escasa evidencia sobre cómo tratar esta comorbilidad en pacientes con trastorno mental grave.

Por lo tanto, esta tesis tiene dos objetivos principales. En primer lugar, comprender el papel del trauma psicológico como un factor de riesgo transdiagnóstico en los trastornos mentales. Y, en segundo lugar, examinar las características del trauma en una muestra de pacientes diagnosticados de Trastorno Bipolar (TB) con historia de trauma e investigar la posibilidad de mejorar su curso clínico mediante el uso de una psicoterapia co-adyuvante centrada en el trauma, como es la Desensibilización y Reprocesamiento por Movimientos Oculares (EMDR), usando el manual EMDR adaptado para TB.

La revisión en paraguas sintetizó los datos de las revisiones sistemáticas y meta-análisis publicados sobre el riesgo de sufrir un trastorno mental tras haber experimentado un trauma psicológico, para proporcionar una odds ratio (OR) global. También se calificó la calidad de los trabajos incluidos utilizando los criterios de Ioannidis para las revisiones en paraguas, y se revisó su adecuación a los criterios transdiagnósticos. Los resultados mostraron que hay pruebas muy indicativas que el trauma psicológico casi triplica el riesgo de sufrir un trastorno mental (OR = 2,92), y cumple criterios para ser un factor transdiagnóstico.

Para dar respuesta al segundo objetivo de la tesis, se llevó a cabo un ensayo clínico controlado y aleatorizado (RCT) en el que participaron tres instituciones médicas de Barcelona y alrededores: el Hospital Benito Menni, el Hospital Clínic y el Hospital del Mar Barcelona. Setenta y nueve pacientes con TB fueron reclutados para el estudio. Los criterios

de inclusión fueron los siguientes: a) entre dos y seis recaídas afectivas en el año anterior, b) actualmente no en fase aguda del TB (según lo determinado por las escalas Bipolar Depression Rating Scale and Young Mania Rating Scale), c) antecedentes de trauma psicológico con síntomas actuales. Los sujetos fueron asignados de forma aleatoria a recibir 20 sesiones semanales de una hora de duración de terapia EMDR adaptado para TB o una terapia de control no centrada en el trauma, la terapia de apoyo (TA). Los síntomas relacionados con el estado de ánimo, las recaídas afectivas, el funcionamiento psicosocial, y cognición, se evaluaron en la visita basal, después del tratamiento y a los 12 y 24 meses después del tratamiento en calidad de visitas de seguimiento. Cabe mencionar que, para llevar un mayor control del estado de ánimo de los pacientes, los síntomas afectivos también se evaluaron a las dos semanas y a los tres meses de la visita basal.

En relación con el segundo trabajo se llevaron a cabo dos estudios. En el primero de ellos se realizó un análisis descriptivo con los datos de la visita basal, en el que los resultados no mostraron diferencias en el perfil de síntomas traumáticos entre los diferentes subtipos de TB, lo que corrobora estudios anteriores. También hubo pocas diferencias en cuanto al curso clínico según el tipo de trauma sufrido o si existía un diagnóstico de por vida de trastorno de estrés postraumático, lo que sugiere que en una muestra traumatizada con un alto nivel de síntomas subsindrómicos, el impacto de los tipos específicos de abuso o de un diagnóstico de TEPT es menor.

En relación con el segundo trabajo en el que se compararon las dos intervenciones, los resultados mostraron que la terapia EMDR fue superior a la TA en la reducción de los síntomas subsindrómicos depresivos, mixtos e hipomaníacos y en la mejora del funcionamiento psicosocial a los seis meses del tratamiento. Las tasas de hospitalización, recaída y abandono fueron similares en los dos grupos de tratamiento. Los síntomas de

trauma se redujeron en ambos grupos de tratamiento en comparación con la visita basal, sin haber diferencias significativas entre EMDR y la TA. Asimismo, no hubo cambios significativos en la cognición en ninguno de los brazos de tratamiento.

En resumen, la presente tesis ha confirmado por primera vez mediante una revisión en paraguas, que el trauma psicológico es un factor de riesgo transdiagnóstico para el trastorno mental. Asimismo, ha evidenciado mediante un ensayo clínico multicéntrico que la terapia EMDR puede aplicarse de manera segura y efectiva en pacientes con TB teniendo un efecto positivo en la reducción de los síntomas afectivos.

Resum

El trauma psicològic s'ha associat amb un major risc de patir diferents trastorns mentals, però el seu paper com a factor de risc transdiagnóstic no s'ha avaluat sistemàticament, i hi ha escassa evidència sobre com tractar aquesta comorbiditat en pacients amb trastorn mental greu.

Per tant, aquesta tesi té dos objectius principals. En primer lloc, comprendre el paper del trauma psicològic com un factor de risc transdiagnóstic en els trastorns mentals. I en segon lloc, examinar les característiques del trauma en una mostra de pacients diagnosticats de Trastorn Bipolar (TB) amb història de trauma i investigar la possibilitat de millorar el seu curs clínic mitjançant l'ús d'una psicoteràpia co-adjuvant centrada en el trauma com es la Dessensibilització i Reprocessament per Moviments Oculars (EMDR), usant el protocol EMDR adaptat per a TB.

La revisió en paraigua va sintetitzar les dades de les revisions sistemàtiques i metanàlisis publicades sobre el risc de sofrir un trastorn mental després d'haver experimentat un trauma psicològic, per a proporcionar una odds ràtio (OR) global. També es va qualificar la qualitat dels treballs inclosos utilitzant els criteris de Ioannidis per a les revisions en paraigües, i es va revisar la seva adequació als criteris transdiagnóstics. Els resultats van mostrar que hi ha proves molt indicatives que el trauma psicològic gairebé triplica el risc de sofrir un trastorn mental (OR = 2,92), i compleix criteris per a ser un factor transdiagnóstic.

Per a donar resposta al segon objectiu de la tesi, es va dur a terme un assaig clínic controlat i aleatoritzat (RCT) en el qual van participar tres institucions mèdiques de Barcelona i voltants: l'Hospital Benito Menni l'Hospital Clínic i l'Hospital del Mar Barcelona. Setanta-nou pacients amb TB van ser reclutats per a l'estudi. Els criteris d'inclusió van ser els següents: a) entre dues i sis recaigudes afectives l'any anterior, b) actualment no en fase aguda del TB

(segons el determinat per les escales
Bipolar Depression Ràting Scale and Young Mania Ràting Scale), c) antecedents de trauma psicològic amb símptomes actuals. Els subjectes van ser assignats de manera aleatòria a rebre 20 sessions setmanals d'una hora de durada de teràpia EMDR adaptat per a TB o una teràpia de control no centrada en el trauma, la teràpia de suport (TA). Els símptomes relacionats amb l'estat d'ànim, les recaigudes afectives, el funcionament psicosocial, i cognició, es van avaluar en la visita basal, després del tractament i als 12 i 24 mesos després del tractament en qualitat de visites de seguiment. Cal esmentar, que per a portar un major control de l'estat d'ànim dels pacients, els símptomes afectius també es van avaluar a les dues setmanes i als tres mesos de la visita basal.

En relació amb el segon treball es van dur a terme dos estudis. En el primer estudi es va realitzar una anàlisi descriptiva amb les dades de la visita basal, en el que els resultats no van mostrar diferències en el perfil de símptomes traumàtics entre els diferents subtipus de TB, la qual cosa corrobora estudis anteriors. També va haver-hi poques diferències quant al curs clínic segons el tipus de trauma sofert o si existia un diagnòstic per a tota la vida de trastorn d'estrès posttraumàtic, la qual cosa suggereix que en una mostra traumatitzada amb un alt nivell de símptomes subsindrómics, l'impacte de tipus específics d'abús o d'un diagnòstic de TEPT és menor.

En relació amb el segon treball en el qual es van comparar les dues intervencions, els resultats van mostrar que la teràpia EMDR va ser superior a la TA en la reducció dels símptomes subsindrómics depressius, mixtes i hipomaníacs i en la millora del funcionament psicosocial als sis mesos del tractament. Les taxes d'hospitalització, recaiguda i abandó van ser similars en els dos grups de tractament. Els símptomes de trauma es van reduir en tots dos grups de tractament en comparació amb la visita basal. Tanmateix, no va haver-hi diferències

significatives entre EMDR i TA. No va haver-hi canvis significatius en la cognició en cap dels braços de tractament.

En resum, la present tesi ha confirmat per primera vegada mitjançant una revisió en paraigua, que el trauma psicològic és un factor de risc transdiagnóstic per al trastorn mental. Així mateix ha evidenciat mitjançant un assaig clínic multicèntric que la teràpia EMDR pot aplicar-se de manera segura i efectiva en pacients amb TB tenint un efecte positiu en la reducció dels símptomes afectius.

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1. Introduction

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1.1 Psychological trauma – definition of traumatic events, diagnoses, and prevalence

1.1.1 Definition and prevalence of traumatic events

Psychological trauma was first conceptualised over a century ago by Pierre Janet, who argued that, when a person experiences emotions which overwhelm their resources, the memory of this traumatic experience is separated from consciousness and returns in fragments, as emotional conditions, somatic states, visual images, or behavioural re-enactments (1,2). This definition still holds true, as can be seen if compared to recent US government guidelines on trauma, where psychological trauma is defined as: “a person experiencing events or circumstances which are physically or emotionally harmful or life threatening, and which have lasting adverse effects on their functioning and mental, physical, social, emotional, or spiritual well-being" (3).

Psychological trauma events can include emotional, physical, or sexual abuse, emotional or physical neglect, death, violence, war, loss, and other emotionally harmful experiences (3). Traumatic experiences can occur at any point throughout the lifespan, from first infancy to old age, and are common: data from the World Mental Health Survey Consortium found that 70.4% of participants reported at least one lifetime traumatic event (4). The most commonly experienced events reported were accidents or injuries (36.3%), the unexpected death of a loved one (31.4%), witnessing or causing bodily harm (26.3%), and intimate partner or sexual violence of any type (22.8%). Higher rates were found in a national survey of US adults, with 89.7% of respondents having experienced a traumatic event according to DSM-5 criteria (5).

Psychological trauma experienced during childhood can be especially harmful because of the impact it has on neural development, which makes children more vulnerable to developing psychopathology in the future (6). Results from a study into adverse childhood experiences, i.e. potentially traumatic events in childhood, involving 51,945 adults across 21 countries, found that over a third of respondents reported having experienced childhood adversity (38.4% in high-income countries, 38.9% in high-middle income countries, and 39.1% in low/lower-middle income countries) (7). However, this study did not include emotional abuse, despite this type of abuse being highly prevalent and associated with a range of psychopathological outcomes (8). More recent studies which have included emotional abuse within the types of trauma evaluated have estimated a higher prevalence of childhood trauma: a US study found 61.6% of adults responded they had experienced at least one adverse event in childhood (9), while a study in Portugal which directly asked 10-year-old children to self-report indicators of adverse childhood experiences, including emotional abuse but excluding sexual abuse, found 96.2% of children had been exposed to at least one adverse event (10). While the data clearly show widespread adversity amongst children, research has indicated that being older, special health care needs, and poverty are all associated with an increased risk of exposure to adverse childhood experiences (11).

1.1.2 Trauma-related diagnoses and their prevalence

Experiencing traumatic events can have an important negative impact resulting in trauma symptoms, which can be categorised in five main types:

1) *Intrusion.* These symptoms can include flashbacks, nightmares, intrusive disturbing memories, and severe mental or physical distress upon being reminded of the traumatic event.

2) *Avoidance*. These symptoms include attempts to avoid thoughts, feelings, or conversations related to the traumatic event, or to avoid people, places or activities which are reminders of it.
3) *Negative alterations in cognition and mood*. Negative alterations can include being unable to remember parts of the traumatic memory, being unable to trust others, feeling guilt or other persistent negative emotions, the sensation of being unable to feel positive emotions, and feeling distant from others.
4) *Alterations in arousal and activity*. Individuals may experience alterations such as being irritable or angry, participating in risky activities despite knowing they can be harmful, feeling hyper-alert and watchful, or being unable to concentrate or sleep well.
5) *Dissociative symptoms.* These symptoms can include amnesia, symptoms of derealisation (the feeling of being disconnected from one's surroundings or feeling they are unreal, for example as in a dream), or symptoms of depersonalisation (feeling detached from one's own body, or as though one is observing it from outside).

Depending on the number, type, and duration of trauma-related symptoms following a traumatic event, a clinical diagnosis of post-traumatic stress disorder (PTSD) according to DSM-5 criteria may be given (12). For this to occur, an event of actual or threatened death, serious injury or sexual violence must have been directly experienced, witnessed, or have occurred to a loved one, or alternatively an individual has suffered repeated or extreme exposure to aversive details of a traumatic event, such as in the case of a police officer working on a sexual abuse case. If, additionally, a minimum number of symptoms of intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and activity are present, plus a negative impact on psychosocial functioning over at least one

month, the symptoms meet the diagnostic criteria for PTSD. When the symptoms and impact on functioning are present but the traumatic event occurred between one month and three days ago, a diagnosis of Acute Stress Disorder is given. In either case, symptoms of derealisation or depersonalisation may be present but are not necessary for a diagnosis (see Table 1 for an overview of the PTSD diagnosis criteria in the DSM-5).

Table 1. Criteria for PTSD in adults, adolescents, and children older than 6 years. Source: DSM-5 (12), pp. 271–272).

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
    1. Directly experiencing the traumatic event(s).
    2. Witnessing, in person, the event(s) as it occurred to others.
    3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
    4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse). **Note:** Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
    1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). **Note:** In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
    2. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event(s). **Note:** In children, there may be frightening dreams without recognizable content.
    3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) **Note:** In children, trauma-specific reenactment may occur in play.
    4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
    5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
    1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
    2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia, and not to other factors such as head injury, alcohol, or drugs).
    2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
    3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
    4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
    5. Markedly diminished interest or participation in significant activities.
    6. Feelings of detachment or estrangement from others.
    7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal or physical aggression toward people or objects.
    2. Reckless or self-destructive behavior.
    3. Hypervigilance.
    4. Exaggerated startle response.
    5. Problems with concentration.
    6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted). **Note**: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify whether:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

The lifetime prevalence of PTSD was found to be 8.3% in a survey of US adults (5), while the World Mental Health surveys estimated this to be 3.9% worldwide, although many countries with armed conflict were not included, so the true figure may be higher (13). This survey found that high income countries had higher rates of PTSD than upper-middle and low/lower-middle income countries (5.0% compared to 2.3% and 2.1% respectively). In relation to gender, the prevalence in females is estimated at between 10% and 12% compared to between 5 and 6% in men (14).

Recently, the International Classification of Diseases, Eleventh Revision (ICD-11) (15) has included a new diagnosis called Complex PTSD (CPTSD), which involves exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible, such as torture, prolonged domestic violence, or repeated childhood sexual or physical abuse. All the core features of PTSD must be present, along with significant functional impairment, but

additionally there must be the presence of severe and pervasive problems in affect regulation, negative persistent beliefs about oneself, and persistent difficulties in interpersonal relationships. The diagnostic criteria can be seen in Table 2. This diagnosis is not yet included in the DSM (12). A US study found that 3.8% of the population had CPTSD, compared to 3.4% with PTSD (16), while other studies have estimated a general population prevalence of CPTSD between 1% and 8% (17).

Table 2. Essential features for a diagnosis of CPTSD according to the International Classification of Diseases, 11th Revision. Source: ICD-11 (15).

- Exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible. Such events include, but are not limited to, torture, concentration camps, slavery, genocide campaigns and other forms of organized violence, prolonged domestic violence, and repeated childhood sexual or physical abuse.
- Following the traumatic event, the development of all three core elements of Post-Traumatic Stress Disorder, lasting for at least several weeks:
    - Re-experiencing the traumatic event after the traumatic event has occurred, in which the event(s) is not just remembered but is experienced as occurring again in the here and now. This typically occurs in the form of vivid intrusive memories or images; flashbacks, which can vary from mild (there is a transient sense of the event occurring again in the present) to severe (there is a complete loss of awareness of present surroundings), or repetitive dreams or nightmares that are thematically related to the traumatic event(s). Re-experiencing is typically accompanied by strong or overwhelming emotions, such as fear or horror, and strong physical sensations. Re-experiencing in the present can also involve feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event, without a prominent cognitive aspect, and may occur in response to reminders of the event. Reflecting on or ruminating about the event(s) and remembering the feelings that one experienced at that time are not sufficient to meet the re-experiencing requirement.
    - Deliberate avoidance of reminders likely to produce re-experiencing of the traumatic event(s). This may take the form either of active internal avoidance of thoughts and memories related to the event(s), or external avoidance of people, conversations, activities, or situations reminiscent of the event(s). In extreme cases the person may change their environment (e.g., move house or change jobs) to avoid reminders.
    - Persistent perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. Hypervigilant persons constantly guard themselves against danger and feel themselves or others close to them to be under immediate threat either in specific situations or more generally. They may adopt new behaviours designed to ensure safety (not sitting with ones' back to the door, repeated checking in vehicles' rear-view mirror). In Complex Post-Traumatic Stress Disorder, unlike in Post-Traumatic Stress Disorder, the startle reaction may in some cases be diminished rather than enhanced.
- Severe and pervasive problems in affect regulation. Examples include heightened emotional reactivity to minor stressors, violent outbursts, reckless or self-destructive behaviour, dissociative symptoms when under stress, and emotional numbing, particularly the inability to experience pleasure or positive emotions.
- Persistent beliefs about oneself as diminished, defeated or worthless, accompanied by deep and pervasive feelings of shame, guilt or failure related to the stressor. For example, the individual may feel guilty about not having escaped from or succumbing to the adverse circumstance, or not having been able to prevent the suffering of others.

- Persistent difficulties in sustaining relationships and in feeling close to others. The person may consistently avoid, deride or have little interest in relationships and social engagement more generally. Alternatively, there may be occasional intense relationships, but the person has difficulty sustaining them.
- The disturbance results in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

Whether psychological trauma leads to PTSD can depend on a variety of factors. These factors can be categorised as pre-traumatic, peri-traumatic, or post-traumatic, according to whether they took place before, during, or after the event (18,19). Pre-traumatic risk factors, present prior to the traumatic event, include prior trauma exposure (in particular to organised violence, physical violence, rape, and sexual assault), cognitive vulnerabilities, a prior history of psychopathology, and genetic vulnerabilities (18–21). Furthermore, female gender is a pre-traumatic risk factor (18,19,21), which may in part be explained by a tendency for women to experience more severe trauma such as sexual abuse at a younger age than men (14). PTSD appears to affect neurodevelopment and stress response differently in males and females (14), which may lead to greater levels of depression and anxiety sensitivity in females, which can mediate the association between gender and PTSD (22). Peri-traumatic risk factors refer to circumstances of the traumatic event itself. Research has shown that certain trauma types, such as sexual abuse, intentional physical injury, or witnessing atrocities events, and where there is a longer duration and/or a continued perception of threat, are all associated with an increased risk of subsequent PTSD (18–20). Finally, post-traumatic factors which occur after the event include a lack of social support, acute pain levels, or rigid cognitions about the traumatic event (18,19). In females, a study showed that negative post-traumatic cognitions were more prevalent in women and contributed to the association with greater PTSD prevalence (22).

1.2 Bipolar Disorder

1.2.1 Types and symptoms

Bipolar disorder (BD) represents a severe mental health condition, which is complex to diagnose and treat and is a leading cause of disability for young people (23). Bipolar disorders comprise Bipolar Disorder Type 1 (BD-I), Bipolar Disorder Type II (BD-II), Cyclothymia, and Other Specified or Unspecified Bipolar-related Disorders (12). BD-I is diagnosed when there has been the presence of at least one manic episode, which is characterised as a period of persistently elevated, expansive, or irritable mood and energy which lasts at least a week, with symptoms such as inflated self-esteem, decreased need for sleep, increased talkability or distractibility, or engagement in activities which can have negative consequences, with marked social or functional impairment, or a hospital admission, or psychotic features. BD-II is diagnosed when there has been at least one hypomanic episode (where there is the enhanced mood and energy of a manic episode but it lasts for at least four days, does not result in significant functional and occupational impairment, and there is no need for hospitalisation and no psychotic symptoms) and at least one depressive episode, characterised by symptoms including consistent low mood, lack of energy, negative thoughts and feelings of hopelessness, anhedonia, or suicidal ideation. Meanwhile Cyclothymia is diagnosed when, for at least half of the previous two-year period, the person has experienced subthreshold hypomanic or depressive symptoms, and they have not had longer than two months at a time without symptoms. Finally, the category of Other Bipolar Disorder is applied where an individual does not meet any of the aforementioned criteria, but has symptoms characteristic of BD which cause significant clinical impairment, for example in the case of someone with repeated major depressive episodes and frequent short hypomanic episodes which do not meet the temporal criteria of a minimum of four days. The Other Bipolar Disorder diagnosis can be specified, detailing why full criteria for another BD

diagnosis are not met, or unspecified. See Table 3 for the DSM-5 criteria for a manic, hypomanic, and major depressive episode, and Table 4 for the diagnostic criteria for each BD type.

Table 3. Definition of manic, hypomanic, and major depressive episodes according to DSM-5 (12) pp. 123-126

Type of episode	Definition according to DSM-5
Manic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary). B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity). 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition. Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis. Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.
Hypomanic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day. B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree: 1. Inflated self-esteem or grandiosity. 2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep). 3. More talkative than usual or pressure to keep talking. 4. Flight of ideas or subjective experience that thoughts are racing. 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed. 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation. 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments). C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic. D. The disturbance in mood and the change in functioning are observable by others.

	E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic. F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment). Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis. Note: Criteria A-F constitute a hypomanic episode.
Major Depressive Episode	A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly attributable to another medical condition. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide. B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. C. The episode is not attributable to the physiological effects of a substance or another medical condition. Note: Criteria A-C constitute a major depressive episode.

Table 4. Summary of DSM-5 criteria for BD-I, BD-II, and cyclothymia. Source: DSM-5 (12) pp. 123-141

BD-I	BD-II	Cyclothymia
The presence of at least one current or past manic episode. Hypomanic episodes and major depressive episodes are common in BD-I but are not necessary for a diagnosis.	The presence of at least one current or past hypomanic episode, as well as at least one current or past major depressive episode.	Fluctuating hypomanic and depressive mood symptoms which do not meet criteria for a full episode, which are present at least half of the time (past 2 years for adults, past year for children and adolescents), which are not due to the physiological effects of a substance, and which cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
	There has never been a manic episode.	Criteria for manic, hypomanic, or major depressive episodes have never been met.
Symptoms are not better explained by any schizoaffective or other schizophrenia spectrum disorder.		

The clinical course of BD can be severe, associated with increased mortality, poor psychosocial functioning, and cognitive impairment (23). It is the psychiatric disorder with the highest suicide rate and is associated with over 20 times the risk of suicide as compared to the general population (24). Over time, symptoms can worsen, and repeated episodes can lead to poorer outcomes, such as greater suicidality, more psychiatric and medical comorbidity, and greater disability and impairment in psychosocial functioning (25–27), as well as poorer response to pharmacological treatment, adjunctive psychotherapy, and group psychoeducation (28–30).

BD-I is associated with the most severe clinical course, and cognitive impairment in BD patients is worsened by a greater number of manic episodes, hospitalisations, and a longer duration of the illness (31). However, BD-II is associated with a higher risk of relapse (32). Relapse rate is an important indicator of disease progression: the risk of relapse within the first year after a BD mood episode is estimated at 44%, but after the first year this falls to 19% (32). However, between mood episodes, subsyndromal symptoms can persist. These symptoms affect between an estimated 20% and 50% of patients (33), and can have not only a negative impact on BD disease course, but also may have a greater negative impact on functioning and quality of life than acute episodes (33), including incapacity to work (34). Studies have shown that people with subsyndromal depressive BD symptoms are more similar to people with major depressive disorder (MDD) than to healthy controls in terms of functional impairment (35,36). Furthermore, persisting subsyndromal symptoms are associated with a higher risk of relapse (32), indicating it is important for these symptoms to be controlled.

In some cases, bipolar patients can experience four of more affective episodes in one year, known as rapid cycling. Rapid cycling has been estimated to affect between 25.8% and 43%

of BD patients at some point in the disease course (37), and evidence suggests it is more prevalent in BD-II, and more common in females across both BD types (38,39). Rapid cycling is a factor implicated in a poorer prognosis, and is associated with a longer course of illness, an earlier age of onset, increased substance use, and increased suicidality (37).

World Mental Health Survey data shows the worldwide lifetime prevalence of BD-I is 0.6% and of BD-II is 0.4%, while subthreshold BD is estimated at 1.4%; thus, approximately 2.4% of the population worldwide is on the bipolar spectrum (40). BD is associated with a decreased life expectancy (41) due to suicide and medical comorbidities, such as cardiovascular diseases (23). The severity of the clinical course is greatest in BD-I and lowest in subthreshold BD (40). BD appears to affect different genders and ethnicities equally (42), although women have an increased risk of BD-II, hypomania, rapid cycling, and mixed episodes (43).

BD is also associated with a large degree of comorbidity. The World Mental Health Survey statistics estimated that 76.5% of people with BD or subthreshold BD had a comorbid disorder in their lifetime: 62.9% had an anxiety disorder, 44.8% had a comorbid behaviour disorder, and 36.6% had a substance use disorder (40). Other common comorbidities include Attention-Deficit Hyperactivity Disorder (ADHD) and personality disorders (23). People with BD-I are most likely to have a comorbid psychiatric disorder (88.2%), compared to BD-II (83.1%) and subthreshold BD (69.1%) (40). BD is also associated with a high degree of physical comorbidity, such as cardiovascular, thyroid, or neurological diseases (23,44).

Given that BD is a disease which progresses and becomes more severe over time, several research groups have proposed a staging model for BD (45–48). Staging models are useful for predicting disease course and optimising treatment, and all concur that the disease course begins with an at-risk or latency stage, followed by a stage with prodromal, subthreshold, or

non-specific symptoms, through to the first bipolar mood episode, followed by a stage with relapses and persistent subsyndromal symptoms between affective episodes, and finally late stage disease marked by persisting mood symptoms, severe cognitive and functional impairment and disease resistance (45–47,49). The staging model has been applied to assist clinical decisions aimed at improving functional outcomes (50). However, for greater clinical utility, further research is required to determine clinical biomarkers for each stage (48).

1.2.2 Aetiology

Evidence has long demonstrated a strong genetic component in the aetiology of BD (51). In a large US cohort study, BD patients had a significantly greater family history of anxiety disorders, MDD, and BD (52). More recent research is focused on understanding which genes are involved in the heritability of BD (53,54). Current evidence points to the aetiology of BD being best explained through a gene x environment interaction (23). One of the most researched environmental factors is psychological trauma, where there is robust evidence to show its implication in the onset and maintenance of BD (55). Psychological trauma has been shown to interact with gene expression in BD (56–58), and this factor may partially mediate the association between family history of mood disorder and the expression of BD (59). Early life stress has been shown to interact with genes such as brain-derived neurotrophic factor, or genes related to biological pathways such as the hypothalamic-pituitary-adrenal (HPA) axis, resulting in an earlier age of BD onset, and a worse disease course, including greater risk of suicide (60,61).

1.2.3 Treatment

Pharmacological treatment is the first-line treatment for BD (62). Acute BD manic symptoms can be treated with atypical antipsychotics such as olanzapine or quetiapine, anticonvulsants such as carbamazepine and valproate, and lithium salts (63). BD depression is challenging to

treat, but treatment can also include atypical antipsychotics such as quetiapine, some anticonvulsants such as lamotrigine, and antidepressants; the latter are controversial regarding their value and safety, especially their potential to cause a switch into a (hypo)manic episode (63,64) or their association with rapid cycling (37). A task force in 2013 acknowledged the use of antidepressants as a clinical reality in BD which can be beneficial for some individual patients, with selective serotonin reuptake inhibitors or bupropion as first-line treatments due to lower switch rates and lower induction of rapid cycling (65). Long-term treatment for BD still includes lithium as the golden standard, followed by lamotrigine, modern atypical antipsychotics such as quetiapine, and off-label use of valproate (63). Often polypharmacy or the use of drugs less commonly prescribed in BD, such as clozapine, is necessary, with research demonstrating that this is especially the case as the disease progresses, with continuous mood episodes and worse functioning (30).

In addition to pharmacological treatment, adjunctive bipolar-specific psychosocial interventions improve outcomes compared with pharmacological treatment alone (66). There is evidence that individual cognitive behavioural therapy (CBT), group psychoeducation, and family therapy are associated with a reduction in relapse as compared to treatment as usual (TAU). Regarding affective symptoms, CBT, family or conjoint therapy, and interpersonal therapy have been associated with reducing depressive symptoms as compared to TAU. Furthermore, CBT, family or conjoint therapy, and psychoeducation have been associated with improved outcomes for manic symptoms as compared to TAU (67). Most of the aforementioned therapies were evaluated compared to a waitlist or TAU condition. However, when psychotherapeutic interventions were tested against a control psychotherapeutic intervention such as supportive psychotherapy (ST), the tendency was for there to be no significant difference in outcomes. Group or family psychoeducation have been found to be

more effective than individual psychoeducation based on guided practice of illness management strategies (67).

The efficacy of psychosocial interventions can vary depending on the patient's characteristics and the illness course (68). Patients who are euthymic when starting treatment, and have had fewer than 12 previous episodes, have been shown to respond better to psychosocial interventions (28), while an analysis on the effectiveness of group psychoeducation found that time to illness recurrence was only improved in patients with fewer than seven previous episodes (29). With patients with seven or eight previous episodes, there was an improvement only in the number of days of manic, depressive and hypomanic episodes, while in patients with nine to 14 previous episodes there was an improvement only in days spent in hypomanic and depressive episodes. Meanwhile, there was no improvement in patients with 15 or more previous episodes (29). These results indicate the need to apply adjunctive psychotherapy early on in the disease course for greatest effect.

Cognitive impairment in BD can be treated through a range of techniques. More research is needed but promising treatments combine effective pharmacotherapy with other techniques such as psychoeducation (to avoid multiple episodes which increase the risk of cognitive impairment), control of comorbidity, treatment of subsyndromal symptoms, and the promotion of healthy habits, alongside procognitive drugs, the enhancement of cognitive reserve, and functional and cognitive remediation (69). Improvements in cognitive impairment can improve psychosocial functioning (69) and functional remediation has been shown to significantly improve psychosocial functioning in BD (70,71). However, more strategies are needed to help patients achieve full functional recovery (72).

1.3 Association between psychological trauma and mental disorders

1.3.1 Psychological trauma and mental disorders

There is robust data showing an association between having experienced traumatic events and experiencing a mental disorder. One prospective study, which assessed childhood trauma up to eight times in childhood and then followed participants and assessed them four times in adulthood, up to 30 years of age, found an increased risk of adult psychiatric outcomes in participants who had experienced childhood trauma (OR=1.3, 95% CI: 1.0-1.5) (73). Similarly, a prospective study in Brazil found an association between lifetime trauma exposure and any type of psychiatric disorder, as well as a specific association with anxiety disorders, at six years old, and between lifetime trauma exposure and any psychiatric disorder, and specifically anxiety disorders, mood disorders, ADHD, and conduct disorders at age 11 (74).

Retrospective studies have found similar results. A large US study (75) detected that childhood adversity was associated with an increased lifetime prevalence of a range of DSM-IV (76) diagnoses in adults, including anxiety, mood, conduct, and substance use disorders, with simulations suggesting they are associated with 44.6% of childhood onset disorders and between 25.9% and 32.0% of adult-onset disorders. Childhood adversity related to maladaptive family functioning (parental mental illness, substance disorder, criminal behaviour, family violence, physical abuse, sexual abuse, and neglect) was the strongest predictor of mental disorder onset (75). Data from adolescents in the same survey found that childhood adversity was associated with 28.2% of all adolescent-onset psychiatric disorders (77). Furthermore, a large meta-analysis found that people who had experienced four or more adverse childhood experiences had a significantly increased risk of suffering depression (4.40, 95% CI 3.54-5.46), anxiety (OR=3.70, 95% CI 2.62-5.22), and problematic alcohol use

(OR=5.84, 95% CI=3.99-8.56) (78). Furthermore, child abuse has been shown to make individuals more vulnerable to recurrences of depressive episodes (79) and chronic depression, and can lead to more severe depressive symptoms (80).

Psychological trauma is associated with over triple the risk of having psychotic experiences, according to transnational data from the World Mental Health survey (OR=3.1, 95% CI 2.7-3.7) (81), while a meta-analysis found that patients with psychosis were 2.78 times more likely to have experienced childhood trauma than controls (OR=2.78, 95% CI 2.34-3.31) (82).

Childhood trauma is also associated with a greater risk of suicide attempts, with complex trauma including repetitive and severe events, similar to the criteria for CPTSD, leading to more than five times the risk of attempting suicide (83). In comparison, sexual abuse was associated with a threefold risk for attempting suicide, while emotional and physical abuse were both associated with a two-and-a-half-fold risk (83).

Evidence suggests that comorbid psychological trauma has a negative impact not only on disease onset, but also on disease progression. A study in patients with severe mental disorders found that childhood trauma was associated with a higher number of hospital admissions, more severe psychotic symptoms, and a greater risk of attempting suicide (84).

Unsurprisingly, comorbidity with PTSD is high in patients with severe mental disorders: estimates range from 20% to 47%, and PTSD is more prevalent in female psychiatric patients (85). Moreover, CPTSD has been estimated at up to 50% in people attending mental health facilities (17). Comorbidity with PTSD in patients with a severe mental disorder is associated with a greater number of hospital admissions, use of health services, and healthcare costs (86). Furthermore, the experience of severe mental illness can lead to PTSD in and of itself: a

review suggested that PTSD related to the experience of psychosis is estimated to occur in between 14% and 47% of people with psychotic episodes (87).

1.3.2 Psychological trauma and BD

There is clear evidence supporting an association between psychological trauma and the onset of BD: a meta-analysis of 19 studies showed a 2.63 increased risk of BD associated with childhood trauma (OR=2.63, 95% CI=2.00-3.47) (88). The association was strongest with emotional abuse (OR=4.04, 95% CI=3.12-5.22), but significant for all types of abuse and neglect: physical abuse (OR=2.86, 95% CI=2.22-3.69), sexual abuse (OR=2.58, 95% CI=2.08-3.20), physical neglect (OR=2.26, 95%CI=1.74-2.93), and emotional neglect (OR=2.62, 95% CI=2.03-3.38) (88). Furthermore, PTSD is a frequent comorbidity in BD, with lifetime prevalence estimates of between 4% and 40% (89). The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, which included a large bipolar sample, found that 9.2% of BD-I patients had current PTSD, and 21.3% had a lifetime PTSD diagnosis, while 5.1% of BD-II patients had current PTSD, and 15.6% had a lifetime PTSD diagnosis (90). Comorbidity with PTSD is associated with female gender, depressive episodes, suicide attempts and comorbid personality disorders (91).

There is little data regarding the prevalence of CPTSD in BD. There have been two studies regarding the prevalence of BD in populations who have experienced extreme trauma of the type which can lead to CPTSD, namely sex-trafficked children and people living in conflict settings (92,93). Both studies found that BD was more prevalent in these populations, but CPTSD was not measured. However, recent research into the prevalence of PTSD and CPTSD in people with psychiatric disorders found that, while there was no significant effect for PTSD, psychiatric patients with CPTSD were significantly less likely to have BD, and significantly more likely to have a personality disorder (94), suggesting that CPTSD is less

common in adults living with BD than in adults with other psychiatric disorders. More research is needed to understand the association between BD and CPTSD.

Comorbidity with psychological trauma has been shown in multiple studies to negatively impact BD disease course. There is robust evidence associating childhood trauma with a worse disease course in terms of earlier age of onset, greater number of hospital admissions, more suicide attempts, greater cognitive impairment, more rapid cycling (i.e. four or more mood episodes within a year), more substance use, lower functioning, more depressive and manic episodes and greater severity of depressive and manic symptoms, and more psychotic symptoms and greater severity of psychotic symptoms (61,95–98). Meanwhile, preliminary data show that comorbid PTSD in BD-I patients is associated with lower quality of life, more rapid cycling, a greater number of suicide attempts, and a lower possibility of maintaining recovery (91,99). A recent article showed that multiple, cumulative traumatic events in BD patients was associated with greater psychiatric comorbidity and lower levels of social support (100).

With regards to the previously mentioned clinical staging model for BD, psychological trauma can be implicated in the at-risk stage, whereby stress can interact with genetic and biological vulnerabilities to increase the risk of BD onset and of a poor prognosis (46,47).

1.3.3 Psychological trauma as a transdiagnostic risk factor for mental disorder

The concept of transdiagnosticity refers to an approach which cuts across psychiatric categories (101). The current diagnostic system, which conceptualises mental disorders as distinct nosological categories, has been criticised for creating artificial separations between symptoms, leading to a high number of comorbid psychiatric diagnoses which may all be expressions of the same underlying transdiagnostic process (102,103). The transdiagnostic

approach can help improve assessment and treatment pathways for patients with comorbid mental disorders (103,104).

In 2011, a model was developed for transdiagnostic constructs in psychopathology to explain how shared underlying factors can lead to different illness disease outcomes and trajectories (104). This model proposed distal risk factors, such as the environmental context or congenital abnormalities, and proximal risk factors, such as biological factors leading to certain emotional, cognitive, or behavioural tendencies, cognitive factors, or individual psychological traits.

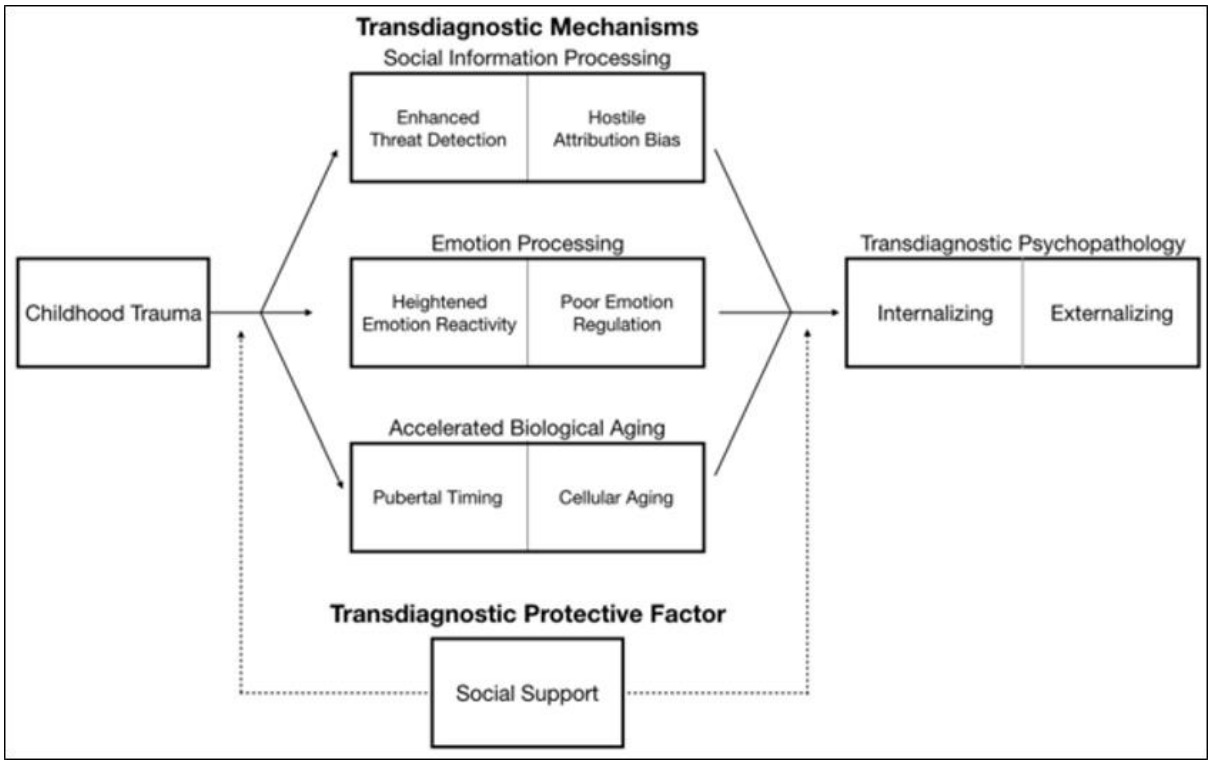
Transdiagnostic constructs that have been proposed in psychopathology include emotional dysregulation (105) or low general decision-making ability (106), as well as functional and structural differences in the brain such as abnormalities in the default mode network (DMN) (107) or deviations from the norm in cortical volume respectively (108). Psychological trauma has also been identified as a transdiagnostic construct in psychopathology. Recently, McLaughlin and colleagues, a team of researchers from Harvard University, proposed a transdiagnostic model for childhood trauma, highlighting key mechanisms by which childhood trauma leads to a range of psychiatric outcomes (109). In this model, the psychiatric outcomes are classified as internalising or externalising: internalising outcomes refer to behavioural problems focused on oneself, such as symptoms of depression and anxiety, whereas externalising outcomes occur in interaction with the social environment (e.g. aggression, impulsivity, or hyperactivity) (110). Within this transdiagnostic model, which can be seen in Figure 1, McLaughlin and colleagues highlighted three mechanisms of risk: 1) social information processing; 2) emotion processing; and 3) accelerated biological ageing. Social information processing refers to how social cues are perceived, identified, and interpreted, and childhood trauma can lead to biases in how this information is processed.

Children who have been exposed to trauma are more likely to identify neutral cues as threatening, and are more sensitive to cues that are expressions of anger or fear, which can lead to greater levels of internalising behaviours and anxiety. According to the model, they are also more likely to attribute hostile intentions to others in ambiguous social situations, which has been associated with externalising problems and psychosis.

Regarding the second mechanism, emotional processing, the model explains how people exposed to childhood trauma can show heightened emotional reactivity, low emotional awareness, and can have difficulties with emotion regulation, which is an important factor in many psychiatric disorders. The model suggests some neurobiological changes which may be implicated, such as changes in the amygdala, and studies showing that children exposed to trauma need to use the prefrontal cortex more than unexposed children in order to use effective emotion regulation strategies. The first two risk mechanisms of the model are supported by findings from a 2016 review published in Nature Reviews Neuroscience (6), which highlighted the changes in brain structure, function, and connectivity which link maltreatment-related childhood trauma and psychopathological outcomes. They summarised neuroimaging findings regarding the impact of childhood maltreatment on the threat-detection and response circuit and found that maltreated individuals were more alert to detecting threats, which they hypothesised was an adaptive measure to help individuals to avoid threats, but which left them later more vulnerable to subsequent stressors and psychopathological outcomes. They also reported on reduced centrality in the network architecture of maltreated individuals, which was related to alterations in regulating emotions, attention, and in social cognition. These findings demonstrate some of the neurobiological changes which underpin the first two risk mechanisms in the McLaughlin model.

The final risk mechanism in the McLaughlin model is accelerated biological ageing, whereby a child's individual development trajectory can be more rapid in a difficult or unpredictable environment, to increase their chances of surviving to reproductive age. However, the exact mechanisms through which this can occur are not yet fully understood. The key indicators of biological ageing referenced in the model are pubertal timing (measured by age of menarche in people with periods) and cellular ageing (measured by leukocyte telomere length and DNA methylation), which the model explains are both robustly associated with childhood trauma, and which have been shown to be associated with a range of psychopathological outcomes.

Figure 1. Transdiagnostic mechanisms linking childhood trauma and psychopathology. Source: McLaughlin et al., (2020) (109).



The model also identifies one protective mechanism, social support (109). While the model points to social support in general helping reduce the risk of developing psychopathology following trauma exposure, it specifically highlights the important role of caregiver support,

which has been shown to help reduce amygdala reactivity, and improve functional coupling of the medial pre-frontal cortex and amygdala, and improve the ability to discriminate between threat and safety cues. In the study by Teicher and colleagues (6), they uncovered a surprising finding that trauma-related neurobiological differences were found consistently across maltreated individuals, with or without psychopathology, but were not generally found in people with psychopathology but no history of trauma. They suggested that in maltreated individuals who are resilient to psychiatric outcomes, there may be other areas of the brain which compensate for the areas affected by trauma. Further research can elucidate this point and understand if social support is one of the mechanisms which improves resilience at a neurobiological level.

The Teicher study (6) also highlighted how childhood maltreatment can affect development of the DMN, which as mentioned has been identified as a transdiagnostic risk factor for psychopathology in a recent large meta-analysis (107). Recent research has shown that the effects of childhood trauma on emotional behaviour were mediated by changes in the DMN, and suggest that DMN alterations could be a valid biomarker to complement psychological evaluations of childhood trauma (111). Finally, deviations from the norm in cortical thickness were also mentioned as a transdiagnostic risk factor for psychopathology (108) and these were also found in response to trauma (6). The Teicher article suggests that these changes in the systems which bring unpleasant experiences to consciousness may have the objective of reducing the distress caused by repeated exposure to traumatic events (6).

The mechanisms by which psychological trauma may impact the brain and development are clearly complex, but the recent body of research helps provide a theoretical framework to understand its role as a transdiagnostic risk factor. However, to date, a key component of the

framework is missing, as psychological trauma has not been systematically evaluated as a transdiagnostic construct across a range of psychopathology.

1.4 Addressing trauma in mental disorder

1.4.1 Trauma-focused treatments for PTSD

Treatment for PTSD can consist of psychological therapy and pharmacological therapy. Guidelines for pharmacological therapy support the use of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, but the tendency is to support the use of trauma-focused psychotherapy as a first-line treatment (112). Trauma-focused therapies differ from standard psychotherapies due to their understanding of how current symptoms are related to previous traumatic events, and usually include an element of exposition to the traumatic event, within a safe and supportive therapeutic environment, which can help the memory to become desensitised, i.e. less triggering, and to ameliorate trauma-related symptoms.

The trauma-focused psychotherapies which are most recommended in international guidelines for the treatment of PTSD are trauma-focused cognitive behavioural therapy (TF-CBT), prolonged exposure therapy, and Eye Movement Desensitisation and Reprocessing (EMDR) therapy (112–114). TF-CBT protocols tend to comprise psychoeducation, management of anxiety symptoms, exposure, and cognitive restructuring, while exposure therapy uses either in vivo or imagined exposure (115), or more recently can include exposure using virtual reality technology. Prolonged exposure is a specific type of trauma-focused CBT where the individual gradually begins to work with the trauma-related memories and related situations and emotions (116). EMDR therapy is an alternative to CBT-based approaches. Within a structured 8-phase protocol, it combines imagined exposure with the simultaneous use of bilateral stimulation, most commonly in the form of eye movements,

to desensitise and reprocess the memory and the emotional and somatic symptoms associated with it (117).

There is also some evidence to support other trauma-focused psychotherapies such as brief eclectic psychotherapy and narrative exposure therapy (112). Brief eclectic therapy is a structured 16-session protocol including psychoeducation, imagined exposure, cognitive restructuring, and then a ritualistic farewell (118). In narrative exposure therapy, the individual develops a narrative for the trauma in order to contextualise and reprocess it (119). Finally, there is limited evidence to support non-trauma-focused therapies such as standard CBT, stress inoculation training, present centred therapy, interpersonal psychotherapy (112) and ST (120,121). Additionally, the non-trauma-focused transdiagnostic psychotherapy protocol called the Unified Protocol (105), which targets emotional dysregulation using CBT techniques, has been trialled in one study with adults with PTSD and has shown potential to reduce clinical trauma symptoms (122).

1.4.2 Trauma-focused treatments in BD and other severe mental disorders

Despite the high prevalence of trauma and PTSD in BD and other severe mental disorders, there has been surprisingly little research into treating psychological trauma in this population. Trauma is often overlooked as a therapeutic objective or ignored for fear of destabilising affective or psychotic symptoms (86), and there is little in the way of guidelines or research into either pharmacological or psychosocial treatment of trauma in patients with comorbid BD or other severe mental disorders. Research from approximately 20 years ago recommends mood stabilisers, antidepressants, antipsychotics, and benzodiazepines as options for BD patients with comorbid PTSD (123,124) and highlights the lack of research into psychotherapy for these patients (124). Although there is a lack of updated research into pharmacological approaches, there is an emerging body of research into trauma-focused

psychotherapies in severe mental disorders, focusing mainly on schizophrenia spectrum disorders, major depressive disorder, and BD. A recent meta-analysis summarised 14 studies of 684 participants with comorbid PTSD and severe mental illness, of whom 89 had BD (125). No study reported separate results for BD, but the review found that prolonged exposure, EMDR, and a brief treatment program all showed evidence for being effective treatments for PTSD in severe mental illness (125). This meta-analysis included results from a CBT-based intervention for PTSD adapted for people with severe mental illness (126). This intervention was tested for cost-effectiveness but was not found to be more cost-effective than a brief control intervention for the majority of patients (127), although it was more effective in reducing trauma symptoms. A more recent non-controlled study found preliminary evidence that narrative exposure therapy is well tolerated in patients with severe mental illness and could be an effective treatment (128); this study included four BD patients.

Regarding studies focusing on trauma in BD patients, there appear to be no studies carried out regarding the effectiveness of prolonged exposure or TF-CBT specifically in this population, but there has been some preliminary research into EMDR therapy in BD. A randomised controlled pilot trial was carried out in 2014 (129) which tested EMDR therapy in BD patients with subsyndromal affective symptoms. In this study, ten subjects were assigned to receive between 14 and 18 sessions of EMDR over 12 weeks, and ten subjects were assigned to treatment as usual. In the EMDR group, there was a significant improvement in symptoms of depression and hypomania and in trauma symptoms post-treatment, and the effect was maintained in trauma symptoms only at 24 weeks. Based on the experience of this study, the research team created an EMDR Manual for Bipolar Disorder (130), Spanish summary (131). This manual includes five subprotocols to address specific bipolar disorder symptoms, to be used where appropriate alongside the standard EMDR

protocol for addressing trauma. The five subprotocols address stabilisation of mood symptoms, awareness of the illness, adherence to pharmacological treatment, prodrome symptoms, and deidealisation of manic symptoms.

Further exploratory data into the effect of EMDR on BD patients comes from a case study using functional magnetic resonance imaging (fMRI) where, in comparison with 30 healthy women, EMDR was shown to modulate the default mode network in a subsyndromal BD patient with a history of trauma (132). Meanwhile, another case study in Korea found EMDR was successful in remitting PTSD in two BD patients with comorbid PTSD in ten sessions (133). A review published in 2020 did not find more studies in EMDR and BD (134), and there is a lack of robust data from randomised controlled trials evaluating the efficacy of any type of trauma-focused treatment.

2. Justification

2. Justification for the thesis

Despite the strong association that has been described between psychological trauma and a range of individual mental disorders, there are some important gaps in the extant literature. Firstly, there has been no overarching review to assess the role of psychological trauma as a general, transdiagnostic risk factor for mental disorders. Secondly, there is scarce data regarding how to address trauma as a comorbidity in severe mental disorders. Therefore, this thesis is divided into two main parts. The first part of the thesis focuses on synthesising the available evidence from existing reviews and meta-analyses regarding psychological trauma in distinct psychiatric diagnoses, to determine whether psychological trauma is a transdiagnostic risk factor for mental disorder. If the umbrella review provides robust evidence for the role of trauma across mental disorders, it will support the importance of researching and investing in prevention and early intervention programmes, and screening for and treating trauma alongside other psychiatric comorbidities in mental health settings.

Within this wider context, the second part of the thesis focuses on understanding and treating psychological trauma in a specific psychiatric disorder, BD. In this disorder, there is robust evidence demonstrating an association between psychological trauma and the onset and poor clinical course of BD, yet there is little evidence on the characteristics of BD patients who have comorbid trauma, or on how to treat trauma in this population. There is currently only one previous study which specifically investigates trauma profiles across different BD subtypes (90). Additionally, there is little evidence regarding the impact of a PTSD diagnosis and the impact of specific abuse types within a sample of patients with a history of comorbid psychological trauma. Further data in this area can help identify patients at risk of poor disease outcomes.

This thesis is also innovative in representing the first application of a trauma-focused psychotherapy, in this case EMDR, in a multicentre randomised controlled trial. Furthermore, it aims to assess the impact of a trauma-focused therapy not only on trauma symptoms, but also on affective relapse rates and mood symptoms. In this study, we use the EMDR Bipolar manual, designed specifically for working with patients with BD and comorbid trauma following a successful pilot trial in BD patients. Novel treatments are needed to improve outcomes in BD, and the data from this trial will provide important information regarding whether EMDR therapy is well-tolerated in euthymic and subsyndromal BD patients, whether it reduces affective relapses and affective symptoms, psychosocial functioning, and cognitive impairment, and whether it positively impacts on trauma symptoms in BD patients.

3. Hypotheses and Objectives

3. Hypotheses and Objectives

3. 1 Hypotheses

Based on the aforementioned research, the first hypothesis of this thesis is that psychological trauma will meet criteria as a transdiagnostic risk factor for a range of mental disorders. The second hypothesis of the thesis is that, within a sample of BD patients with a history of psychological trauma, a PTSD diagnosis, a history of physical abuse, and a history of sexual abuse will each be associated with a worse disease course, but there will be no difference in symptom profile between BD-I and BD-II. The final hypothesis of the thesis is that treatment with an adjunctive trauma-focused psychotherapy adapted for BD, the EMDR Bipolar manual, as compared to a non-trauma-focused psychotherapy, ST, will be associated with a reduction in trauma symptoms a lower number of affective relapses, improved affective symptoms, psychosocial functioning, and cognition.

3.2 Objectives

3.2.1 General objectives

The overall objective of the thesis is to understand the role of psychological trauma as a transdiagnostic risk factor across mental disorders, and then to examine in a specific disorder, BD, the characteristics of people with BD and comorbid trauma, and to research the possibility of improving the BD clinical course and trauma symptoms through the use of an adjunctive trauma-focused psychotherapy adapted to BD, the EMDR Bipolar protocol.

3.2.2 Specific objectives

1. To assess psychological trauma as a transdiagnostic risk factor for mental disorder.

2. To describe the clinical and sociodemographic characteristics of a sample of patients with BD and a history of psychological trauma, and to compare the trauma profiles of BD-I and BD-II.
3. To analyse the impact of a lifetime PTSD diagnosis, physical abuse, and sexual abuse on the clinical course of BD.
4. To assess the efficacy of a trauma-focused psychotherapy, EMDR, as compared to a non-trauma-focused therapy, ST, in reducing affective relapses and hospital admissions in a sample of patients with BD and a history of psychological trauma, through a multicentre randomised controlled trial.
5. To assess the efficacy of a trauma-focused psychotherapy, EMDR, as compared to a non-trauma-focused therapy, ST, in improving depressive and manic symptoms, psychosocial functioning, cognition, and trauma-related symptoms in a sample of patients with BD and a history of psychological trauma, through a multicentre randomised controlled trial.

4. Methods and Results

4. Methods and Results

4.1 Manuscript 1: Psychological Trauma as a Risk Factor for Mental Disorder: an Umbrella Review

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ORIGINAL PAPER

Psychological trauma as a transdiagnostic risk factor for mental disorder: an umbrella meta-analysis

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Abstract

This umbrella review is the first to systematically examine psychological trauma as a transdiagnostic risk factor across psychiatric conditions. We searched Pubmed, Scopus, and PsycNET databases from inception until 01/05/2021 for systematic reviews/meta-analyses evaluating the association between psychological trauma and at least one diagnosed mental disorder. We re-calculated the odds ratio (OR), then classified the association as convincing, highly suggestive, suggestive, or weak, based on the number of cases and controls with and without psychological trauma, random-effects *p* value, the 95% confidence interval of the largest study, heterogeneity between studies, 95% prediction interval, small-study effect, and excess significance bias. Additional outcomes were the association between specific trauma types and specific mental disorders, and a sensitivity analysis for childhood trauma. Transdiagnosticity was assessed using TRANSD criteria. The review was pre-registered in Prospero CRD42020157308 and followed PRISMA/MOOSE guidelines. Fourteen reviews met inclusion criteria, comprising 16,277 cases and 77,586 controls. Psychological trauma met TRANSD criteria as a transdiagnostic factor across different diagnostic criteria and spectra. There was highly suggestive evidence of an association between psychological trauma at any time-point and any mental disorder (OR = 2.92) and between childhood trauma and any mental disorder (OR = 2.90). Regarding specific trauma types, convincing evidence linked physical abuse (OR = 2.36) and highly suggestive evidence linked sexual abuse (OR = 3.47) with a range of mental disorders, and convincing evidence linked emotional abuse to anxiety disorders (OR = 3.05); there were no data for emotional abuse with other disorders. These findings highlight the importance of preventing early traumatic events and providing trauma-informed care in early intervention and psychiatric services.

Keywords Psychological trauma · Mental disorders · Risk factors · Odds ratio

Introduction

The aetiology of mental illness is multifactorial, with genetic factors, environmental factors and early and late life experiences all playing a role [1]. One factor which is implicated in the onset and maintenance of a range of mental disorders is psychological trauma. Psychological trauma can be defined as a person experiencing events or circumstances which are physically or emotionally harmful or life threatening, and which have lasting adverse effects on their functioning and mental, physical, social, emotional, or spiritual well-being [2], and can include experiences of physical, psychological, emotional or sexual abuse, or the presence of any traumatic life event such as accidents, disasters, illness diagnosis, or loss of loved ones, among others [3, 4]. While trauma exposure is a pre-requisite for stressor-related disorders such as post-traumatic stress disorder (PTSD) [5], it is also associated with a range of other mental disorders, such as depression, anxiety, substance use and psychosis [6–10]. It is also a factor predicting a poorer prognosis in mental disorder, leading to more resistant symptoms, a greater number of hospitalizations and more days of admission [6, 11], and exacerbating the cost for the health system [11–13].

Traumatic events are highly prevalent, with studies across a broad range of countries estimating between 70.4 and 89.7% of adults have suffered at least one traumatic event during their lifetime, and 30.5% had been exposed to four or more [14, 15]. Trauma often occurs in childhood: a World

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Health Organization study into a sample of 51,945 adults from 21 countries found that 38–39% of the interviewed population had suffered at least one adverse event in childhood [16].

Given the high prevalence and impact of psychological trauma, it is perhaps surprising that until now it has not received more attention in research outside of the diagnoses of PTSD and other stress-related disorders. A growing body of research has focused on limitations of the current nosological diagnostic system in psychiatry [17, 18], suggesting that the high comorbidity between mental disorders [6] is not true comorbidity but a result of an artificial categorisation system [17], and arguing that there are underlying transdiagnostic processes which underpin a range of mental illnesses [18]. A transdiagnostic approach can help improve understanding by focusing on underlying dysfunctional processes that cut across the artificial categorisation system, providing greater understanding of the high comorbidity between disorders and providing more effective avenues for assessment and treatment [18, 19]. The mechanisms by which transdiagnostic constructs in psychopathology can lead to divergent outcomes and trajectories have been suggested by one model which proposes both distal and proximate risk factors, linked by a range of mechanisms and moderators, to explain the variance in outcome [19]. More recently, a specific model for psychological trauma as a transdiagnostic construct in psychopathology has been developed, comprising three transdiagnostic risk mechanisms: social information processing, emotion processing, and accelerated biological ageing, and one transdiagnostic protective factor: social support [20].

Research regarding transdiagnosticity in psychiatry has generally been found to lack rigour to date, according to a recent review [21]. To address this, and improve the quality of appraising and reporting on transdiagnostic constructs, the TRANSD criteria have been elaborated [22]. The TRANSD criteria require research to be based on valid diagnoses according to Diagnostic and Statistical Manual of Mental Disorders (DSM) [23] or International Classification of Disease (ICD) [24] criteria, a clear conceptual framework (whether the transdiagnostic construct goes across existing diagnostic categories or goes beyond them), statistical rigour in proving the transdiagnostic approach fits the data, and for results to be replicable across two or more studies.

To date, although psychological trauma has been linked to a range of mental disorders, it has not yet been systematically tested as a transdiagnostic construct. This review aims to be the first to evaluate whether psychological trauma fulfils criteria as a transdiagnostic risk factor cutting across various diagnostic categories and spectra. Transdiagnosticity will be assessed against the framework of the TRANSD criteria. The paper additionally aims to analyse the association of psychopathology with specific trauma type.

Methods

Search strategy and selection criteria

We conducted an umbrella review analysis [25] to investigate psychological trauma as a risk factor for the development of a range of psychiatric disorders. Data from published systematic reviews and meta-analyses only were included, and the review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [26] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [27]. Both are presented in the supplementary material. The study protocol was registered a priori in PROSPERO (No: CRD42020157308).

The search was initially carried out in the Scopus and PubMed databases from inception to 12th February, 2020, and then updated with searches in the PubMed and PsycNET databases to include studies until 1st May, 2021. Each search was carried out independently by two separate researchers. The search strategy included systematic review or meta-analysis articles containing MESH terms related to both "Trauma and Stressor Related Disorders" and "Mental Disorder" and excluding "Neurocognitive Disorders". The MESH terms are hierarchically organised, and thus these main headings include all subheadings relating to, for example, trauma, psychological trauma, posttraumatic stress, or specific mental disorders. In the case of PsycNET, umbrella terms relating to "Psychological Trauma" and "Mental Disorder" were used. We also hand-searched the reference lists of the systematic reviews and meta-analyses reaching full-text review. The following inclusion criteria were applied: (i) Systematic review and/or meta-analysis; (ii) Assesses the association between psychological trauma and at least one mental disorder, diagnosed using DSM or ICD criteria; (iii) Inclusion of a control group, resulting in all cases in 4 groups: those with a psychiatric disorder and trauma, those with a psychiatric disorder and no trauma, those with no psychiatric disorder and trauma, and those with no psychiatric disorder and no trauma; and (iv) in English or Spanish language. Exclusion criteria applied were (i) evaluates psychiatric disorders without a formal diagnosis or valid diagnostic tool; (ii) does not assess the association between psychological trauma and mental disorder; (iii) reports insufficient data for the analysis; (iv) focuses solely on neurocognitive disorders or intellectual disability.

Search results were uploaded into the software Rayyan QCRI (https://rayyan.qcri.org/) and screened independently in a two-step procedure by two researchers, first reviewing the title/abstract and then reviewing the full-text article. At each stage, discrepancies were resolved in

a consensus meeting. A full list of excluded article citations can be obtained from the authors upon request. Study quality was assessed using the AMSTAR [28], which was also applied by two separate researchers and discrepancies were resolved in a consensus meeting with the senior author. Where data were insufficient, study authors were contacted.

Data analysis

Data extraction was carried out by two separate researchers and discrepancies resolved in a consensus meeting with the senior author. Data extracted from selected studies included first author name, year, type of mental disorder, type of psychological trauma, whether the study was prospective or not, the measure used (e.g. Odds Ratio [OR], Relative Risk [RR], etc.) and its value with confidence interval, the number of participants exposed and not exposed to trauma, the number of participants with mental disorder (cases) and without mental disorder (controls), and the means and standard deviations for number of cases and controls exposed and not exposed to trauma.

Our main aim was to investigate the evidence of the association between each type of psychological trauma and any mental disorder (without differentiating between disorders). We conducted a random-effects meta-analysis of the RR or OR of developing a mental illness in those with psychological trauma compared to matched controls to analyse each association. We saved the RR or OR along with its confidence interval and p value, the I^2 statistic, and the 95% prediction interval from each meta-analysis. I^2 values above 50% represent large between-study heterogeneity [29]. The 95% prediction interval estimates the likely effect expected in a new study. Therefore, when the prediction excludes the null value (1 for RR or OR), it is likely that such association remains statistically significant in new studies. We also computed the Egger test [30] to assess whether there were hints of potential small-study effects. Finally, we performed a binomial test comparing the observed vs. the expected numbers of studies yielding statistically significant results to assess whether there was an excess of studies reporting statistically significant findings [31].

We used the Ioannidis' evidence criteria to quantify the strength of each association and provide a classification for the credibility of the evidence, thus transmitting our level of confidence in each result [31, 32]. Accordingly, we classified the associations into *convincing* (class I), *highly suggestive* (class II), *suggestive* (class III), or *weak* (class IV). *Convincing evidence* required a large number of cases ($n > 1000$), a highly statistically significant association ($p < 10^{-6}$), a low between-study heterogeneity with $I^2 < 50\%$, a 95% prediction interval excluding one, and the absence of small-study effects and excess significance bias. *Highly suggestive evidence* also required $n > 1000$, a highly statistically significant association ($p < 10^{-6}$), and that the largest study had a statistically significant effect. *Suggestive evidence* required $n > 1000$ and $p < 0.001$. *Weak evidence* required no specific number of cases and $p < 0.05$. We present these categories for level of evidence alongside the odds ratios to provide context for interpretation of results. Higher levels of evidence provide greater levels of confidence in the replicability of the results, while results for weak evidence must be interpreted with caution.

We analysed the association between each type of psychological trauma and developing any mental disorder when at least three included studies had investigated the association, with results shown in a table and boxplot. We also performed subgroup analyses to investigate the specific association between each type of trauma and later developing each specific mental disorder. As an additional analysis, we decided to examine the association between any trauma (without differentiating between types of trauma) and later developing each specific mental disorder. Finally, given the large proportion of studies focusing on childhood trauma, we also conducted a sensitivity analysis including only studies with childhood traumas, to see if this explained the association. Additionally, a second sensitivity analysis including only studies with trauma experienced during adulthood was conducted.

TRANSD criteria [22] assess whether a factor or construct can be defined as transdiagnostic according to whether the following criteria are met: (i) transparent definition, comprising which specific diagnoses are included according to which definition (DSM or ICD) and whether they are primary or secondary; (ii) report, including the primary outcome, study design used and transdiagnostic construct being tested; (iii) appraise the conceptual framework, detailing which diagnoses and diagnostic spectra are included; (iv) numerate the diagnostic categories, spectra and non-clinical samples; (v) show the degree of association, comprising the diagnostic-specific and transdiagnostic statistical results; and (vi) demonstrate the generalizability, where results must be being replicated across at least two independent studies.

Results

The initial systematic search yielded 707 results, and the updated search provided 148 more articles, a total of 855, which reduced to 850 after removing duplicates. Following the title/abstract screening, we retrieved 176 updated full-text articles for review, of which 14 met the inclusion criteria [3, 33–45]. The search process can be seen in Fig. 1. These papers comprised 106 individual studies meeting our inclusion criteria, including a total of 93,863 participants (16,277 cases and 77,586 controls) and ten categories of psychological trauma:

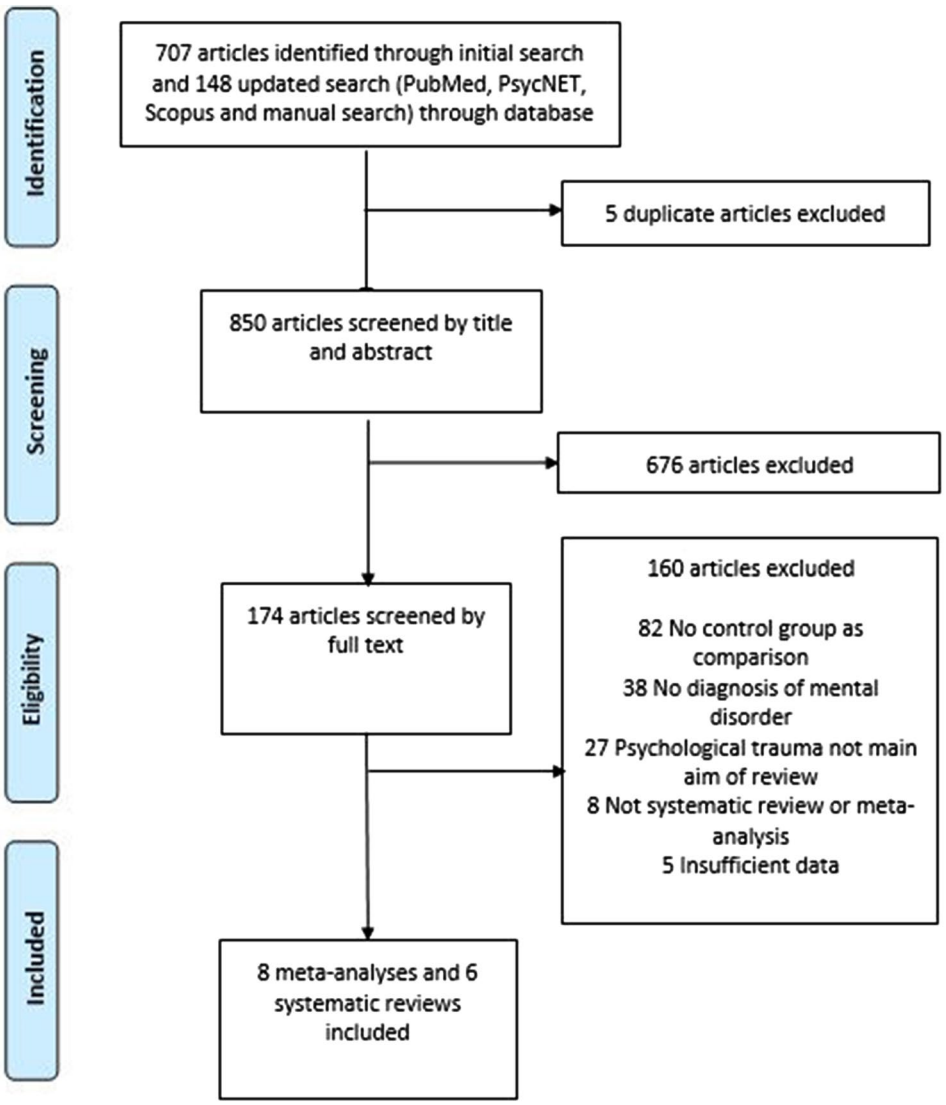

Fig. 1 PRISMA flow diagram

sexual abuse ($n=26$), physical abuse ($n=15$), emotional abuse ($n=8$), person under train incidents ($n=4$), military deployment to a warzone ($n=4$), disaster ($n=3$), illness diagnosis ($n=3$), parental loss during childhood ($n=3$), general traumatic event ($n=1$) and non-specific childhood trauma ($n=39$). This final category combines specific types of trauma experienced in childhood where there were fewer than three studies (death of a sibling by homicide, bullying, domestic violence, family abuse) along with studies not specifying the adverse event, and results from a meta-analysis which combined different trauma types (including physical and emotional abuse and neglect and sexual abuse) into one variable. Most studies focused on specific mental disorders such as anxiety disorders, specifically generalized anxiety disorder, panic disorder, or social anxiety disorder ($n=31$), psychosis, specifically schizophrenia, schizoaffective disorder, or psychotic disorder ($n=25$), bipolar disorder (BD; $n=13$), post-traumatic stress disorder (PTSD; $n=12$), obsessive–compulsive disorder (OCD; $n=8$), borderline personality disorder (BPD; $n=4$), or major depressive disorder (MDD; $n=3$) while others ($n=10$) investigated either disorders where there too few studies to create a separate variable categorised as "Other Mental Disorder" which represents Attention Deficit Hyperactivity Disorder (ADHD; $n=2$), conduct disorder ($n=1$), bulimia nervosa ($n=1$), any personality disorder ($n=1$), and any mood disorder ($n=2$), as well as studies which investigated any mental disorder ($n=3$).

A description of the studies included in our review and respective AMSTAR scores can be seen in Table 1.

Association between any type of trauma and mental disorder

There was highly suggestive (Class II) evidence of an association between any type of mental disorder and any type of trauma (OR = 2.92; 95% CI: 2.60, 3.28).

An analysis regarding specific trauma types showed that seven of nine types (77.8%, namely emotional abuse, physical abuse, sexual abuse, non-specific childhood trauma, military deployment to a warzone, person under train incident, and disaster) showed statistically significant evidence of association with the development of any mental disorder at $p < 0.05$, of which five (55.6%) reached a $p < 10^{-6}$. Physical abuse met criteria for convincing (Class I) evidence of an association with any mental disorder (OR = 2.36; 95% CI: 2.13, 2.62). There was highly suggestive (Class II) evidence of an association between mental disorder and sexual abuse (OR = 3.43; 95% CI: 2.75, 4.27), non-specific childhood trauma (OR = 3.01; 95% CI: 2.42, 3.74) and emotional abuse (OR = 2.92; 95% CI: 2.26, 3.77). Disaster (OR = 2.92; 95% CI: 1.09, 7.80), military deployment to a warzone (OR = 5.10; 95% CI: 3.82, 6.80), and person under train (OR = 3.78; 95% CI: 1.44, 9.91) all met criteria for weak (Class IV) evidence due to, among other factors, the lower number of cases. The associations with illness diagnosis and parental loss during childhood did not reach significance. Results are presented in Supplementary Table 1 and Fig. 2.

Table 1 Overview of included systematic reviews ($n = 6$) or meta-analyses ($n = 8$) evaluating the impact of psychological trauma on the onset of mental disorders

First author, year	Type of article	Factors examined	*K* (total)	*K* (specifically childhood)	Diagnosis	AMSTAR score	Number of cases†	Number of controls†
Bendall 2008 [37]	SR	Sexual abuse	2	2	Psychosis	3	37	67
Cabizuca 2009 [41]	MA	Illness diagnosis	1	0	PTSD	3	14	33
Martins 2011 [38]	SR	Sexual abuse, Childhood trauma, Physical abuse, Emotional abuse	3, 3, 1, 1	3, 3, 1, 1	MDD, PTSD, BPD, Other mental disorder	5	1261	8609
Varese 2012 [3]	MA	Childhood trauma	22	22	Psychosis	8	5135	19,892
Van Denderen 2013 [35]	SR	Disaster	1	1	Any mental disorder as per DISC	4	13	12
Wang 2013 [34]	SR	Disaster	3	3	Any mental disorder (DSM-IV and CIDI interview),PTSD	5	586	1704
Cunningham 2015 [42]	MA	Childhood trauma	1	1	Psychosis	6	30	2850
Fernandes 2015 [44]	MA	Emotional abuse, Physical abuse, Sexual abuse	6, 11, 14	6, 10, 13	Anxiety Disorders	6	6169	18,875
Brander 2016 [40]	SR	Emotional abuse, Physical abuse, Sexual abuse, Childhood trauma	1, 2, 4, 1	0, 1, 4, 1	OCD	6	403	2151
Palmier-Claus 2016 [39]	MA	Parental loss in childhood, Childhood trauma, Physical abuse	3, 9, 1	3, 9, 1	BD	10	1259	1118
Swartzman 2016 [45]	MA	Illness diagnosis	2	0	PTSD	7	326	5298
Spencer 2016 [36]	MA	Childhood trauma	2	2	ADHD	6	233	281
de Aquino Ferreira 2018 [43]	SR	Sexual abuse	4	4	BPD	5	201	213
Petereit-Haack 2020 [33]	MA	Person under train, Military deployment to a warzone, Traumatic event	4, 4, 1	0, 0, 0	MDD, PTSD	10	610	16,483

ADHD attention deficit hyperactivity disorder, *AMSTAR* Assessment of Multiple Systematic Reviews Tool, *BD* bipolar disorder, *BPD* borderline personality disorder, *DISC* Diagnostic Interview Schedule for Children, *K* number of studies for each factor examined, *MA* meta-analysis, *MDD* major depressive disorder, *OCD* obsessive–compulsive disorder, *PTSD* post-traumatic stress disorder, *SR* systematic review

†Cases with mental disorder

†Controls with no mental disorder

Results by specific mental disorder showed a significant association between any trauma type and each of the mental disorder categories at $p < 0.05$, with five reaching statistically significant evidence of an association at $p < 10^{-6}$ (see Supplementary Table 2 and Supplementary Fig. 1). There was highly suggestive (Class II) evidence for BD (OR = 2.79; 95% CI: 1.98, 3.93), anxiety disorder (OR = 2.66; 95% CI: 2.39, 2.97), and psychosis (OR = 2.66; 95% CI: 1.99, 3.56). There was suggestive (Class III) evidence for PTSD (OR = 4.42; 95% CI: 2.19, 8.93) and the category of "other mental disorder" (OR = 2.17; 95% CI: 1.49, 3.14). All the aforementioned studies showing between study heterogeneity. There was weak (Class IV) evidence for BPD (OR = 15.66; 95% CI: 7.23, 33.95), OCD (OR = 4.94; 95% CI: 3.34, 7.31) and MDD (OR = 2.88; 95% CI: 1.57, 5.31). The weak evidence was due to, among other factors, $n < 1000$ cases.

A further analysis of associations between specific trauma types and specific disorders showed convincing evidence (Class I) of an association between anxiety disorder and emotional abuse (OR = 3.05; 95% CI: 2.42, 3.83) and between anxiety disorder and physical abuse (OR = 2.35; 95% CI: 2.12, 2.61) while there was highly suggestive evidence (Class II) of an association between anxiety disorders and sexual abuse (OR = 2.68; 95% CI: 2.14, 3.35) and between psychosis and non-specific childhood trauma (OR = 2.49; 95% CI: 1.86, 3.33; please see Supplementary Fig. 2). A further 17 associations met criteria for evidence of a weak (Class IV) association (please see Supplementary Table 3).

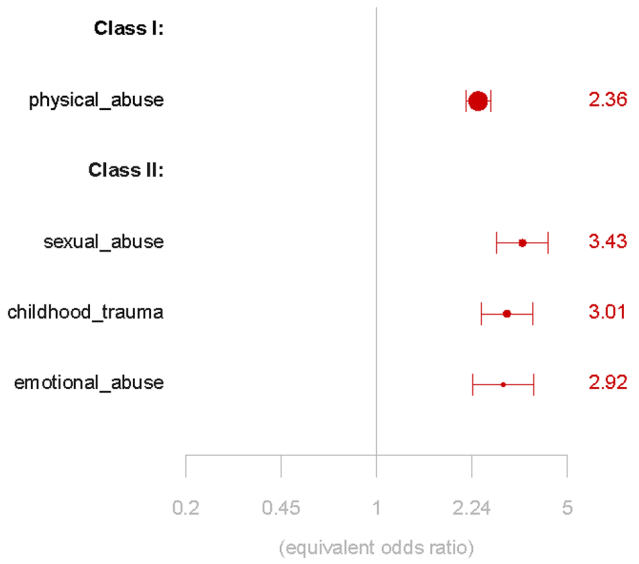

Fig. 2 Associations between specific trauma type and any mental disorder showing convincing (Class I) or highly suggestive (Class II) evidence

Association between childhood trauma and mental disorder

84.9% of included studies referred to trauma suffered during childhood (90 of 106 studies), with a total of 67,875 participants (14,128 cases and 53,747 controls) and six types of trauma: non-specific childhood trauma ($n = 39$), sexual abuse ($n = 25$), physical abuse ($n = 13$), emotional abuse ($n = 7$), disaster ($n = 3$), and parental loss during childhood ($n = 3$). There was highly suggestive (class II) evidence of an association between any type of trauma in childhood and any mental disorder, with an OR of 2.90 (95% CI: 2.58, 3.26).

In terms of separate categories of childhood trauma and any mental disorder, five of the six types of psychological trauma (83.3%, namely emotional abuse, physical abuse, sexual abuse, non-specific childhood trauma, and disaster) showed statistically significant evidence of association with the development of any mental disorder at $p < 0.05$, of which four (66.7%) reached a $p < 10^{-6}$. Physical abuse in childhood showed convincing (Class I) evidence of association with developing any mental disorder with an OR of 2.38 (95% CI: 2.11, 2.68). Sexual abuse (OR = 3.47; 95% CI: 2.77, 4.35), non-specific childhood trauma (OR = 3.01; 95% CI: 2.42, 3.74), and emotional abuse (OR = 2.81; 95% CI: 2.16, 3.65) all showed highly suggestive (Class II) evidence of association with developing any mental disorder (see Supplementary Table 4 and Supplementary Fig. 3). Disaster (OR = 2.92; 95% CI: 1.09, 7.80) showed weak (class IV) evidence of association with any mental disorder. Only parental loss during childhood did not show a significant association with mental disorder.

Similar to the results from the main analysis, all eight mental disorders showed an association with any childhood trauma type. There was highly suggestive (Class II) evidence for BD (OR = 2.79; 95% CI: 1.98, 3.93), Anxiety Disorder (OR = 2.67; 95% CI: 2.38, 2.99) and psychosis (OR = 2.66; 95% CI: 1.99, 3.56), and suggestive (Class III) evidence for the category of other mental disorder (OR = 2.17; 95% CI: 1.49, 3.14; please see Supplementary Fig. 4). Other disorders (BPD, MDD, OCD and PTSD) all showed weak (Class IV) evidence as, amongst other factors, there were $n < 1000$ cases. For BPD and PTSD, the ORs were over ten (15.66 and 12.31 respectively, please see Supplementary Table 5 for full information). In terms of associations between specific childhood trauma types and specific mental disorders, there was a significant association between each trauma type and each mental disorder analysed (please see Supplementary Table 6 and Supplementary Fig. 5). Physical abuse was linked to anxiety disorders, OCD and BD, while sexual abuse was linked to anxiety disorders, BPD, psychosis, and OCD, and emotional abuse was associated with anxiety disorders.

Association between trauma experienced in adulthood and any mental disorder

Eleven studies referred to trauma experienced in adulthood (military deployment to a warzone: $n=4$; person under train incident: $n=4$, illness diagnosis: $n=3$), comprising a total of 750 cases and 13,578 controls.

For the sensitivity analysis of any type of trauma experienced in adulthood with any type of mental disorder, there was weak (Class IV) evidence of an association, with an OR of 3.76 (95% CI: 2.45, 5.77). This figure comprises twelve studies, nine on PTSD and nine on MDD. Evidence was classed as weak due to $n<1000$ cases, as well as large between-study heterogeneity and the 95% prediction interval did not exclude the null value. Five studies, (comprising 316 cases and 10,210 controls) did not specify a timeframe for the trauma event (physical abuse: $n=2$, emotional abuse: $n=1$; sexual abuse: $n=1$, general traumatic event: $n=1$), and no sensitivity analysis was carried out on this data.

Application of TRANSD criteria

The application of the TRANSD criteria can be seen in Table 2. In brief, the studies included in our review comprised diagnoses made according to DSM-III, DSM-III-R, DSM-IV, DSM-5 or ICD 9, 10, or 11 criteria, pertaining to Anxiety Disorders (diagnostic group comprising Generalised Anxiety Disorder, Panic Disorder and Social Anxiety Disorder), BD, BPD, OCD, MDD, Psychosis (diagnostic group comprising Psychotic Disorder, Schizophrenia, Schizoaffective Disorder), and PTSD (TRANSD criteria 1), with psychological trauma as a risk factor for mental disorder the primary outcome in each study, and psychological trauma the transdiagnostic construct we investigated (criteria 2). As per the TRANSD criteria, the conceptual framework can be across-diagnoses (comparing different ICD/DSM categorical diagnoses against each other), beyond-diagnoses (employing ICD/DSM diagnostic information to go beyond it, testing new diagnostic constructs such as biotypes), or other (with an explanation of the conceptual framework). Our umbrella review used the conceptual framework of across diagnoses, across several spectra (criteria 3), and included 7 diagnostic categories, across 7 diagnostic spectra, with 1 non-clinical sample (healthy controls without mental disorder; criteria 4). Each individual disorder was compared with all other disorders pooled together, by means of subgroup meta-analysis. The magnitude of effect size was medium across pooled disorders (OR = 2.92), and no significant difference emerged in subgroup meta-analyses (p values ranged from 0.089 to 0.842), with the exception of borderline personality disorder, in which the effect size was substantially larger (OR = 15.66, $p<0.001$; criteria 5). The latter finding may indicate that while trauma is a transdiagnostic risk factor, it has an additional role in the onset of BPD. Generalizability was demonstrated with psychological trauma associated with mental disorder replicated in 78 of 106 case control studies (null hypothesis rejected; criteria 5). Thus, application of TRANSD criteria demonstrated that psychological trauma is a transdiagnostic risk factor for mental disorder, across seven diagnostic categories and spectra (Schizophrenia Spectrum Disorders, Anxiety Disorders, BD, Depressive Disorders, Personality Disorders, Obsessive–Compulsive and Related Disorders, and Trauma and Stressor-related disorders); this can be seen in Fig. 3.

Discussion

This umbrella review is, to our knowledge, the first to synthesize evidence from systematic reviews and meta-analyses to determine the role of psychological trauma as a transdiagnostic risk factor for mental disorder against standardised criteria. Our results showed highly suggestive evidence that psychological trauma is associated with a nearly three times greater risk of having a mental disorder (OR = 2.92), and demonstrate that psychological trauma is a transdiagnostic risk factor for psychopathology.

The potential processes by which psychological trauma can act as a transdiagnostic risk factor across different mental disorders are complex and varied. Psychological trauma is known to significantly impact neurobiological development [46, 47], especially in childhood which accounts for the large majority of our studies. In the event of acute stress, the body's physiological response includes the activation of the endocrine system, the autonomic nervous system, and the immune system to deal with the stressor stimuli and keep the biological variables within normal range, a phenomenon called homeostasis [48]. Furthermore, a chronic stress condition can lead to epigenetic modifications in genes that regulate the secretion of glucocorticoid hormones and, consequently, affect the homeostasis of the hypothalamus and pituitary (HPA) axis, further impairing the hormonal physiological regulation of neuronal plasticity [48–51]. Thereby, individuals who have suffered childhood trauma and are exposed to stress are more likely to experience abnormalities in cortisol levels and greater perceived stress. HPA axis abnormalities have been found in BD, psychosis, MDD [52], anxiety disorders, PTSD, OCD, [53] and BPD [54]. However, changes in the brain in response to trauma and maltreatment in childhood can also be understood as having an adaptive function, for example making individuals more sensitive to fearful stimuli so they can better avoid threats [46, 55]: these neurobiological changes can help increase chances of survival but later put individuals at risk of psychopathology. Childhood maltreatment has been shown to impact the network architecture of the brain, with decreased

Table 2 Application of TRANSD Criteria

Domain	Subdomain	Evidence
(*T*) Transparent definition	Gold standard	Diagnosis according to DSM-III, DSM-III-R, DSM-IV, DSM-5 or ICD 9, 10, or 11
	Diagnostic types	Anxiety Disorders (diagnostic group comprising Generalised Anxiety Disorder, Panic Disorder and Social Anxiety Disorder), BD, BPD, OCD, MDD, Psychosis (diagnostic group comprising Psychotic Disorder, Schizophrenia, Schizoaffective Disorder), PTSD
	Primary or secondary diagnoses	Primary diagnoses
(*R*) Report	Primary outcome	Psychological trauma as a risk factor for mental disorder
	Study design	Meta-analyses or Systematic reviews including case control studies
	Transdiagnostic construct	Psychological trauma
(*A*) Appraise the conceptual framework	Transdiagnostic type	Across diagnoses, across several spectra
(*N*) Numerate the diagnostic categories, spectra and non-clinical samples	Number of diagnoses	7
	Number of spectra	7
	Non-clinical sample	1 (Healthy controls without mental disorder)
(*S*) Show the degree of association	Diagnostic-specific Odds Ratios (ORs)	Anxiety Disorders (OR = 2·66, 95% CI 2·39, 2·97) BD (OR = 2·79; 95% CI: 1·98, 3·93) BPD (OR = 15·66; 95% CI: 7·23, 33·95) OCD (OR = 4·94; 95% CI: 3·34, 7·31) MDD (OR = 2·88; 95% CI: 1·57, 5·31) Psychosis (OR = 2·66; 95% CI: 1·99, 3·56) PTSD (OR = 4·42; 95% CI: 2·19, 8·93)
	Transdiagnostic	Any mental disorder (OR = 2·92; CI: 2·60, 3·28) No significant difference in individual vs pooled effect size subgroup metaanalyses, except in the case of BPD ($z = 4.19$; $p < 0.001$)
(*D*) Demonstrate the generalizability	Results replicated across at least 2 independent RCTs	Psychological trauma associated with mental disorder replicated in 78 of 106 case control studies (null hypothesis rejected)

BD bipolar disorder, *BPD* borderline personality disorder, *MDD* major depressive disorder, *OCD* obsessive–compulsive disorder, *PTSD* post-traumatic stress disorder

centrality (i.e. interconnectedness) in the left ACC, temporal pole, and middle front gyrus, linked to emotional regulation, social cognition and attention, and increased centrality in the right anterior insula and precuneus reflecting increased self-awareness [46].

The impact of trauma may be increased during certain sensitive stages of development [46, 47] and there is

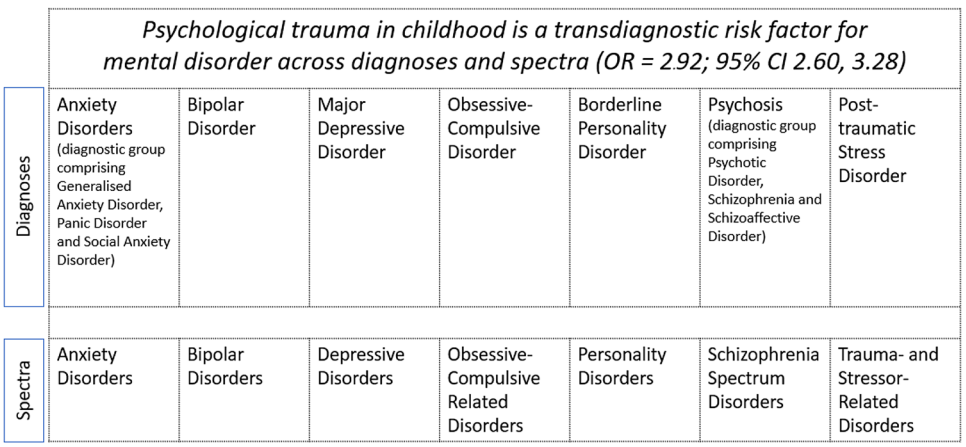

Fig. 3 Diagnoses and Spectra meeting TRANSD criteria for psychological trauma as a transdiagnostic risk factor

substantial evidence that genetic vulnerability is implicated in some of the neurobiological systems regulating stress and synaptic plasticity, demonstrating a gene x environment reaction where early life stress interacts with genetic expression, influencing outcomes in disorders such as psychosis and schizophrenia spectrum disorders [56, 57], BD [57], BPD [58], and MDD [59]. Additionally, the gene x environment interaction influences outcomes through epigenetic mechanisms [56, 59]. Evidence has pointed to significant genetic overlap between certain disorders, such as BPD, MDD and schizophrenia [60], so it is possible that the interaction between early life stress and gene expression may to some extent explain the impact of psychological trauma across different diagnoses and diagnostic spectra.

With the range of mechanisms involved, it is evident that different trauma experiences at different developmental stages, in conjunction with each individual's DNA and specific environment, can lead to disparate mental health outcomes. Using the transdiagnostic model of mechanisms linking childhood trauma to psychopathology as a framework, which comprises social information processing, emotion processing, accelerated biological ageing as risk factors, and social support as a protective factor [20], we can see how some of the aforementioned neurobiological processes feed in to the transdiagnostic mechanisms identified in the model: for example, the HPA axis dysregulation which can result from childhood trauma negatively impacts social cognition [61], and can lead to accelerated cellular ageing as measured by telomere length [62, 63], while changes in network architecture are related to problems with emotion regulation and social processing [46].

Our results showing a significantly higher association between trauma and BPD are in line with previous research showing a large magnitude of association between BPD and childhood adversity [64]. Early life adverse experiences are related to several distinct BPD processes, such as affect instability, emotion dysregulation, and self-destructive behaviours [65], and childhood trauma has been linked to BPD through affectations in the HPA axis, neurotransmission, endogenous opioid system, and in neuroplasticity [66]. Thus, according to McLaughlin et al.'s model [20], several different transdiagnostic mechanisms are at play in the case of BPD, and the transdiagnostic protective factor of social support may be missing, as neglect is significantly associated with BPD [64].

While our results overwhelmingly focused on childhood trauma, our results regarding trauma experienced specifically in adulthood showed, interestingly, a higher OR than for trauma experienced in childhood, with an OR of 3.76 compared to an OR of 2.90 in childhood trauma, although the class of evidence was lower. This evidence was based on twelve studies, of which nine (75.0%) measured PTSD. It is reasonable to assume therefore that the higher OR is due to the focus on PTSD, which showed a higher OR (OR = 4.42) than disorders such as anxiety disorders, BD, psychosis or MDD.

In our review, we also analysed data regarding the association between specific abuse types and mental disorder. Physical abuse shows convincing evidence as a risk factor increasing the risk of mental disorder (OR = 2.36), with data showing it cuts across three diagnostic categories and spectra (anxiety disorders, BD, and OCD). Sexual abuse showed highly suggestive evidence of being associated with over triple the risk of mental disorder (OR = 3.47), with data showing it to be a risk factor across four diagnostic categories and spectra (anxiety disorders, BPD, psychosis, and OCD). Our results add further strong scientific evidence that early physical and sexual abuse represent important risk factors for the development of mental disorders in adult life. Meanwhile, there was convincing evidence for the association of emotional abuse with anxiety disorders (OR = 3.05), which is a clinically highly relevant finding, as emotional abuse is the most prevalent form of childhood trauma worldwide [67] and anxiety disorders are also the most prevalent class of psychiatric conditions [68]. However, the lack of data in other disorders points to emotional abuse as an oft overlooked risk factor in research and highlights the need for further studies in this area.

Preliminary evidence from neuroimaging studies has shown that different types of childhood trauma may impact the brain in different ways, according to a review in Nature Reviews Neuroscience [46] for example, verbal abuse was shown to impact an important language processing pathway [69], sexual abuse was associated with thinning in parts of the somatosensory cortex associated in processing tactile sensations from the genitalia, and emotional abuse was associated with cortical thinning in areas related to self-awareness and self-evaluation [70]. Further research can help identify the exact processes involved with each abuse type, and their implications for treatment.

Our results, demonstrating that psychological trauma is a transdiagnostic risk factor across a range of costly and debilitating mental disorders, clearly position psychological trauma as a major public health issue, where prevention, improved access to treatment, and interventions at community and societal level are needed [71]. Our results demonstrate the need for increased investment in services protecting vulnerable children, to save great financial and human cost later on, and for the need for trauma-informed mental health care, which benefits both service users and workers [72], and for expanding trauma-informed early intervention services [73]. In addition, understanding psychological trauma as a transdiagnostic construct opens new avenues for improved prevention, early intervention, and treatment. Treatment efforts can focus on the underlying risk factor

of psychological trauma, such as through trauma-focused psychotherapy, or by targeting one of the transdiagnostic mechanisms by which it can lead to psychopathology, for instance by interventions focused on improving social support or emotional regulation. Clinical implications for early intervention programmes include focusing on reducing the presence of trauma and increasing social support as a protective factor, for example through educating parents and providing mental health counselling, social service referrals, or social support for vulnerable families and their infants [74, 75], while specific interventions to improve emotional dysregulation could reduce a range of psychopathology.

In prior research, understanding transdiagnostic processes has led to innovative new treatment options, such as the cognitive behavioural therapy-based Unified Protocol for emotional disorders, which has shown efficacy in treating a range of anxiety and depressive disorders by focusing on the underlying transdiagnostic construct of neuroticism [76]. To the best of the authors' knowledge, to date no trauma-focused therapy protocol has been developed and tested as a transdiagnostic treatment. However, preliminary studies have shown trauma-focused therapies may be safe and feasible for treating a range of disorders over and above PTSD: for example, trauma-focused cognitive behaviour therapy (TF-CBT) in psychosis [77], and eye movement desensitization and reprocessing (EMDR) therapy in psychosis [78], bipolar disorder [79], anxiety disorders [80], OCD [81], and depression [82]. Large-scale studies into the effectiveness of trauma-focused psychotherapies in psychosis and bipolar are currently underway [83–85]. In future, there could be potential for a protocol to be put in place for a trauma-focused psychotherapy which can be applied across various diagnoses and in cases of patient comorbidity.

Strengths of this umbrella review include the rigorous methodology, with the systematic search, study selection and data extraction all performed by two independent researchers. We applied strict inclusion criteria, only including studies where there was a confirmed psychiatric diagnosis according to DSM or ICD criteria, and only included studies with a control group. Our search resulted in a large sample size from which it is possible to draw robust conclusions.

Our work also includes some limitations which must be taken into consideration. The method for assessing trauma varied widely between studies, and was in many cases retrospective, with only two of 106 studies being prospective, and trauma was evaluated by self-report, meaning it can be affected by recall bias and an individual's subjective interpretation [86]. However, a prior study emphasizes the importance and clinical relevance of subjective memories, including retrospective designs, of childhood maltreatment. In a recent Nature Human Behaviour publication, the authors compared in a cohort of 1196 children both objective, court-documented evidence of maltreatment and subjective reports of their childhood maltreatment histories, and found psychopathology in adulthood to be associated with subjective rather than objective measures of experience of childhood maltreatment [87]. Additionally, after applying the inclusion and exclusion criteria, Substance Use Disorder was notably missing from our review. This highlights a significant area for future research, as first evidence has been published underlying the negative impact of childhood trauma in this population as well [88]. Furthermore, of the fourteen reviews or meta-analyses included in our review, three returned scored of "low quality" according to the AMSTAR tool and non-English or non-Spanish studies were not included in the search strategy. Finally, it is important to mention that there are several psychological trauma types, which have not appeared in the analysed articles (such as, reproductive losses, burn injuries or witnessing domestic violence), but also have potential to contribute to the onset of mental disorders and must be clinically considered.

In summary, our umbrella review provides strong evidence that psychological trauma is a transdiagnostic construct associated with nearly triple the risk of experiencing psychopathology. We also highlight the role of physical and sexual abuse across disorders and point to the need for further studies in mental illness. The majority of our studies focused on childhood trauma and further research can elucidate the exact mechanisms by which psychological trauma impacts the brain at different developmental stages. Our findings highlight the importance of psychological trauma as a public health concern, with implications for increased investment in prevention services and trauma-informed care across early intervention and treatment services, and opens up the possibility for innovative treatment approaches based on psychological trauma as a transdiagnostic construct.

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Author contributions BLA conceived the original idea for the paper. AM-A, AV-G, BH, BLA, IG-S and JR were involved in the design of the work. AM-A, ARR, AV-G, BH and IG-S carried out the article search and data extraction. LF and JR were involved in the analysis of the data. All authors were involved in the interpretation of the data and in writing and revising the draft of the manuscript. All authors have given final approval of the version to be published and are accountable for all aspects of the work.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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Supplementary Table 1. Types of trauma showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence of association with any mental disorder, with a minimum the three number of studies.

Type of trauma	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
Physical abuse	15	5171	OR	2.36 (2.13, 2.62)	4.2e-59	(2.02, 2.75)	5.2	0.064	0.55	(2, 3.16)	I
Sexual abuse	26	5436	OR	3.43 (2.75, 4.27)	7.3e-28	(1.53, 7.67)	64.6	0.025	1.1e-05	(1.49, 2.57)	II
NS childhood trauma	39	7413	OR	3.01 (2.42, 3.74)	6.8e-23	(0.99, 9.16)	70.4	0.81	46	(1.4, 5.36)	II
Emotional abuse	8	3643	OR	2.92 (2.26, 3.77)	2.7e-16	(1.45, 5.87)	58.5	0.62	0.69	(1.98, 2.93)	II
Military deployment to a warzone	4	380	OR	5.1 (3.82, 6.8)	1.3e-28	(2.71, 9.59)	0	0.9	0.59	(3.6, 7.1)	IV
Person under train	4	30	OR	3.78 (1.44, 9.91)	0.0069	(0.45, 31.37)	0	0.36	0.31	(0.6, 225.82)	IV
Disaster	3	586	OR	2.92 (1.09, 7.8)	0.033	(0, 487121.06)	93.1	0.26	0.12	(0.96, 1.36)	IV

Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; NS: Non-specific.

Supplementary Table 2. Types of mental disorder showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence of association with any trauma type, with a minimum the three number of studies.

Type of disorder	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
BD	13	1259	OR	2.79 (1.98, 3.93)	4.6e-09	(0.9, 8.61)	66.1	0.64	0.096	(1.39, 2.64)	II
Anxiety disorder	31	13011	OR	2.66 (2.39, 2.97)	2.4e-68	(1.77, 4.01)	50.8	0.11	0.0028	(1.49, 2.57)	II
Psychosis	25	5302	OR	2.66 (1.99, 3.56)	4.5e-11	(0.75, 9.41)	74	0.94	0.097	(1.4, 5.36)	II
PTSD	12	1362	OR	4.42 (2.19, 8.93)	3.4e-05	(0.41, 48.17)	87.4	0.7	0.39	(0.03, 0.3)	III
Other_mental_disorder	10	1706	OR	2.17 (1.49, 3.14)	4.4e-05	(0.73, 6.46)	66.7	57	0.32	(1.24, 6.59)	III
BPD	4	201	OR	15.66 (7.23, 33.95)	3.2e-12	(2.87, 85.58)	0	0.75	0.59	(4.49, 69.26)	IV
OCD	8	472	OR	4.94 (3.34, 7.31)	1.1e-15	(3.03, 8.05)	0	61	0.025	(0.57, 11.42)	IV
MDD	3	68	OR	2.88 (1.57, 5.31)	67	(0.06, 150.43)	0	0.56	1	(0.72, 9.4)	IV

Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; BD: Bipolar Disorder; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder, OCD: Obsessive-Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder.

Supplementary Table 3. Associations between specific trauma types and specific mental disorders showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence, with a minimum the three number of studies.

Association	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
Anxiety_disorder_emotional_abuse	6	3435	OR	3.05 (2.42, 3.83)	1.2e-21	(1.7, 5.46)	43.8	0.68	0.6	(1.98, 2.93)	I
Anxiety_disorder_physical_abuse	11	4680	OR	2.35 (2.12, 2.61)	1.00E-59	(2.09, 2.65)	0	0.14	0.48	(2, 3.16)	I
Anxiety_disorder_sexual_abuse	14	4896	OR	2.68 (2.14, 3.35)	9.2e-18	(1.34, 5.34)	65.7	0.42	0.1	(1.49, 2.57)	II
Psychosis_NS childhood_trauma	23	5265	OR	2.49 (1.86, 3.33)	8.2e-10	(0.73, 8.51)	74	0.57	0.27	(1.4, 5.36)	II
PTSD_disaster	1	114	OR	29.32 (8.99, 95.61)	2.1e-08	(NA, NA)	NA	NA	1	(8.99, 95.61)	IV
BPD_sexual_abuse	4	201	OR	15.66 (7.23, 33.95)	3.2e-12	(2.87, 85.58)	0	0.75	0.59	(4.49, 69.26)	IV
PTSD_Person under train	2	15	OR	13.83 (1.74, 109.86)	0.013	(NA, NA)	0	NA	1	(0.6, 225.82)	IV
OCD_NS childhood_trauma	1	263	OR	13.69 (1.83, 102.64)	0.011	(NA, NA)	NA	NA	1	(1.24, 69.4)	IV
Psychosis_sexual_abuse	2	37	OR	12.24 (3.92, 38.17)	1.6e-05	(NA, NA)	0	NA	1	(3.22, 65.41)	IV
PTSD_traumatic event	1	200	OR	0.1 (0.03, 0.31)	4.5e-05	(NA, NA)	NA	NA	1	(0.03, 0.3)	IV
PTSD_NS childhood_trauma	1	313	OR	6.4 (4.41, 9.27)	1.2e-22	(NA, NA)	NA	NA	1	(4.41, 9.28)	IV
PTSD_military deployment	4	380	OR	5.1 (3.82, 6.8)	1.3e-28	(2.71, 9.59)	0	0.9	0.59	(3.6, 7.1)	IV
OCD_physical_abuse	2	69	OR	5.01 (1.65, 15.19)	0.0044	(NA, NA)	35.1	NA	1	(0.57, 11.42)	IV
OCD_emotional_abuse	1	33	OR	4.9 (2.1, 11.46)	0.00024	(NA, NA)	NA	NA	1	(2.1, 11.46)	IV
OCD_sexual_abuse	4	107	OR	4.48 (2.64, 7.62)	2.9e-08	(1.4, 14.35)	0	48	0.3	(1.42, 8.6)	IV
Other_mental_disorder_NS childhood_trauma	4	771	OR	3.79 (1.41, 10.19)	0.0082	(0.09, 161.01)	54.6	66	0.63	(1.24, 6.59)	IV
Bipolar_Disorder_NS childhood_trauma	9	748	OR	3.67 (2.85, 4.72)	4.8e-24	(2.38, 5.65)	11.4	0.31	0.18	(1.68, 3.82)	IV
Other_mental_disorder_sexual_abuse	2	195	OR	3.49 (1.84, 6.62)	0.00013	(NA, NA)	24	NA	0.15	(2.34, 8.19)	IV
MDD_childhood_trauma	1	53	OR	3 (1.44, 6.27)	0.0034	(NA, NA)	NA	NA	1	(1.42, 6.33)	IV
Other_mental_disorder_physical_abuse	1	93	OR	2.91 (1.27, 6.67)	0.011	(NA, NA)	NA	NA	1	(1.27, 6.69)	IV
Bipolar_Disorder_physical_abuse	1	329	OR	1.9 (1.33, 2.71)	0.00039	(NA, NA)	NA	NA	1	(1.39, 2.64)	IV

Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; OCD: Obsessive-Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder.

Supplementary Table 4. Associations between specific childhood trauma types and any mental disorder showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence, with a minimum the three number of studies.

Childhood trauma type	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
Physical abuse	13	5055	OR	2.38 (2.11, 2.68)	4.3e-46	(1.88, 3.01)	17.8	0.061	0.32	(2, 3.16)	I
Sexual abuse	25	5353	OR	3.47 (2.77, 4.35)	6.6e-27	(1.52, 7.9)	66	0.028	4.5e-05	(1.49, 2.57)	II
NS Childhood trauma	39	7413	OR	3.01 (2.42, 3.74)	6.8e-23	(0.99, 9.16)	70.4	0.81	0.045	(1.4, 5.36)	II
Emotional abuse	7	3610	OR	2.81 (2.16, 3.65)	1.4e-14	(1.35, 5.82)	60.3	0.91	1	(1.98, 2.93)	II
Disaster	3	586	OR	2.92 (1.09, 7.8)	0.033	(0, 487121.06)	93.1	0.26	0.11	(0.96, 1.36)	IV

Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; NS: Non-specified.

Supplementary Table 5. Associations between specific mental disorder and any childhood trauma type showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence, with a minimum the three number of studies.

Mental disorder	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
Bipolar Disorder	13	1259	OR	2.79 (1.98, 3.93)	4.6e-09	(0.9, 8.61)	66.1	0.64	0.097	(1.39, 2.64)	II
Anxiety_disorder	29	12845	OR	2.67 (2.38, 2.99)	1.8e-63	(1.74, 4.09)	54.1	0.11	0.011	(1.49, 2.57)	II
Psychosis	25	5302	OR	2.66 (1.99, 3.56)	4.5e-11	(0.75, 9.41)	74	0.94	0.097	(1.4, 5.36)	II
Other_mental_disorder	10	1706	OR	2.17 (1.49, 3.14)	4.4e-05	(0.73, 6.46)	66.7	0.00057	0.32	(1.24, 6.59)	III
BPD	4	201	OR	15.66 (7.23, 33.95)	3.2e-12	(2.87, 85.58)	0	0.75	0.59	(4.49, 69.26)	IV
PTSD	2	427	OR	12.31 (2.78, 54.53)	0.00094	(NA, NA)	83	NA	1	(4.41, 9.28)	IV
OCD	6	406	OR	5.27 (3.33, 8.36)	1.5e-12	(2.75, 10.13)	0	0.044	0.098	(1.42, 8.6)	IV
MDD	1	53	OR	3 (1.44, 6.27)	0.0034	(NA, NA)	NA	NA	1	(1.42, 6.33)	IV

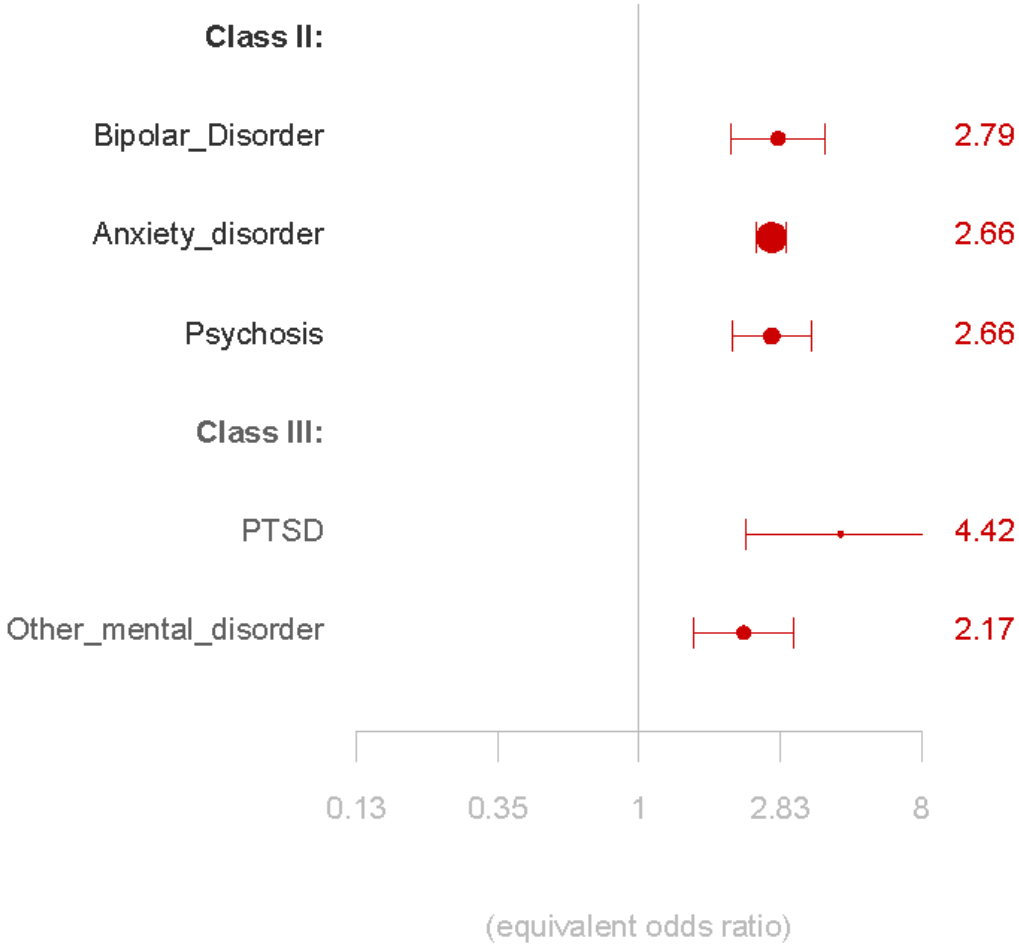
Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; Borderline Personality Disorder; MDD: Major Depressive Disorder; OCD: Obsessive-Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder.

Supplementary Table 6. Associations between specific childhood trauma types and specific mental disorders showing convincing (class I), highly suggestive (class II), suggestive (class III), and weak (class IV) evidence, with a minimum the three number of studies.

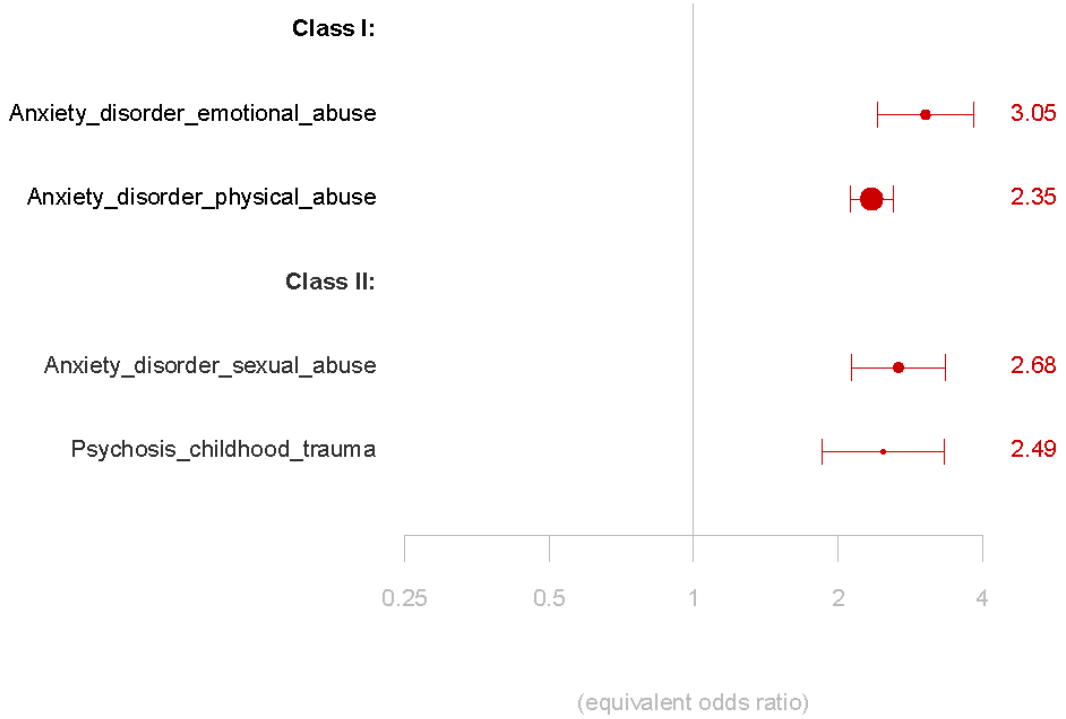
Association	K	N	Measure	ES (95% CI)	p	95% PI	I2 (%)	SSE p	ESB p	LS 95% CI	Class
Anxiety_disorder_emotional_abuse	6	3435	OR	3.05 (2.42, 3.83)	1.2e-21	(1.7, 5.46)	43.8	0.68	0.6	(1.98, 2.93)	I
Anxiety_disorder_physical_abuse	10	4597	OR	2.34 (2.11, 2.6)	5.5e-58	(2.07, 2.65)	0	0.12	0.7	(2, 3.16)	I
Anxiety_disorder_sexual_abuse	13	4813	OR	2.68 (2.12, 3.38)	1.7e-16	(1.3, 5.5)	68.4	0.45	0.17	(1.49, 2.57)	II
Psychosis_NS childhood_trauma	23	5265	OR	2.49 (1.86, 3.33)	8.2e-10	(0.73, 8.51)	74	0.57	0.27	(1.4, 5.36)	II
PTSD_disaster	1	114	OR	29.32 (8.99, 95.61)	2.1e-08	(NA, NA)	NA	NA	1	(8.99, 95.61)	IV
BPD_sexual_abuse	4	201	OR	15.66 (7.23, 33.95)	3.2e-12	(2.87, 85.58)	0	0.75	0.59	(4.49, 69.26)	IV
OCD_NS childhood_trauma	1	263	OR	13.69 (1.83, 102.64)	0.011	(NA, NA)	NA	NA	1	(1.24, 69.4)	IV
Psychosis_sexual_abuse	2	37	OR	12.24 (3.92, 38.17)	1.6e-05	(NA, NA)	0	NA	1	(3.22, 65.41)	IV
OCD_physical_abuse	1	36	OR	7.72 (2.7, 22.09)	0.00014	(NA, NA)	NA	NA	1	(2.7, 22)	IV
PTSD_NS childhood_trauma	1	313	OR	6.4 (4.41, 9.27)	1.2e-22	(NA, NA)	NA	NA	1	(4.41, 9.28)	IV
OCD_sexual_abuse	4	107	OR	4.48 (2.64, 7.62)	2.9e-08	(1.4, 14.35)	0	0.048	0.3	(1.42, 8.6)	IV
Other_mental_disorder_NS childhood_trauma	4	771	OR	3.79 (1.41, 10.19)	0.0082	(0.09, 161.01)	54.6	0.066	0.63	(1.24, 6.59)	IV
Bipolar Disorder_childhood_trauma	9	748	OR	3.67 (2.85, 4.72)	4.8e-24	(2.38, 5.65)	11.4	0.31	0.18	(1.68, 3.82)	IV
Other_mental_disorder_sexual_abuse	2	195	OR	3.49 (1.84, 6.62)	0.00013	(NA, NA)	24	NA	0.14	(2.34, 8.19)	IV
MDD_NS childhood_trauma	1	53	OR	3 (1.44, 6.27)	0.0034	(NA, NA)	NA	NA	1	(1.42, 6.33)	IV
Other_mental_disorder_physical_abuse	1	93	OR	2.91 (1.27, 6.67)	0.011	(NA, NA)	NA	NA	1	(1.27, 6.69)	IV
Bipolar Disorder_physical_abuse	1	329	OR	1.9 (1.33, 2.71)	0.00039	(NA, NA)	NA	NA	1	(1.39, 2.64)	IV

Key. K: number of studies; N: number of participants; OR: Odds Ratio; ES: Effect Sizes; CI: Confidence Interval; PI: Prediction Interval; I2: statistic denoting between-study heterogeneity; SSE: Small Study Effects; ESB: Excess of Significant Bias; LS: Effect size of study with largest number of participants; NS: Non-specified; BPD: Borderline Personality Disorder; MDD: Major Depressive Disorder; OCD: Obsessive-Compulsive Disorder; PTSD: Post-Traumatic Stress Disorder.

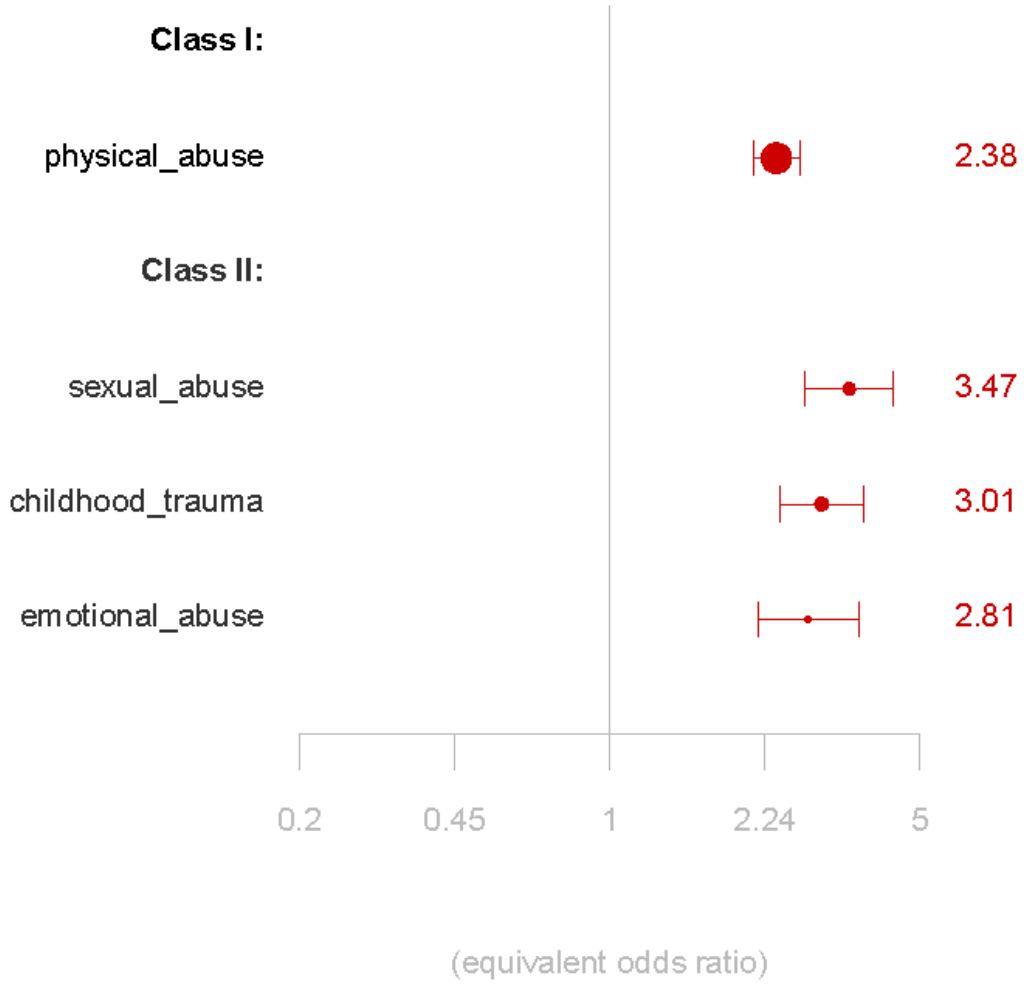
Supplementary Fig.1 Associations between specific mental disorder and any trauma type showing highly suggestive (Class II) or suggestive (Class III) evidence



Supplementary Fig. 2 Associations between specific mental disorder and specific trauma type showing highly suggestive (Class II) or suggestive (Class III) evidence, with a minimum of three studies

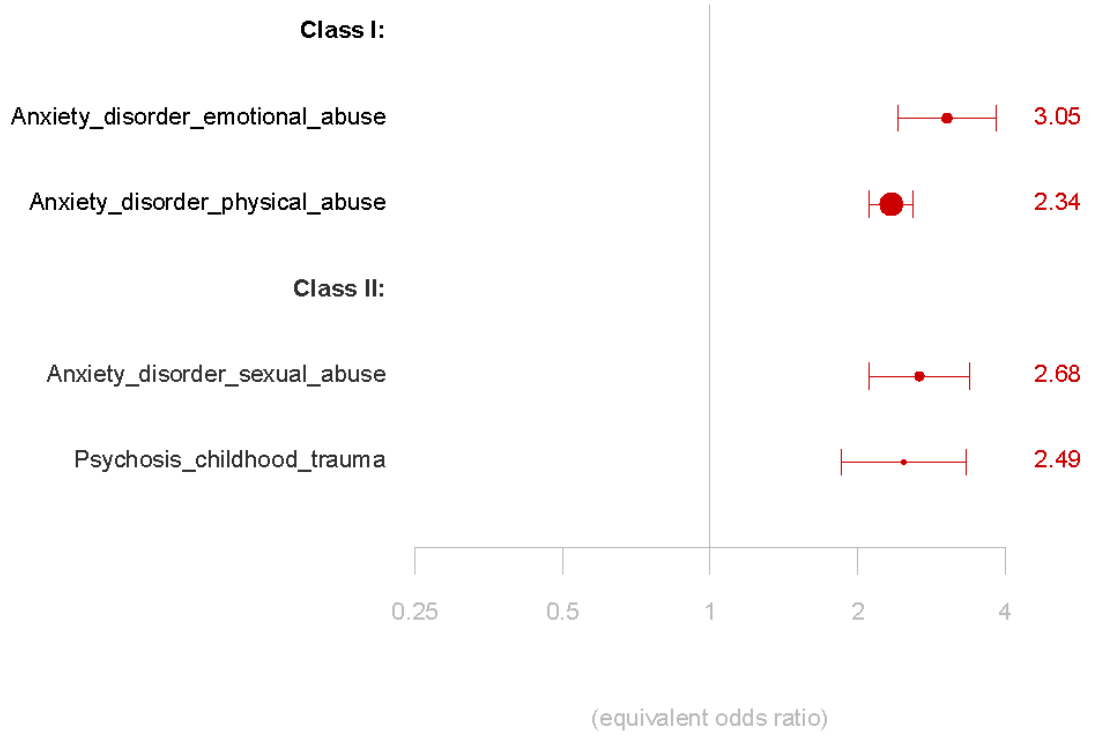


Supplementary Fig. 3 Associations between specific childhood trauma type and any mental disorder meeting criteria for convincing (Class I) or highly suggestive (Class II) evidence, with a minimum of three studies



Supplementary Fig. 4 Associations between specific mental disorder and any childhood trauma type meeting criteria for convincing (Class I) or highly suggestive (Class II) evidence, with a minimum of three studies

Supplementary Fig. 5 Associations between specific mental disorder and specific childhood trauma type meeting criteria for convincing (Class I) or highly suggestive (Class II) evidence, with a minimum of three studies



Supplementary Information 1. PRISMA Statement

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1, 3, 4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5, 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5,6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6,7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6,7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6,7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6,7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6,7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6,7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6,7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	na
Study characteristics	17	Cite each included study and present its characteristics.	8
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	8-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary info
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12-14
	23b	Discuss any limitations of the evidence included in the review.	15,16
	23c	Discuss any limitations of the review processes used.	15,16
	23d	Discuss implications of the results for practice, policy, and future research.	13,14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1, 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	1, 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	na
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	16

Supplementary Information 2. MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4,5
2	Hypothesis statement	4,5
3	Description of study outcome(s)	6,7
4	Type of exposure or intervention used	5,6
5	Type of study designs used	6,7
6	Study population	5,6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5
8	Search strategy, including time period included in the synthesis and key words	5
9	Effort to include all available studies, including contact with authors	6
10	Databases and registries searched	6
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	6
13	List of citations located and those excluded, including justification	8
14	Method of addressing articles published in languages other than English	16
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	6-7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6-7
24	Provision of appropriate tables and graphics	Tables 1-2, Fig 1-3, suppl info
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2,3, Table 2 suppl. info
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	Suppl info
28	Indication of statistical uncertainty of findings	8-11

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8-11, suppl info
30	Justification for exclusion (eg, exclusion of non-English language citations)	16
31	Assessment of quality of included studies	Table 1
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	12-14
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	12-14
34	Guidelines for future research	15
35	Disclosure of funding source	16

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

4.2 Manuscript 2: High incidence of PTSD diagnosis and trauma-related symptoms in a trauma exposed Bipolar I and II sample

Hogg B, Valiente-Gómez A, Redolar-Ripoll D, Gardoki-Souto I, Fontana-McNally M, Lupo W, Jiménez E, Madre M, Blanco-Presas L, Reinares M, et al. High incidence of PTSD diagnosis and trauma-related symptoms in a trauma exposed bipolar I and II sample. *Front Psychiatry* (2022) 13: doi: 10.3389/FPSYT.2022.931374/FULL

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High incidence of PTSD diagnosis and trauma-related symptoms in a trauma exposed bipolar I and II sample

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Background: Post-traumatic stress disorder (PTSD) is an established comorbidity in Bipolar Disorder (BD), but little is known about the characteristics of psychological trauma beyond a PTSD diagnosis and differences in trauma symptoms between BD-I and BD-II.

Objective: (1) To present characteristics of a trauma-exposed BD sample; (2) to investigate prevalence and trauma symptom profile across BD-I and BD-II; (3) to assess the impact of a lifetime PTSD diagnosis vs. a history of trauma on BD course; and (4) to research the impacts of sexual and physical abuse.

Methods: This multi-center study comprised 79 adult participants with BD with a history of psychological trauma and reports baseline data from a trial registered in Clinical Trials (https://clinicaltrials.gov; ref: NCT02634372). Clinical variables were gathered through clinical interview, validated scales and a review of case notes.

Results: The majority (80.8%) of our sample had experienced a relevant stressful life event prior to onset of BD, over half of our sample 51.9% had a lifetime diagnosis of PTSD according to the Clinician Administered PTSD scale. The mean Impact of Event Scale-Revised scores indicated high levels of trauma-related distress across the sample, including clinical symptoms in the PTSD group and subsyndromal symptoms in the non-PTSD group. Levels of dissociation were not higher than normative values for BD. A PTSD diagnosis (vs. a history of trauma) was associated with psychotic symptoms [2(1) = 5.404, $p = 0.02$] but not with other indicators of BD clinical severity. There was no significant difference between BD-I and BD-II in terms of lifetime PTSD diagnosis or trauma symptom profile. Sexual abuse significantly predicted rapid cycling [2(1) = 4.15, $p = 0.042$], while physical abuse was not significantly associated with any clinical indicator of severity.

Conclusion: Trauma load in BD is marked with a lack of difference in trauma profile between BD-I and BD-II. Although PTSD and sexual abuse may have a negative impact on BD course, in many indicators of BD severity there is no significant difference between PTSD and subsyndromal trauma symptoms. Our results support further research to clarify the role of subsyndromic PTSD symptoms, and highlight the importance of screening for trauma in BD patients.

KEYWORDS

bipolar disorder, PTSD—post-traumatic stress disorder, psychological trauma, sexual abuse, physical abuse and neglect, dissociation

Introduction

Bipolar disorder (BD) is a severe mental illness which negatively impacts life expectancy (1) and is characterized by depressive and at least one manic or hypomanic episode in the case of BD Type I (BD-I), and by depressive and at least one hypomanic episode in the case of BD Type 2 (BD-II) (2). The aetiology of BD is understood to be complex, involving multiple genes (3) and *gene x environment* interactions (4), as well as environmental risk factors (5).

One factor which has received increasing attention in the aetiology and prognosis of BD is psychological trauma, which predicts increased comorbidity with other mental and somatic disorders (6), including, notably, post-traumatic stress disorder (PTSD) (7). The prevalence of PTSD in bipolar patients has been estimated between 4 and 40% according to reviews (8, 9), compared to an estimated lifetime prevalence of 6.2% in the general population (10). Research suggests there may be a higher prevalence of PTSD in patients with BD-I compared to BD-II (9, 11), but the symptom presentation appears to be similar across both subtypes (11).

Comorbidity of PTSD and BD leads to a higher symptom burden and lower quality of life (9), and psychological trauma during childhood has been associated with a more severe form of the disease: it has been implicated in an earlier onset of BD, increased suicidality, increased substance abuse, lower functioning, more hospitalizations, and faster cycling frequencies (6, 7, 12–14). It has also been associated with more psychosocial stressors occurring before the first and most recent affective episodes (6). Psychological trauma may partially mediate the relationship between a family history of mood disorder and its expression (15), and studies have shown that early life stress may interact with genes of several biological pathways to lead to a poorer prognosis in BD, including lower age at onset, or increased suicide risk (4, 12). Even at the subsyndromal level, post-traumatic stress symptoms are, like full PTSD, associated with significant social and work impairment and a greater number of suicide attempts in the general population (16), and were found to be associated with increased symptoms of anxiety in BD patients during the COVID-19 pandemic (17).

Evidence suggests that different forms of psychological trauma can increase the risk of psychiatric disorders in different ways (18). Physical, emotional, and sexual abuse in childhood are all independently associated with a greater risk of BD (15), and have all been shown to predict an increased number of suicide attempts and lower age of onset (6, 14, 19, 20), as well as cognitive impairment (21). However, childhood physical abuse and sexual abuse have also both been found to be associated with faster cycling frequencies, more substance abuse and comorbidity with other disorders, and more psychosocial stressors occurring before the first and most recent affective episode (6, 19, 20). Specifically, sexual abuse has been shown to be the strongest predictor of rapid cycling (20), and also to be associated with an increased number of mood episodes and with psychotic episodes (14). Meanwhile, physical abuse was associated with self-harm episodes, and both emotional abuse and physical abuse were associated with lower functioning (14), while more research is needed into the impact of emotional abuse in severe mental illness (22).

Despite strong evidence of the link between trauma and BD, and high comorbidity with PTSD, there has been little focus on how to treat this comorbidity (9). Additionally, more research is needed into dissociative disorders in patients with BD and other severe mental illnesses (22). To address these gaps in current research, a multi-center study (23) was implemented to evaluate the effectiveness of a trauma-focused psychotherapy called Eye Movement Desensitization and Reprocessing (EMDR) (24) in a trauma-exposed sample of adult BD I and BD II patients. During the baseline visit for this trial, we collected data covering the detailed retrospective trauma history, symptoms related to reported trauma and dissociation, and the clinical characteristics of a sample of 79 participants with BD and a history of psychological trauma.

In this paper, we present this data, the first to our knowledge to review the sociodemographic and clinical characteristics of a trauma-exposed bipolar disorder sample, with or without the presence of a diagnosis of PTSD. Based on the aforementioned research, we hypothesized that there would be significantly greater comorbidity between BD-I and PTSD and BD-II and PTSD, but that there would not be significant differences in the presentation of trauma symptoms according to BD subtype. Furthermore, we hypothesized that comorbidity with PTSD in a sample of traumatized BD patients would be associated with a worse disease course, and that reported sexual abuse and physical abuse would each be associated with a worse disease course. Therefore, our primary research objectives were the following:

1. To present the sociodemographic, trauma, and clinical characteristics of a sample of trauma-exposed BD patients.
2. To investigate if there is significantly greater comorbidity between BD-I and PTSD than between BD-II and PTSD.
3. To investigate if the presentation of trauma symptoms, in terms of re-experiencing, avoidance, arousal, or dissociative symptoms, is the same across BD-I and BD-II.

Our secondary research objectives were:

1. To investigate if a lifetime PTSD diagnosis as compared to never having received a PTSD diagnosis is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, a lower level of functioning, and a greater degree of cognitive impairment.
2. To investigate if reporting having experienced sexual abuse, compared to not reporting having experienced sexual, is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, and a greater number of hospital admissions.
3. To investigate if reporting having experienced physical abuse, compared to not reporting having experienced physical abuse, is associated with a history of psychotic symptoms, suicidal ideation and suicide attempts, current rapid cycling, an earlier onset of disease, and a greater number of hospital admissions.

Materials and methods

Data

The data in this paper is the baseline data from a study evaluating the effectiveness of a trauma-focused therapy in traumatized bipolar patients (23). This was a multicenter project comprising three hospitals from the Barcelona area of Spain (Hospital Benito Menni, Hospital Clínic of Barcelona and Hospital Parc de Salut Mar). The trial was registered prior to starting enrolment at Clinical Trials (https://clinicaltrials.gov) under reference NCT02634372.

Participants

Participants who met criteria for BD-I or BD-II according to DSM-IV criteria, based on clinical interview and a review of case notes, were referred to the study by their referent psychiatrist. The inclusion criteria for participants was: (1) to be aged between 18 and 65; (2) to have experienced two to six affective episodes over the previous 12 months; (3) current clinical status of euthymia or subsyndromal symptoms at the moment of the assessment, defined by a score representing the past week on the Bipolar Depression Rating Scale (BDRS) of <14 and a score representing the previous 2 days on the Young Mania Rating Scale (YMRS) of <12; (4) Presence of a traumatic

event according to the Clinician Administered PTSD CAPS-DX scale 0; (5) Current trauma symptoms as indicated by a score >0 on the Impact of Events Scale-Revised (IES-R). The inclusion criteria were designed to enable the testing of the primary hypothesis of the clinical trial comparing EMDR therapy with Supportive Psychotherapy. The EMDR therapy protocol was designed for use with all patients excluding those with active acute symptoms in the present moment, and therefore we screened for active acute symptoms. To be able to test the impact on number of affective episodes, it was necessary to include patients with multiple previous episodes, and the 12-month criteria ensures recent instability as well as permitting classification into rapid cycling (≥4 episodes in the previous year) or not. Exclusion criteria were: (1) current substance abuse/dependency, i.e., not meeting criteria for early remission (three to 12 months without meeting criteria) or sustained remission (over 12 months without meeting criteria) (25), with the exception of nicotine; (2) neurological disease or brain trauma history; (3) current suicidal ideation; (4) having received a trauma-focused therapy within the previous 2 years.

Variables of study

Patient data was collected by trained evaluators who were all qualified psychologists or psychiatrists working within the participating centers. Each patient was assigned a code, and this was used throughout the data collection to ensure anonymity. A Case Report Form (CRF) was designed to capture baseline data such as sociodemographic variables and clinical variables related to the onset and course of BD. The following data was collected through clinical interview contrasted with a review of medical case notes:

1. Age of onset, defined as the first manic, hypomanic, mixed or depressive episode as per DSM-IV criteria. This data was based on patient recall during the clinical interview, contrasted with notes from medical records.
2. History of psychotic symptoms, defined as having ever experienced psychotic symptoms in line with DSM-IV criteria, based on clinical interview and a review of medical records.
3. Number of relapses over the last year, with a relapse defined as a manic, hypomanic, mixed, or depressive affective episode as per DSM-IV criteria, with data gathered through clinical interview and a review of medical records.
4. Current rapid cycling, defined as four or more affective episodes over the previous 12 month period, with data gathered through clinical interview and a review of medical records.
5. History of suicide attempts, based on patient recall and review of medical records.
6. Current pharmacological treatment, based on their current prescription, and current psychological treatment, based on patient report and medical records.
7. Family history of psychiatric disorder, based on patient recall and review of medical records.
8. Use of substances, collected through patient self-report.

Clinical features, trauma history and symptomatology, functioning and cognitive impairment were all assessed by means of validated scales. Where available, we used scales specifically designed for use in a BD population, and where this was not possible we used the gold standard or most widely used scale. Clinical severity was measured using the following scales:

1. The Bipolar Depression Rating Scale (BDRS) (26), Spanish validation (BDRS-S) (27). This clinician-administered scale is used to assess depressive and mixed symptoms in BD-I and BD-II patients. The BDRS includes 20 items, which sum to a total score between zero and 50. Scores of <8 indicate euthymia and ≥8 and <14 the presence of subsyndromal symptoms. A score of ≥14 indicates the presence of an acute depressive episode. The Spanish validation was carried out with a relatively small sample size but shows robust psychometric properties and captures depressive and mixed symptoms in Spanish bipolar patients.
2. The Young Mania Rating Scale (YMRS) (28), Spanish validation (29), is a clinician-administered scale composed of 11 items aimed at quantifying the severity of manic and hypomanic features. Of the 11 items, four items (irritability, speech, thought content and disruptive/aggressive behavior) are graded on a scale of 0 to 8, while the remaining seven items are graded on a 0 to 4 scale. Total scores range between 0 and 60: scores of <6 indicate euthymia, between ≥7 and <12 indicate the presence of subsyndromal symptoms, while scores of ≥12 indicate the presence of moderate to severe manic symptomatology. The Spanish validation shows this is a reliable tool for the assessment of manic symptoms in patient with manic or hypomanic symptoms in Spain.

Reported trauma history and symptomatology were evaluated using the below scales:

1. The Clinician-Administered PTSD Scale (CAPS-DX) (30), Spanish validation (31). The CAPS is the gold standard for determining a diagnosis of PTSD according to DSM-IV criteria. It provides a diagnosis of both current and lifetime PTSD. The Spanish validation showed good reliability, internal consistency and rest-retest values, similar to the original version.
2. The Impact of Event Scale-Revised (IES-R) (32), Spanish validation (33). The IES-R is a 22-item self-report scale.

It measures the presence of subjective distress related to a specific traumatic event, yielding an overall score and one for each of its three subscales, intrusion, avoidance, and hyperarousal, which correspond to the DSM-IV diagnostic criteria for PTSD. Higher scores indicate greater distress and a score of >32 has been suggested as the cut off for the presence of PTSD symptoms (34). The Spanish validation in a large sample showed adequate internal consistency and convergent validity with other scales of psychopathology, but some difficulties with the test-retest validity.

3. The Holmes-Rahe Life Stress Inventory (35), Spanish validation (36). This scale measures the number of stressful events that have occurred over the previous 12 months. Each potential stressful event is accorded a weighted score depending on how stressful it is estimated to be, and these are summed to provide a total score. A score of under 150 reflects low levels of stress and a low risk of stress-related illness, scores from 150–299 reflect a moderate level of stress which can imply a 50% risk of developing a stress-related illness, and scores of 300 and over reflect a high level of stress which can imply an 80% risk of developing a stress-related illness. The Spanish validation includes a cultural adaptation of the items.
4. Dissociative Experiences Scale (DES) (37), Spanish validation (38). This scale assesses the presence of dissociation, by asking participants the percentage of time they experience a range of dissociative symptoms. The results yield an average total score and an average score for each of the three subscales: amnesia, absorption, and depersonalization. Total scores of 30 or higher indicate a potential Dissociative Identity Disorder. The DES is the scale most often employed to measure dissociative symptoms in bipolar patients (39). The Spanish validation was carried out in healthy adults and in inpatients with schizophrenia. The scale was shown to be valid in both populations, with improved validity in a psychiatric population when the scale was administered by a clinician.

The level of functioning and cognitive impairment was evaluated using the following scales:

1. Functioning Assessment Short Test (FAST) (40). This scale evaluates level of functioning through 24 items assessing six domains: autonomy, work, cognitive functioning, finances, interpersonal relationships, and leisure. Each item is scored from 0–3, and overall scores range from 0-72. Higher scores indicate a lower level of functioning. This scale was originally developed in Spanish for a Spanish population.
2. Screen for Cognitive Impairment in Psychiatry (SCIP) (41), Spanish validation (42). The SCIP is a clinician-administered scale which assesses cognitive impairment in psychiatric patients. This scale briefly assesses five different cognitive domains: immediate verbal learning, delayed verbal learning, working memory, verbal language, and processing speed. The scale provides a score for each subdomain and then a global score obtained by summing all scores. Lower scores indicate a greater level of cognitive impairment. The Spanish validation was carried out in a psychiatric population of patients with schizophrenia, and showed good validity and reliability.

Data analysis

Since the data in this paper come from a study where the sample size was determined to understand the effectiveness of EMDR therapy compared to Supportive Therapy, in which the sample size calculation was based on a survival analysis using the statistical package "powerSurvEpi" for R (http://www.r-project.org/) (40), we performed a second sample size calculation to ensure the sample size is sufficient to meet the objectives of the current paper. In this case, the sample size was based on a correlation test, given the difficulty of exact data regarding the prevalence of BD patients with a history of psychological trauma in the population. A sample of 79 patients, with a statistical power of 80% and a type I error rate of 0.05, is sufficient to detect low correlations ($R = 0.31$) (43, 44).

All statistical analyses were carried out using STATA Statistics/Data analysis, version 16.1 (StataCorp LLC, Texas, USA). Fitness to parametric assumptions was checked for all variables, and the Shapiro–Wilk test was used to assess the normality of data distribution. With regards to the descriptive analysis of the sociodemographic and clinical data, the arithmetic mean was used for quantitative variables and the proportion for categorical variables. In the case of the impossibility of reconciling patient recall data with medical history, or failure to log a valid response to an item, listwise deletion was applied and analyses are based on the total number of valid responses for each question. The standard area and the confidence interval, set at 95%, were calculated for both quantitative and categorical variables. Pearson Chi squared test was used to analyze the relationship between two binomial categorical variables, and a two-sample *t*-test was used for analysing the relationship with the quantitative dependent variables.

Firstly, the relationship between BD-I or BD-II and a lifetime diagnosis of PTSD was analyzed. The lifetime PTSD group comprised both those with a current and lifetime diagnosis of PTSD; while those who had never met criteria for PTSD comprised the non-PTSD group. The current and lifetime PTSD diagnoses were included together as most of the variables against which it was planned to be analyzed were not current (e.g., lifetime number of hospital admissions, lifetime number of suicide attempts, ever having experienced psychotic symptoms, ever having experienced suicidal ideation). Secondly, analyses were carried out for the relationship between BD-I and BD-II

and the impact of the traumatic event (IES-R) and dissociative symptoms (DES). Thirdly, the relationship between a lifetime diagnosis of PTSD and a range of clinical symptoms: having experienced suicidal ideation, attempted suicide, experienced psychotic symptoms, rapid cycling, number of suicide attempts, age of BD onset, number of hospital admissions, stressful events over the previous 12 months (Holmes & Rahe scale), level of functioning (FAST), and level of cognitive impairment (S-SCIP) was analyzed. Fourthly, analyses were carried out to determine the relationship between sexual abuse and four categorical variables (whether the participant had experienced suicidal ideation, had a history of suicide attempts, had experienced psychotic symptoms, and rapid cycling), and two quantitative variables (age of onset of BD, and number of hospital admissions). Finally, this analysis was repeated with physical abuse instead of sexual abuse as the independent variable. In all analyses, *p*-value significance was set at <0.05.

We also present adjusted *p*-values based on applying the Holm-Bonferroni correction for multiple comparisons (45). Although only two independent groups are compared in the study, several dependent variables are evaluated. Performing multiple comparisons of the two independent groups for the independent variables may increase the type I error (alpha α1 type error), increasing the risk of falsely rejecting the null hypothesis, being true in the population. To account for this possible effect, we performed the Holm-Bonferroni procedure. However, applying the adjustment for multiple comparisons increases the risk of a type II error, of falsely accepting the null hypothesis, and this risk is arguably greater where the analyses are pre-planned and based on prior evidence (46–49). Therefore, we present both adjusted and unadjusted *p*-values.

Ethical approval

The study received ethical approval from the Ethics Committee of the Germanes Hospitalàries del Sagrat Cor de Jesús (reference number: PR-2014-15), the Hospital Clínic of Barcelona (reference number: HCB/2015/1005) and the Hospital Parc de Salut Mar (reference number: 2015/6502/l). All participants signed informed consent prior to enrolment.

Results

Sociodemographic and clinical variables

In total, 82 subjects agreed to participate in the study, but three did not complete the baseline assessment, leaving a total sample of 79. Most of our sample were females (77.2%, $n = 61$) and Caucasian (94.6%, $n = 70$). The mean age was 46.56 [SD (standard deviation) ± 8.408] and participants had spent an average of 13.74 (SD ± 3.834) years in education. Of the sample, 40.5% ($n = 32$) were single, 38.0% ($n = 30$) married or in a civil partnership, 1.3% ($n = 1$) widowed and 20.3% ($n = 16$) separated. The majority (61.8%, $n = 47$) were on temporary or permanent sick leave, while 22.3% ($n = 17$) were employed and working either full- or part-time. These results can be seen in full in Table 1.

The average age of onset of BD in our sample was 29.53 (SD ± 10.840) years old. Age of onset was significantly higher in BD-II patients than BD-I (33.10 years compared to 28.39 years, $p = 0.044$), and in women compared to men (30.89 years compared to 24.65 years, $p = 0.017$).

Patients had experienced on average 3.27 hospital admission during their lifetime, and 2.48 affective episodes in the previous 12 months. In our sample, 73.4% ($n = 58$) had a diagnosis of BD-I compared to 26.6% ($n = 21$) with a diagnosis of BD-II, 13.9% ($n = 11$) experienced rapid cycling, and 46.2% ($n = 36$) had experienced psychotic symptoms. Regarding suicidality, 79.7% ($n = 63$) had experienced suicidal ideation and 39.7% ($n = 31$) had attempted suicide. Data regarding severity was available for 29 patients, and in over half of those cases (51.7%; $n = 15$) the attempt had resulted in severe injury. The most common medications taken by our sample were mood stabilizers (94.6%; $n = 70$) and anti-psychotics (75.7%; $n = 56$).

Comparison of the sociodemographic and clinical variables in the current study, as compared to large BD samples from four other studies which are not specifically in a traumatized population (45–48), as well as sociodemographic data for the Barcelona area can be seen in Supplementary Table S1. Our sample had a higher proportion of females and higher age of onset than other studies. The proportion of BD-II patients was, while a minority, greater than in the majority of other studies. Educational level was lower than in other studies and reflected the norms for the Barcelona area. Suicidality was similar to other studies, while a history of psychotic symptoms and current rapid cycling were lower than in most other studies.

Reported trauma symptoms and profile

The majority (79.7%; $n = 59$) had experienced a relevant stressful life event prior to onset of BD. Over half of our sample (51.9%; $n = 40$) had a lifetime diagnosis of PTSD according to the CAPS. In more than half of these cases, the lifetime diagnosis of PTSD was current, meaning 27.3% of the total sample ($n = 21$) had a current PTSD diagnosis. To carry out the clinical interview for PTSD, using the CAPS scale, participants are asked for the reported traumatic event which most affects them. In nearly half of cases (45.3%; $n = 34$), this was not related to a specific reported traumatic event category. Following this, physical abuse, sexual abuse, and the sudden death of a loved one were all chosen by 12.0% of participants ($n = 9$), followed by violent death (9.3%; $n = 7$), followed by a life-threatening illness (5.3%; $n = 4$) and transport accident (4.0%; $n = 3$). The average

TABLE 1 Sociodemographic characteristics of the sample.

Variable		Obs/Freq	Mean /Percentage*	Std. Err.	[95% Conf.	Interval]
Age		79	46.56	1	45	48
Education (years of studies)		57	13.74	1	13	15
Sex	Male	18	22.8%	0.050	0.142	0.34
	Female	61	77.2%	0.050	0.661	0.858
Race	Caucasian	70	94.6%	0.027	0.857	0.979
	Latin American	3	4.1%	0.024	0.013	0.125
	Asian	1	1.4%	0.014	0.002	0.096
Relationship status	Single	32	40.5%	0.058	0.299	0.528
	Married/civil partnership	30	38.0%	0.057	0.261	0.486
	Widowed	1	1.3%	0.014	0.002	0.096
	Separated/divorced	16	20.3%	0.048	0.130	0.324
Employment status	Student	4	5.3%	0.027	0.021	0.143
	Homemaker	1	1.3%	0.014	0.002	0.096
	Employed full-time	14	18.4%	0.047	0.119	0.308
	Employed part-time	3	3.9%	0.020	0.007	0.108
	Temporary sick leave	32	42.1%	0.059	0.325	0.555
	Permanent disability payments due to mental illness	14	18.4%	0.044	0.098	0.277
	Permanent disability payments for other reasons	1	1.3%	0.014	0.002	0.096
	Unemployed	5	6.8%	0.030	0.029	0.160
	Other	2	2.6%	0.014	0.002	0.096

Data are presented as mean or number (%).
Obs/Freq: Number of cases observed/Frequency; Std. Error: Standard Error; Conf.: Confidence.
*Age and education data are presented as means. The rest of the variables are presented as percentages.

age of the participant at the time of the event was 24.18 (SD ± 16.327). However, approximately half of our sample (50.0%; $n = 38$) reported having experienced sexual abuse, while a lower percentage reported having experienced physical abuse (42.1%, $n = 32$). In our sample, over the previous 12 months, participants reported on the Holmes and Rahe scale having experienced an average of 6.72 stressful events each, with an average total score of 214, indicating a moderate level of stress. These results can be seen in Table 2.

Across our sample, the mean score on the IES-R was 38.95, indicating PTSD symptoms. In this scale, participants with a lifetime diagnosis of PTSD had a significantly higher average score of 47.19 compared to 29.72 in the non PTSD group [$t(72) = -2.783$, $p = 0.007$]. Regarding dissociative symptoms, the average score on the DES was 13.24, and was significantly higher in the PTSD group (an average score of 15.53 compared to 10.75), [$t(70) = -2.224$, $p = 0.029$].

BD subtype and presence of lifetime diagnosis of PTSD

The Chi squared analysis found no significant between-group differences between Bipolar Type (BD-I or BD-II) and the presence or not of a lifetime diagnosis of PTSD [$\chi^2(1) = 0.702$, $p = 0.402$].

Trauma symptom profile per BD subtype

Our results showed no significant differences in the expression of trauma symptoms between BD subtypes in terms of intrusion, avoidance, hyperarousal, or dissociative symptoms. These results can be seen in Supplementary Table S2.

Impact of PTSD on disease course and cognition

A lifetime PTSD diagnosis was significantly associated with having experienced psychotic symptoms [$\chi^2(1) = 5.404$, $p = 0.02$]. Our results showed that PTSD did not have a significant impact on disease course in terms of suicidal ideation or behavior, or rapid cycling (please see Table 3). No significant difference was found between lifetime PTSD diagnosis and age of onset, number of hospital admissions, level of functioning according to the FAST, or cognition according to the SCIP, when compared to the sample without a PTSD diagnosis. These results

TABLE 2 Clinical characteristics of the sample.

Variable		Obs/Freq	Mean/Percentage*	Std. Err.	(95% Conf. Interval)	
Age of onset of bipolar disorder		78	29.53	1	28	33
Number of hospital admissions		77	3.27	1	2	5
Number of affective episodes in the last year		79	2.48	0	2	3
Number of suicide attempts		78	0.85	0	0	1
BDRS (total score)		79	9.29	1	8	11
YMRS (total score)		79	2.23	0	2	3
Holmes and Rahe Scale (number of events)		74	6.72	1	6	8
Holmes and Rahe Scale (total score)		74	214	18	177	251
Age of CAPS event		57	24.18	2	20	29
IES-R (total score)		75	38.95	2.973	33.1	44.8
DES (total score)		74	13.24	1.105	11.1	15.4
BD subtype	BD-I	58	73.4%	0.093	0.447	0.815
	BD-II	21	26.6%	0.093	0.185	0.553
Presence of rapid cycling	No	68	86.1%	0.071	0.6424	0.944
	Yes	11	13.9%	0.071	0.056	0.358
Ever experienced psychotic symptoms	No	42	53.8%	0.093	0.447	0.815
	Yes	36	46.2%	0.093	0.185	0.553
Stressful event at time on onset	No	15	20.3%	0.077	0.079	0.399
	Yes	59	79.7%	0.077	0.601	0.921
Ever experienced suicidal ideation	No	16	20.3%	0.052	0.018	0.275
	Yes	63	79.7%	0.052	0.725	0.982
Suicide attempt	No	47	60.3%	0.056	0.494	0.712
	Yes	31	39.7%	0.056	0.288	0.506
Severity of Suicide attempt	No	14	48.3%	0.098	0.276	0.658
	Yes	15	51.7%	0.098	0.342	0.724
Adherence to treatment	Good	73	94.8%	0.063	0.684	0.964
	Partial	4	5.2%	0.063	0.036	0.316
Mood stabilizers	No	4	5.4%	0.052	0.018	0.275
	Yes	70	94.6%	0.052	0.725	0.982
Antipsychotic	No	18	24.3%	0.071	0.056	0.358
	Yes	56	75.7%	0.071	0.642	0.944
Anxiolytic	No	41	55.4%	0.095	0.214	0.589
	Yes	33	44.6%	0.095	0.411	0.786
Antidepressant	No	42	57.5%	0.097	0.376	0.755
	Yes	31	42.5%	0.095	0.214	0.589
Other Meds	No	59	79.7%	0.077	0.601	0.921
	Yes	15	20.3%	0.077	0.079	0.399
CAPS selected event	Accident (transport)	3	4.0%	0.052	0.018	0.275
	Physical abuse	9	12.0%	0.071	0.056	0.358
	Sexual abuse	9	12.0%	0.063	0.036	0.316
	Life-threatening illness	4	5.3%	0.038	0.005	0.246
	Violent death	7	9.3%	0.052	0.018	0.275
	Sudden death	9	12.0%	0.071	0.056	0.358
	Other	34	45.3%	0.095	0.214	0.589

Data are presented as mean or number (%).
Obs/Freq: Number of cases observed/Frequency; Std. Error: Standard Error; Conf.: Confidence; BDRS: Bipolar Depression Rating Scale; YMRS: Young Mania Rating Scale; IES-R: Impact of Event Scale-Revised; DES: Dissociative Experiences Scale.
*Variables up to and including "DES Score" are presented as means. The rest of the variables are presented as percentages.

can be seen in Table 4. The *p*-values were no longer significant following application of the Holm-Bonferroni to adjust for multiple comparisons.

We conducted sensitivity analyses to understand whether there was a significantly different impact from a current PTSD diagnosis as compared to a historical (but not current) PTSD diagnosis. We found no significant differences between the current and historical PTSD group, or the current and never PTSD groups, on any of the variables tested (total FAST score, total SCIP score, rapid cycling, history of psychotic symptoms, age of onset, history of suicide attempts or suicidal ideation). The only significant difference on these variables when comparing the lifetime PTSD group with the never PTSD group was in the history of psychotic symptoms [$\chi^2(1) = 6.175$, $p = 0.013$; please see Supplementary Table S3], in line with the findings from our main analysis.

Impact of sexual and physical abuse on disease course

Sexual abuse was shown to be significantly associated with rapid cycling [$\chi^2(1) = 4.15$, $p = 0.042$]; results were not significant following application of the Holm-Bonferroni to adjust for multiple comparisons. There was no significant association between sexual abuse and suicidal ideation, psychotic symptoms, or history of ever having attempted suicide, or physical abuse and any of the aforementioned variables (see Table 3). Similarly, there was no significant association between sexual or physical abuse and number of suicide attempts, age of onset of BD, or number of hospital admissions. These results can be seen in full in Supplementary Table S4.

Discussion

Our study is one of the first to analyze a range of clinical and trauma variables in a sample of BD patients exclusively with a history of psychological trauma. Our sample was mostly Caucasian and 77.2% were female, which was higher than the proportion of females in previous studies with large bipolar samples (see Supplementary Table S1) and despite evidence showing BD is estimated to affect both genders almost equally (49). The large proportion of females in our specific sample of BD patients with a history of trauma may reflect evidence showing women are more likely to experience high-impact trauma, experience trauma at an earlier age, and are approximately two to three times more likely to suffer from PTSD (50). In BD patients, PTSD is a more common comorbidity in female BD patients than in male (49, 51). Just over half of our sample (54.1%) had a lifetime diagnosis of PTSD, with this being current in 30.4% of the total sample, and the average age at which the most important traumatic event occurred was 24.18.

The level of education of our participants was representative for the Barcelona area (see Supplementary Table S2), and lower than in other studies, where the samples were found to be more highly educated than the general population (45, 46, 48). Most patients in our sample were unable to work either temporarily or permanently due to BD. Most of our sample of traumatized BD patients (79.7%) had suffered from suicidal ideation at some point in their lives, and 39.7% had carried out a suicide attempt, comparable to data from other BD samples (see Supplementary Table S2). Of note, current suicidal ideation was a criterion for exclusion in our study. In our sample, 13.9% currently experienced rapid cycling, lower than in other samples but participants were excluded from our study if they had experienced >6 mood episodes in the previous 12 months. A history of psychotic symptoms was present in 46.2% of our overall sample, lower than in some other samples but this may partially be due to the higher proportion of BD-II patients, where psychotic symptoms are not a feature of the disease course.

The average age of participants in our sample was 46.56 years and the average age of BD onset was 29.53 years. The age of onset in our study is much higher than the late teens and early twenties reported in other studies (see Supplementary Table S1). This may partially be explained by the fact that, as compared to other studies, the mean age of our sample was higher, there was a higher percentage of females, and BD-II patients formed a larger proportion of the total sample than in other studies: females were shown in our study to have a significantly later age of onset than males, and the same pattern was found for BD-II patients as compared to BD-I, both patterns reflected in other research (52). However, a surprising finding was that there was no significant association between age of onset and physical abuse, sexual abuse, or a lifetime PTSD diagnosis, although our data showed a non-significant trend towards a higher age of onset than participants who had never had a PTSD diagnosis. This tendency was against expectations, given the prior research showing that childhood trauma is associated with a significantly lower age of onset (12). In our study, in the majority of cases (79.7%), BD onset happened in the context of a stressful life event, which supports previous findings that adverse life events can precede mood symptoms (53, 54), and that traumatic stress disorders can significantly increase the probability of subsequent onset of BD (55). However, our data points to a bidirectional relationship between BD and trauma. Firstly, our results showed that the sample had on average experienced levels of stressful life events in the 12 months prior to evaluation which put them at a 50% risk of developing a stress-related illness, which supports previous findings that BD patients suffer more adverse life events in general than healthy controls (56). Furthermore, the average age for the most traumatic event experienced by our sample was 24.18 (although this figure is subject to bias as this variable was the only one

TABLE 3 The impact of a lifetime PTSD diagnosis, sexual and physical abuse on categorical variables of disease course.

		No	Yes	Mean	Std. Err.	95% CI		$\chi^2(1)$	*P*-value
Lifetime PTSD diagnosis									
History of psychotic symptoms	**No**	24	16	0.333	0.079	0.179	0.487	**5.404**	**0.020**
	Yes	12	24	0.6	0.077	0.448	0.752		
History of suicidal ideation	**No**	8	7	0.784	0.068	0.651	0.916	0.208	0.648
	Yes	29	33	0.825	0.060	0.707	0.943		
History of suicide attempts	**No**	24	22	0.333	0.079	0.179	0.487	1.079	0.299
	Yes	12	18	0.45	0.079	0.296	0.604		
Rapid Cycling	**No**	34	32	0.081	0.045	−0.007	0.169	2.220	0.136
	Yes	3	8	0.2	0.063	0.076	0.324		
Sexual abuse									
History of psychotic symptoms	**No**	24	17	0.351	0.078	0.198	0.505	3.065	0.080
	Yes	13	21	0.553	0.081	0.395	0.711		
History of suicidal ideation	**No**	10	6	0.737	0.071	0.597	0.877	1.267	0.260
	Yes	28	32	0.842	0.059	0.726	0.958		
History of suicide attempts	**No**	22	24	0.405	0.081	0.247	0.564	0.108	0.742
	Yes	15	14	0.368	0.078	0.215	0.522		
Rapid Cycling	**No**	36	30	0.053	0.036	−0.018	0.124	**4.146**	**0.042**
	Yes	2	8	0.211	0.066	0.081	0.340		
Physical abuse									
History of psychotic symptoms	**No**	25	16	0.432	0.075	0.285	0.578	0.199	0.656
	Yes	19	15	0.484	0.090	0.308	0.660		
History of suicidal ideation	**No**	10	6	0.773	0.063	0.649	0.897	0.176	0.675
	Yes	34	26	0.813	0.069	0.677	0.948		
History of suicide attempts	**No**	30	16	0.318	0.070	0.181	0.456	2.105	0.147
	Yes	14	15	0.484	0.090	0.308	0.660		
Rapid Cycling	**No**	36	30	0.182	0.058	0.068	0.296	2.308	0.129
	Yes	8	2	0.063	0.043	−0.021	0.146		

Std. Error: Standard Error; CI: Confidence Interval.

with a substantial amount of missing data [$n = 57$], due to not being systematically collected in the CAPS). In nearly a third of the sample where age of trauma event was available (32.14%, $n = 18$), the traumatic event selected for the CAPS occurred after the onset of bipolar disorder, and in 14.29% ($n = 8$) of cases, the traumatic event stemmed from a BD affective episode, While there is a body of research showing that the experience of psychosis can cause PTSD (57), there has been no similar research to the authors' knowledge into PTSD related to BD mood episodes, despite these clearly having the potential to be traumatic based on our data. Our data points to the importance of research focusing not just on childhood trauma but also on adult traumatic experiences, including experiences related to severe mood episodes and hospitalization experiences, to further elucidate the complex relationship between trauma and clinical disease course. Additionally, clinicians may need to include ongoing assessment of the occurrence and impact of adult trauma experiences, experienced in the context of the BD disease course, in addition to screening for childhood trauma.

The data from our study showed participants experienced on average high levels of current trauma symptoms. The impact caused by the traumatic event, measured by the IES-R, was on average well above the cut off for clinical post-traumatic stress symptoms in the group with lifetime PTSD diagnosis, with an average score of 47.19 compared to a cut off score of >32 (34), indicating high levels of distress caused by the traumatic event. Yet it is of note that the group with no lifetime diagnosis of PTSD also had on average symptoms nearing this cut off point (29.72), suggesting a high level of subsyndromal post-traumatic stress symptoms even in those in our sample without a lifetime PTSD diagnosis. In terms of dissociation, there was a significantly higher level of dissociative symptoms in the lifetime PTSD group than in the non-lifetime PTSD group. However, the scores in both groups were well below the >25 score correlated with PTSD, and in line with the

TABLE 4 Impact of lifetime diagnosis of PTSD on quantitative variables of disease course.

	Obs	Mean	Std. Err.	Std. Dev.	95% Conf. Interval		*t*	Deg. Freedom	*P*-value
Age of onset									
No lifetime PTSD Dx	37	27.892	1.809	11.002	23.851	36.788	0.748	74	0.162
Lifetime PTSD Dx	39	31.410	1.716	10.718	27.400	40.275			
Number of hospital admissions									
No lifetime PTSD Dx	36	2.778	1.105	6.629	0.535	5.021	−0.747	73	0.458
Lifetime PTSD Dx	39	3.744	0.710	4.435	2.306	5.181			
FAST total									
No lifetime PTSD Dx	37	30.703	2.187	13.304	26.267	35.138	0.748	75	0.457
Lifetime PTSD Dx	40	28.275	2.379	15.045	23.463	33.087			
SCIP total									
No lifetime PTSD Dx	36	65.667	2.833	16.996	59.916	71.417	−0.237	73	0.813
Lifetime PTSD Dx	39	66.641	2.955	18.455	60.658	72.624			

Obs: Number of cases observed; Std. Error: Standard Error; Conf.: Confidence; Deg.: Degrees of; Dx: Diagnosis; FAST: Functioning Assessment Short Test for Bipolar Disorder; SCIP: The Screen for Cognitive Impairment in Psychiatr.

mean score of 14.8 on this scale for BD patients, according to a recent meta-analysis which found bipolar disorder patients to be the psychiatric group with lowest levels of dissociation (58). Our results also support dissociative symptoms not being at a clinical level, even in a sample of traumatized BD patients, and our results indicate that the sample was not characterized by complex PTSD, where it has been argued that dissociation is a major feature (59). Our data is useful given the previous lack of information focusing on dissociative symptoms in severe mental illness (22), but contrasts with some prior studies which have found higher levels of dissociation in BD patients (39, 60). One possible explanation for this is that these studies appear to have applied the DES as a self-administered scale, whereas to improve validity and avoid inflated scores in psychiatric patients, we applied the DES as a clinician-administered scale (38). Additionally, in our study, no participants were in an acute affective phase, and further research can clarify the effect of an acute mood episode on dissociative symptoms.

Of note, in our study, we use retrospective reports of trauma. Retrospective and prospective reports show a poor level of agreement (61), and while retrospective reports of adverse childhood experiences can predict negative life outcomes and psychopathology (62, 63), retrospective reports of childhood maltreatment are more strongly associated with early adult life psychopathology than prospective reports, suggesting that the recollection of having been maltreated is more closely associated with psychopathology than prospective measures (64), although other studies have found both retrospective and prospective reports of childhood trauma predict psychopathology (65, 66). There is a dearth of studies analyzing the association between BD and prospective measures of trauma, and our data should be interpreted in the context of the relationship between patient recall of trauma and clinical BD course.

Regarding our first hypothesis, an association was found between BD comorbidity with PTSD and psychotic symptoms. This no longer reached statistical significance once adjustments for multiple comparisons, to decrease possibility of a type I error (i.e., a false positive) were applied. However, adjustments for multiple comparisons increase the risk of a type II error (i.e., a false negative), and arguably are not indicated in situations where hypotheses are planned a priori based on prior evidence, rather than testing for multiple random associations (67–70). Therefore, we present both adjusted and unadjusted *p*-values and note that the interpretation of results must be made with caution.

The tendency in our results to a link with psychosis is unsurprising given the large body of literature which supports a link between trauma and psychosis generally (71). Psychological trauma may increase risk of psychotic symptoms in people vulnerable to psychosis (72), and previous research has shown a link between comorbid PTSD in BD and psychotic symptoms (73). Within our sample, 46.2% had experienced psychotic symptoms, lower than in some studies which have estimated that over half of BD patients experience psychotic symptoms (74, 75), although our study included BD-II patients. It has been argued that psychotic symptoms do not necessarily reflect a worse disease course as they do not have a significant impact on functioning (75) yet psychotic symptoms can be traumatizing for those experiencing them (76). The association between psychotic symptoms in BD and PTSD and its implications for treatment warrant further research.

No significant association was found between PTSD and an earlier onset of BD or suicidality, which was somewhat unexpected given previous research (6, 7, 51). There was also no

significant difference found in level of functioning or cognitive impairment. Our results are striking compared to the wide body of literature showing that a PTSD diagnosis in non-BD patients is associated with increased suicidality (77) and can negatively affect functioning and cognition (78, 79). Furthermore, previous research in BD patients has shown that comorbid PTSD has a significant further negative impact (20) over and above the negative impact that BD itself has on functioning and cognition (80, 81). Our sample only included BD patients with a history of trauma, which is not representative of all BD patients. In fact, a trauma history may be present in as few as 50% of BD patients (82), although other studies suggest higher estimates (73). One possible explanation for our results is the high level of subsyndromal psychological trauma symptoms even in the non-PTSD diagnosis group. Indeed, subsyndromal PTSD has been shown in other populations to be associated with significant psychosocial impairment (83, 84) and with increased suicidality (85). One study which compared three groups of BD patients (patients with comorbid PTSD, patients with trauma but no PTSD diagnosis, and patients with no trauma history), found that BD patients with PTSD were significantly more likely than BD patients with no trauma to have a worse disease course, in terms of significantly more rapid cycling and manic symptoms, but there was no significant difference when comparing the comorbid PTSD group with the trauma group, or the trauma group with the no trauma group (86). The impact of comorbidity between BD and psychological trauma, without a diagnosis of PTSD, warrants further investigation. If psychological trauma without a PTSD diagnosis has a similar impact on disease course, this would have important ramifications for screening for and treating psychological trauma in BD patients.

Our second hypothesis, that there would be significantly more cases of PTSD in BD-I patients than BD-II, was not proven, which contrasted with prior evidence from Hernandez et al. (11). In the study by Hernandez and colleagues, the lifetime PTSD diagnosis was 21.3% in BD-I and 15.6% in BD-II. Unsurprisingly, in our sample of BD patients with a history of trauma, the proportion was higher: 49.1% of BD-I and 57.1% of BD-II patients had a lifetime PTSD diagnosis. It is possible that BD-I patients may suffer more rates of psychological trauma but, within BD subtypes with a trauma history, there is not a significantly greater chance of developing PTSD. Indeed, our third hypothesis, that there would be no difference in trauma symptom profile between BD-I and BD-II was shown to be correct: there was no significant difference in levels of post-traumatic stress symptoms or levels of dissociation. This adds to previous evidence (9, 11) which suggests that the different BD subtypes do not influence the expression of trauma symptoms. This data suggests also that addressing PTSD as a comorbidity in BD does not need to differentiate by BD subtype, which could be a useful insight for planning therapeutic approaches for addressing the presentation of trauma symptoms in BD.

Our fourth hypothesis, that the presence of reported sexual abuse would be correlated with a worse disease course, was proven only in the case of rapid cycling, when *p*-values were unadjusted. This is in line with previous studies that found childhood trauma is related to rapid cycling (12) and sexual abuse is the strongest predictor of it (20). Rapid cycling can indicate poor prognosis and be associated with a greater number of suicide attempts (87). The impact of sexual abuse can be treated with psychological treatments such as Trauma Focused Cognitive Behavioral Therapy (TF-CBT) and EMDR (88), and these therapeutic approaches can be adapted specifically for PTSD within the context of bipolar disorder (89, 90). Further research can investigate whether including trauma-focused treatment for BD patients with a history of sexual abuse can improve symptoms of rapid cycling.

Our fifth hypothesis, that reported physical abuse would be correlated with a worse disease course as compared to not reporting having experienced physical abuse, was not proven with any variables. Our findings for sexual and physical abuse do not support previous findings regarding their negative impact on disease course (6, 14, 20). Our results are the first, to the authors' knowledge, to review the impact of physical and sexual abuse only in a sample of BD patients with a psychological trauma history. Therefore, while sexual and physical abuse have been shown in previous research to have a significant impact on disease course, this effect seems to be muted when compared against people who have suffered trauma but not specifically sexual or physical abuse. Another explanation is that our study did not specify physical and sexual abuse in childhood, and there is a strong body of evidence showing that the impact of trauma is greater in childhood (18). Further research can clarify the specific effects of sexual, physical, and emotional abuse at different life stages within a traumatized sample, and whether these warrant specific treatment approaches.

Regarding the clinical implications of our research, the high rates of PTSD within our traumatized sample reflect an important comorbidity which not only can impact prognosis (13) and treatment outcomes (91) but also warrants treatment as a clinical disorder with its own impact on functioning and suffering. Our research supports not only general screening for comorbid psychological trauma and comorbid PTSD in BD patients, which is already implemented in some countries and settings but is not universal, but also ongoing evaluating of whether there has been a traumatic impact due to a BD mood episode or hospitalization.

Clinicians can use information about comorbid trauma symptoms to tailor the BD treatment plan, paying particular attention to possible indicators of worse prognosis such as rapid cycling or psychotic symptoms. Additionally, the inclusion of pharmacological and psychological treatment for clinical trauma symptoms can help clinicians in alleviating the overall symptomatology in patients, and future research should elucidate if this can improve the prognosis of BD course itself.

Strengths of this multicentric study include the exhaustive trauma evaluation, including dissociative symptoms which have received little attention to date (22), and which were assessed through a clinician-administered scale to reduce bias (38), and the PTSD diagnosis which was determined through clinical interview using the gold-standard CAPS. A further strength is that we included "real world" bipolar patients within a pragmatic randomized controlled trial (RCT) with few exclusion criteria. However, some limitations have to be considered as well. We did not evaluate further psychiatric comorbidities using a (semi) structured diagnostic interview, although comorbidities were checked through a review of case notes. Our patients clinically had further psychiatric and somatic comorbidities and it would have been interesting including this variable in our analysis, as prior results indicate negative effects on the course of the illness (92). Furthermore, our study did not include a control group of BD patients without psychological trauma, as the data was taken from a RCT comparing EMDR vs. ST in trauma-exposed bipolar patients. The lack of a non-traumatized control group makes interpretation of the impact of subsyndromic trauma symptoms more challenging. In our study, we collected data regarding the total lifetime number of BD episodes for each participant but many subjects struggled to identify hypomanic episodes or quantify episodes, so this data was not reliable enough to be used. Additionally, emotional abuse was not evaluated, and the timepoint for reported sexual abuse and physical abuse was not assessed. Due to the cross-sectional design of this study, conclusions about causality cannot be drawn. Trauma history was based on subjective recall, which can result in recall bias (93). However, it has been shown that psychopathology is associated more with subjective than objective recall of traumatic events (94). Additionally, trauma history was gathered through use of the gold standard CAPS interview, and we have clarified throughout the paper that this is reported trauma history.

In summary, our paper provides further evidence of the lack of difference in how trauma symptoms are presented across BD subtypes, and provides important data regarding the high levels of trauma symptoms in BD subjects, even when criteria for a PTSD diagnosis are not met. The evidence shows there are few differences in clinical BD severity between the PTSD and subsyndromic PTSD group, although we also found a possible tendency for there to be a correlation between PTSD and psychotic symptoms, as well as between sexual abuse and rapid cycling, which can be clinically helpful in the identification and treatment of both. It prompts further investigation to understand the impact of comorbidity with a history of psychological trauma in BD patients, including subsyndromal PTSD symptoms, and highlights the importance of screening for psychological trauma in the BD population.

Data availability statement

The data that support the findings of this study are openly available in Figshare at https://figshare.com/articles/dataset/Bipolar_Disorder_and_psychological_trauma/19601359.

Ethics statement

The study received Ethical Approval from the Ethics Committee of the Germanes Hospitalàries del Sagrat Cor de Jesús (Reference Number: PR-2014-15), the Hospital Clínic of Barcelona (Reference Number: HCB/2015/1005) and the Hospital Parc de Salut Mar (Reference Number: 2015/6502/l). The patients/participants provided their written informed consent to participate in this study.

Author contributions

BA conceived the idea for the study and led the study. AM-A coordinated the study. BH, AV-G, IG-S, WL, EJ, MM, LB-P, MR, RC, AM-R, and JC were involved in the recruitment and evaluation of patients and data collection. BH, IG-S, MF-M, and AM-A prepared the data for analysis. DR carried out the statistical analysis. BH worked on the first draft of the paper with BA, AM-A, DR-R, and AV-G. All authors contributed to the interpretation of results and the final draft and approved the final draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.931374/full#supplementary-material

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Supplementary Table S1. Comparison of our sample to other large BD samples on a range of sociodemographic data.

	Current study sample	**BDI-BDC (47)**	**JoBS (2004) (48)**	**STEP-BD (49)[a]**	**Stanley Foundation Bipolar Disorders Network (46)[a]**	**Barcelona population [b]**
Sample *n*	79	217	191	1000	261	NA
Sample type	BD outpatients with a history of trauma with euthymic or subsyndromic symptoms	Outpatients	In- and out-patients	Any patient presenting for treatment	Outpatients	NA
Diagnosis	BD-I or BD-II as per DSM-IV	BD-I, BD-II, or BD-NOS as per DSM-IV	BDI-I, BD-II, or BD-NOS according to DSM-IV	BDI-I, BD-II, BD-NOS or cyclothymia), diagnostic manual not specified	BDI-I, BD-II, BD-NOS or schizoaffective disorder, bipolar type according to DSM-IV	NA
Country	Spain	Australia	Finland	USA	USA and Netherlands	Spain
Gender						
Female	61 (77.2%)	120 (55.3%)	101 (52.9%)	586 (58.6%)	145 (55.6%)	52.7%
Male	18 (22.8%)	97 (44.7%)	90 (47.1%)	412 (41.2%)	116 (44.4%)	47.3%
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0%)	NA
Age of sample (years) (mean ±SD)	46.56 ± 8.4	38.6 ± 12.6	37.7 ± 12.2	41.0 ± 12.6	43.1 ± 1.3 [c]	NA
Ethnicity						NA
White or Caucasian	70 (94.6%)	NA	NA	926 (92.6%)	243 (93.0%)	NA
Hispanic/Latino	3 (4.1%)	NA	NA	37 (3.7%)	NA	NA
Black or African American	0 (0.0%)	NA	NA	34 (3.4%)	4 (2.0%)	NA
Native American	0 (0.0%)	NA	NA	NA	NA	NA
Asian	1 (0.014%)	NA	NA	NA	NA	NA
Other	0 (0.0%)	NA	NA	2 (0.2%)	14 (5%)	NA
Relationship status [d]						
Single	32 (40.5%)	48.0%	25 (27.8%)	352 (35.2%)	80 (30.6%)	44.8%
Married [e]	30 (38.0%)	35.7%	38 (42.5%)	362 (36.2%)	113 (43.3%)	41.7%
Widowed	1 (1.3%)	1.2%	2 (2.2%)	16 (1.6%)	4 (1.5%)	8.5%
Separated/divorced	16 (20.3%)	15.2%	25 (27.8%)	235 (23.5%)	64 (24.5%)	4.9%
Employment Status						
Full time	14 (18.4%)	23.6%	105 (54.4%)	345 (34.5%)	86 (32.9%)	NA
Part time	3 (3.9%)	15.8%		146 (14.6%)	35 (13.4%)	NA
Unemployed	5 (6.8%)	38.2%	24 (12.6%)	220 (22.0%)	17 (6.5%)	NA
Disabled/medically retired	15 (19.7%)		45 (23.0%)	153 (15.3%)	55 (21.1%)	NA
Temporary sick leave	32 (42.1%)	NA	NA	NA	NA	NA
Student	4 (5.3%)	10.4%	19 (9.9%)	NA	NA	NA
Retired	0 (0.0%)	3.6%	NA	NA	13 (5.0%)	NA
Homemaker	1 (1.3%)	8.5%	NA	NA	16 (6.1%)	NA
Other	2 (2.6%)	NA	NA	137 (13.7%)	39 (14.9%)	NA
Educational level						
Less than high school	17 (21.5%)	20.5%	75 (39.8%)	39 (3.9%)	4 (2.0%)	22.1%
High school	20 (25.3%)	13.0%		138 (13.8%)	11 (5.4%)	46.4%
Tertiary education not completed	17 (21.5%)	66.4%	74 (38.7%)	823 (82.3%)	77 (37.9%)	
Tertiary education	25 (31.6%)				111 (54.7%)	30.0%
Vocational school	NA	NA	41 (21.4%)		NA	NA
BD subtype						
BD-I	58 (73.4%)	89.7%	90 (47.1%)	710 (71.0%)	211 (80.8%)	NA
BD-II	21 (26.6%)	10.3%	101 (52.9%)	239 (23.9%)	42 (16.1%)	NA
BD-NOS	NA	0.0%	NA	41 (4.1%)	5 (1.9%)	NA
Cyclothymia	NA	NA	NA	0 (0.0%)	NA	NA

Schizoaffective disorder, bipolar type	NA	NA	NA	7 (0.7%)	3 (0.7%)	NA
Other	NA	NA	NA	3 (0.3%)	NA	NA
Age of onset (years)	29.5 ± 10.8	21.0 ± 7.9	21.2 (median)	17.4 ± 8.6	22.9 ± 10.4	NA
Presence of current rapid cycling	11 (13.9%)	NA	62 (32.5%)	200 (20.0%)	NA	NA
History of psychotic symptoms	36 (46.2%)	64.8%	95 (49.7%)	390 (39.0%)	155 (59.4%)	NA
History of suicide attempts	31 (39.7%)	40.7%	NA	357 (35.7%)	75 (28.7%)	NA

NA: Not available (data not part of study set or not in comparable format).

[a] Later papers have been published from these studies with larger datasets, but these papers have been chosen as having the most complete clinical information for preparation with our study.

b Source: https://ajuntament.barcelona.cat/estadistica/

[c] Data taken from comparison table in Mitchell et al (47).

[d] Unable to calculate *n* for relationship status data in the BDI-BDC study

[e] Married refers to married/cohabiting in the BDI-BDC, JoBS and Stanley Foundation Bipolar Network studies. In the present study, it refers to married/civil partnership.

Supplementary Table S2. Trauma symptoms by Bipolar Type.

	Obs	Mean	Std. Err.	Std. Dev.	95% Conf. Interval		t	Deg. Freedom	P value
		IES-Intrusion							
BD-I	55	12.655	1.217	9.025	10.215	15.094	-0.299	73	0.766
BD-II	20	13.35	1.929	8.628	9.312	17.388			
		IES-Avoidance							
BD-I	55	14.345	1.308	9.698	11.724	16.967	-0.021	73	0.983
BD-II	20	14.4	2.293	10.257	9.600	19.200			
		IES-Hyperarousal							
BD-I	55	10.963	1.351	10.017	8.256	13.672	-1.173	73	0.245
BD-II	20	14	2.150	9.614	9.501	18.499			
		IES-Total							
BD-I	55	37.964	3.430	25.435	31.088	44.840	-0.546	73	0.587
BD-II	20	41.65	6.056	27.083	28.975	54.325			
		DES-Amnesia							
BD-I	55	7.873	1.087	8.062	5.693	10.052	0.402	72	0.689
BD-II	19	7	1.930	8.413	2.945	11.055			
		DES-Absorption							
BD-I	55	21.255	1.857	13.768	17.532	24.977	0.739	72	0.462
BD-II	19	18.579	3.000	13.078	12.276	24.882			
		DES-Depersonalization							
BD-I	55	6.636	1.243	9.218	4.144	9.128	0.809	72	0.421
BD-II	19	4.842	1.098	4.787	2.535	7.150			
		DES-Total							
BD-I	55	13.473	1.320	9.783	10.828	16.117	0.351	72	0.726
BD-II	19	12.579	2.032	8.859	8.309	16.849			

Obs: Number of cases observed; Std. Error: Standard Error; Conf.: Confidence; Deg.: Degrees of

Supplementary Table S3. Comparisons of participants with current PTSD, historical (lifetime but not current) PTSD, and who have never had a PTSD diagnosis.

Variable	Historical PTSD vs current PTSD	Historical PTSD vs never PTSD	Current PTSD vs never PTSD
History of psychotic symptoms	*n*=41, $\chi^2(1) = 1.735$, p=0.420	*n*=55, $\chi^2(1) = 6.175$, p=0.013	*n*=56, $\chi^2(1) = 2.416$, p=0.120
History of suicidal ideation	*n*=41, $\chi^2(1) = 0.286$, p=0.867	*n*=56, $\chi^2(1) = 0.271$, p=0.603	*n*=57, $\chi^2(1) = 0.080$, p=0.777
History of suicide attempts	*n*=41, $\chi^2(1) = 0.885$, p=0.643	*n*=55, $\chi^2(1) = 1.038$, p=0.308	*n*=56, $\chi^2(1) = 0.411$, p=0.521
Rapid cycling	*n*=41, $\chi^2(1) = 1.168$, p=0.558	*n*=56, $\chi^2(1) = 3.399$, p=0.065	*n*=57, $\chi^2(1) = 0.499$, p=0.480
Age of onset	*n*=39, p=0.915	*n*=55, p=0.248	*n*=58, p=0.263
No. of hospital admissions	*n*=39, p=0.234	*n*=54, p=0.281	*n*=57, p=0.915
FAST total	*n*=40, p=0.552	*n*=56, p=0.823	*n*=58, p=0.310
SCIP total	*n*=39, p=0.591	*n*=54, P=0.604	*n*=57, p=0.912

n: number of patients

Supplementary Table S4. The impact of sexual and physical abuse on quantitative variables of disease course

	Obs	**Mean**	**Std. Err.**	**Std. Dev.**	**95% Conf. Interval**		**t**	**Deg. Freedom**	**P value**
Age of onset of Bipolar Disorder									
Sexual Abuse No	37	29.342	1.942	11.245	23.686	3.899	-0.215	73	0.831
Sexual Abuse Yes	38	28.892	1.853	10.936	23.238	33.447			
Physical Abuse No	43	31.093	1.776	11.649	29.461	39.661	1.355	73	0.179
Physical Abuse Yes	32	27.625	1.759	9.951	26.109	36.077			
Number of Hospital Admissions									
Sexual Abuse No	36	2.722	0.511	3.067	1.685	3.760	-0.559	72	0.578
Sexual Abuse Yes	38	3.421	1.117	6.880	1.160	5.682			
Physical Abuse No	42	2.524	0.437	2.830	1.642	3.406	-1.027	72	0.308
Physical Abuse Yes	32	3.813	1.321	7.472	1.118	6.507			

Obs: Number of cases observed; Std. Error: Standard Error; Conf.: Confidence; Deg.: Degrees of

4.3 Unpublished data

4.3.1 Complementary analysis for Manuscript 2: gender analysis

Table 5. Age of onset is the only clinical baseline variable where there is a significant difference by gender.

Variable	Females (n=61)	Males (n=18)	Statistics
Age	46.23(SD±8.609)	47.67(SD±8.203)	t(0.629), p=0.531
Number of years studied	13.89(SD±3.859)	13.23(SD±3.855)	t(-0.538), p=0.593
Age of onset	30.89(SD±10.775)	24.65(SD±9.886)	**t(2.147), p=0.017**
Number of hospital admissions	3.46(SD±6.157)	2.67(SD±2.473)	t(-0.530), p=0.598
Number of episodes in past year	2.52(SD±0.976)	2.33(SD±0.686)	t(-0.775), p=0.441
BDRS	9.85 (SD±5.534)	7.39(SD±5.215)	t(1.040), p=0.097
YMRS	2.51 (SD±2.580)	1.28(SD±1.406)	t(-2.630), p=0.057
Holmes & Rahe score	217.36(SD±171.053)	202.50(SD±105.265)	t(-1.935), p=0.743
Holmes & Rahe number of events	6.83(SD±5.106)	6.31(SD±3.177)	t(-0.330), p=0.703
IES-R	41.29(SD±26.256)	30.94(SD±22.868)	t(-0.382), p=0.146
DES	13.983(SD±9.629)	10.765(SD±8.927)	t(-1.230), p=0.223
FAST	29.67(SD±14.569)	29.00(SD±11.667)	t(-0.178), p=0.860
SCIP	69.07(SD±11.171)	67.47(SD±12.570)	t(-0.503), p=0.616

Key. BDRS: Bipolar Depression Rating Scale; YMRS – Young Mania Rating Scale; Holmes & Rahe: the Holmes and Rahe Social Readjustment Rating Scale; IES-R: The Impact of Events Scale-Revised; DES: Dissociative Experiences Scale; FAST: Functioning Assessment Short Test; SCIP: Screening for Cognitive Impairment in Psychiatry.

Table 6. No gender differences in categorical clinical baseline variables.

	Females (n)	Males (n)	Statistics
BD Type			
BD-I	46	12	X^2(0.544), p=0.546
BD-II	15	6	
Current PTSD diagnosis			
Yes	19	4	X^2(0.419), p=0.765
No	41	13	
Lifetime PTSD diagnosis			
Yes	32	8	X^2(0.438), p=0.595
No	27	10	
Psychotic symptoms			
Yes	28	8	X^2(0.007), p=1.000
No	33	9	
Rapid cycling			
Yes	9	2	X^2(0.154), p=0.519
No	52	16	
Suicidal ideation			
Yes	49	14	X^2(0.056), p=0.752
No	12	4	
Suicide attempt			
Yes	26	5	X^2(0.969), p=0.407
No	35	12	

4.3.2 Manuscript 3 (preprint): EMDR therapy vs. Supportive Therapy as an adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial

This article is not yet published in a peer-reviewed journal but is available as a preprint:

Hogg B, Radua J, Gardoki-Souto I, Fontana-McNally M, Lupo W, Reinares M, Jiménez E, Madre M, Blanco-Presas L, Cortizo R, Massó-Rodríguez A, Castaño J, Argila I, Castro-Rodríguez JI, Comes M, Macias C, Sánchez-González R, Mur E, Novo P, Rosa AR, Vieta E, Padberg F, Pérez-Solà V, Valiente-Gómez A, Moreno-Alcázar A, Amann BL. EMDR Therapy vs. Supportive Therapy ad adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial. *PsyArXiv Preprints* (2023) doi: 10.31234/osf.io/s5hrf; https://psyarxiv.com/s5hrf/.

EMDR therapy vs. Supportive Therapy as adjunctive treatment in trauma-exposed bipolar patients: a randomized controlled trial.

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Short Title: EMDR vs Supportive Therapy in traumatised bipolar patients.

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Abstract

Background. Patients with Bipolar Disorder (BD) are frequently exposed to traumatic events which worsen disease course, but this study is the first multicentre randomised controlled trial to test the efficacy of a trauma-focused adjunctive psychotherapy in reducing BD affective relapse rates.

Methods. This multicentre RCT included 77 patients with BD and current trauma-related symptoms. Participants were randomised to either 20 sessions of trauma-focused Eye Movement Desensitization and Reprocessing (EMDR) therapy for BD, or 20 sessions of supportive therapy (ST). The primary outcome was relapse rates over 24-months, and secondary outcomes were improvements in affective and trauma symptoms, general functioning, and cognitive impairment, assessed at baseline, post-treatment, and at 12- and 24-month follow-up. The trial was registered prior to starting enrolment in clinical trials (NCT02634372) and carried out in accordance with CONSORT guidelines.

Results. There was no significant difference between treatment conditions in terms of relapse rates either with or without hospitalization. EMDR was significantly superior to ST at the 12-month follow up in terms of reducing depressive symptoms ($p=0.0006$, $d=0.969$), manic symptoms ($p=0.027$, $d=0.513$), and improving functioning ($p=0.038$, $d=0.486$). There was no significant difference in dropout between treatment arms.

Conclusions. Although the primary efficacy criterion was not met in the current study, trauma-focused EMDR led to the reduction of affective symptoms and improvement of functioning, with benefits maintained at six months following the end of treatment. Importantly, focusing on traumatic events did increase relapses or dropouts, suggesting psychological trauma can safely be addressed in a BD population using this protocol.

Keywords: Bipolar Disorder, EMDR, PTSD, psychological trauma, relapse prevention.

Introduction

Bipolar disorder (BD) is characterised by episodes of elevated mood and depression, affects >1% of the population worldwide, and is associated with increased mortality (Anderson *et al.*, 2012; Vieta *et al.*, 2018). It can be severely disabling, and lead to cognitive and functional impairment (Grande et al., 2016).

BD presents challenges for both diagnosis and treatment (Anderson *et al.*, 2012; Vieta *et al.*, 2018). Pharmacological interventions include antipsychotic drugs, mood stabilisers, antidepressants and some anticonvulsants (Baldessarini *et al.*, 2019). Adjunctive BD-specific psychosocial interventions are recommended (Anderson *et al.*, 2012), based on research showing they consistently provide better results than pharmacological treatment alone (Reinares *et al.*, 2014; Swartz and Swanson, 2014). Family therapy, cognitive behavioural therapy (CBT), and psychoeducational therapy are all associated with a reduction in BD affective relapses when compared to treatment as usual (Miklowitz *et al.*, 2021), but full functional recovery in BD patients is difficult to achieve, meaning novel approaches are needed (Dean *et al.*, 2018).

BD has a strong genetic component (Craddock and Sklar, 2013), and environmental factors as well as gene x environment interactions can best explain its aetiology (Vieta *et al.*, 2018). A genetic interaction with childhood trauma can result in an increased risk for developing BD and an earlier age of onset (Bastos et al., 2020; Park et al., 2020). A meta-analysis shows that childhood adversity is associated with a 2.63 greater risk of having BD (Palmier-Claus *et al.*, 2016). Furthermore, childhood trauma impacts BD prognosis in terms of a greater number of mood episodes and hospital admissions, a lower age of onset, increased suicidality, more rapid cycling (Leverich et al., 2002; Larsson et al., 2013; Aas et al., 2016) and poor response to treatment (Kim and Lee, 2016).

Given the association between trauma and BD, it is unsurprising that post-traumatic stress disorder (PTSD) is a frequent comorbidity in BD, estimated in 4-40% of patients (Cerimele *et al.*, 2017), as compared to 1.3% to 8.8% in the general population (Atwoli *et al.*, 2015). The high rates of trauma and PTSD in BD, and its negative impact on disease course, have important implications for treatment (Palmier-Claus *et al.*, 2016). However, there is a dearth of investigation into the safety and acceptability of employing trauma-focused interventions in a BD population, and into whether alleviating trauma symptoms can have a positive impact on the course of BD itself.

Eye Movement Desensitisation and Reprocessing (EMDR) therapy (Shapiro, 2001) is recommended as a first line treatment for PTSD (World Health Organisation, 2013; Yunitri *et al.*, 2023), and comprises a structured eight-phase protocol which includes bilateral stimulation to help patients heal from traumatic events. EMDR was piloted in BD patients with comorbid trauma and showed positive results in reducing depression, hypomania and trauma symptoms (Novo *et al.*, 2014). Following these positive preliminary results, the current multicentre, randomised controlled trial (RCT) was developed to compare the efficacy of an EMDR protocol for BD, developed specifically for this study, with supportive therapy (ST), a control condition used previously in BD adjunctive psychotherapy studies (Cottraux *et al.*, 2008; Meyer and Hautzinger, 2012).

The primary objective of this study was to investigate whether the EMDR Bipolar protocol could reduce affective relapses, as compared to ST. Secondary objectives were to investigate the effect of EMDR

therapy on affective and trauma-related symptoms, and on cognition and on psychosocial functioning, as compared to ST.

Materials and Methods

This study is a single-blind RCT comparing EMDR therapy with ST in bipolar patients with a history of psychological trauma. The trial was registered in clinical trials (www.clinicaltrials.gov; NCT02634372), carried out according to CONSORT guidelines (Schulz *et al.*, 2010), and the protocol was published (Moreno-Alcázar *et al.*, 2017).

This multicentre study recruited participants from three large medical centres in the Barcelona area of Catalonia, Spain (Parc de Salut Mar, Hospital Benito Menni, and Hospital Clínic). Potential participants were referred by their psychiatrist to the study coordinator (AM-A) for enrolment. Inclusion criteria were: 1) age 18 to 65; 2) between two and six affective episodes in the previous 12 months; 3) current euthymic or subyndromal symptoms: i.e. scores <15 on the Bipolar Depression Rating Scale (BDRS) (Berk *et al.*, 2007) and <13 points on the Young Mania Rating Scale (YMRS); 4) at least one traumatic event according to the Clinician-Administered PTSD Scale (CAPS) (Blake *et al.*, 1995) with current trauma symptoms (score >0 on the Impact of Event Scale-Revised (IES-R) (Weiss, 2007). Exclusion criteria were: 1) current substance abuse or dependency not in remission (i.e., within previous three months), except nicotine; 2) history of brain trauma and/or neurological disease; 3) acute suicidal ideation at enrolment; 4) having received any type of trauma-focused psychotherapy in the previous 24 months; and 5) planning to receive any type of concurrent psychotherapy during the study (both active and follow-up).

Sample size calculation

The sample size was calculated based on a survival analysis, with risk of relapse after treatment as the dependent variable, using the statistical software "powerSurvEpi" for R (http://www.r-project.org). To be able to detect a hazard ratio of two in a Cox regression with a statistical power of 80%, and an alpha set at 0.005 to allow for multiple comparisons, 36 people in each intervention arm are needed. Allowing for dropouts, 41 patients should be recruited for each study arm. This sample size is sufficient to show clinically relevant differences (Chambless and Hollon, 1998).

Randomisation

Evaluators provided the study coordinator (AM-A) with the age, sex, illness duration and number of affective episodes over the previous year of each new participant, who sent these to JR at Hospital Clínic for randomisation using the following procedure: participants were assigned to either the EMDR or ST condition according to the covariate-adaptive allocation procedure (Chambless and Hollon, 1998). In this procedure, the first two patients are randomly assigned to one of the two intervention arms at p=0.5. Next, if one treatment arm includes two or more patients more than the other group, the participant is assigned to the smaller group with p=0.8. Otherwise, the participant was assigned to the treatment arm (p=0.8) which led to the lowest simulated between-group square standardised differences in terms of age, sex, illness duration, and number of affective episodes in the past year, to ensure groups that were balanced in terms of these variables. AM-A then contacted each participant to explain the randomisation outcome and organise the psychotherapy. Randomisation was not stratified by centre, but this was adjusted for in the analysis.

Ethical approval

Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/I). Informed consent was signed by all participants prior to enrolment in the study.

Interventions

Both study arms provided 20 x 1-hour weekly therapy sessions. Participants were randomly assigned to either EMDR or ST, and attended sessions either in the medical facility for their area or the assigned therapist's office. During the first COVID-19-related lockdown, this was altered to permit online sessions, which affected two participants from the EMDR group and two from the ST group. All EMDR therapists were fully accredited by the Spanish EMDR Association, and received specific training and supervisions throughout with the EMDR consultant involved in elaborating the EMDR Bipolar protocol (WL). All ST therapists were accredited with the Official College of Psychology in Catalonia (COPC) and received training regarding the study.

EMDR

In the EMDR arm, the EMDR Bipolar protocol was used (Novo *et al.*, 2014), which first employs five optional BD sub-protocols, applied according to each participant's clinical needs: 1) mood stabilisation, 2) treatment adherence, 3) illness awareness, 4) detection of prodromal symptoms, and 5) de-idealisation of manic symptoms. A detailed description is in the study protocol (Moreno-Alcázar *et al.*, 2017). Following stabilisation of BD symptoms, trauma symptoms were treated with the standard EMDR eight-phase protocol (Shapiro, 2001): 1) patient history, 2) preparation with emotional regulation resources, 3) assessment of the target memory, 4) desensitisation, 5) installation of a positive belief, 6) body scan, 7) closure, and 8) re-evaluation of the target memory. Phases three to eight are repeated with each target memory.

Supportive Psychotherapy

In ST, patients were given the opportunity to evaluate and express the impact BD is having on their lives, with the therapist providing emotional support, active listening, general information about BD without the use of structured material, support in recognising and managing moods, relaxation exercises and training in problem-solving. This control condition provides the same level of support, but without any structured material related to BD or trauma-focused component.

Outcome variables

Data were collected through a specific Case Report Form (CRF) and validated scales at baseline, six-months (post-treatment), 12- and 24-months (follow-up). Additionally, data regarding affective symptoms was collected at two weeks and three months to evaluate clinical symptoms and possible relapses. The CRF gathered sociodemographic data and clinical history through patient interview and a review of medical history at baseline, and gathered information on relapses at each timepoint.

Evaluators were blind to the treatment arm; patients could not be blind to their treatment condition due to the distinctive bilateral stimulation techniques in EMDR therapy.

Clinical Variables

Bipolar Depression Rating Scale (BDRS) (Berk *et al.*, 2007), Spanish validation (Sarró *et al.*, 2015): This 22-item scale measures depressive and mixed symptoms in BD during the previous week, with a higher score denoting a greater degree of clinical severity.

Young Mania Rating Scale (YMRS) (Young *et al.*, 1978), Spanish validation (Colom *et al.*, 2002): This 11-item scale measures symptoms of mania in patients over the previous two days, with a higher score indicating a greater degree of clinical severity.

Trauma presence and symptoms

Clinician-Administered PTSD Scale (CAPS) (Blake *et al.*, 1995), Spanish validation (Bobes *et al.*, 2000): this is the gold standard diagnostic test used to determine the presence of a current or lifetime PTSD diagnosis, according to DSM-IV criteria.

Impact of Events Scale-Revised (IES-R) (Weiss, 2007), Spanish validation (Báguena *et al.*, 2001): this scale evaluates trauma symptoms (intrusion, avoidance, and hyperarousal) over the previous week: higher scores indicate greater affectation.

Dissociative Experiences Scale (DES) (Bernstein, E. M., Putnam, 1995), Spanish validation (Icaran *et al.*, 1996): this scale measures the presence of dissociative symptoms, with higher scores denoting more symptoms. This scale was included after the initial protocol was developed but before enrolment began to provide a more complete assessment of trauma symptoms.

Functioning and cognition

Functioning Assessment Short Test (FAST) (Rosa *et al.*, 2007), developed originally in Spanish: this scale measures psychosocial functioning in BD patients, with higher scores indicating poorer functioning.

Screen for Cognitive Impairment in Psychiatry (SCIP-S) (Purdon, 2005), Spanish Validation (Pino *et al.*, 2008): this scale was designed to detect cognitive impairment in psychiatric patients. Lower scores indicate poorer cognitive function.

Furthermore, the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BD) (Spearing et al., 1997), Spanish version (Vieta et al., 2002) and the Meyer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer et al., 2002a) were in the protocol but data were not analysed due to, respectively, discrepancies between centres in measuring changes on the CGI-BD compared to baseline, and reported difficulties from participants in answering the Spanish version of the MSCEIT (Mayer et al., 2002b). Finally, the social readjustment rating scale (Holmes and Rahe, 1967), Spanish version (González de Rivera and Morera Fumero, 1983) was used to measure stressful life events over the previous year: this scale was applied at baseline only, as per the protocol, and analysed in a previous paper (Hogg et al., 2022).

Comparison of the risk of relapse and hospital admission

We fitted a mixed-effects Cox proportional hazards model to analyze whether the risk of relapse (or hospital admission) differed between groups. The dependent variable was the time to relapse (or the time to last completed evaluation in case of no relapse) and the relapse status. The primary independent variable was the group. The covariates were sex, age, illness duration, number of affective episodes in the previous year, and centre (as a random factor). We conducted this analysis twice: once for relapses (with or without hospital admission) and once for hospital admissions. The statistician was blind to the treatment condition.

Comparison of affective/trauma-related symptoms and cognitive/psychosocial functioning

To conduct an intention-to-treat analysis, we performed multiple imputations of the missing scores. Specifically, we imputed the missing scores of the second time point based on the scores of the first time point. Next, we imputed the missing scores of the third time point based on the (observed or imputed) scores of the second time point, and so on.

To impute the missing values, we fitted a mixed-effects linear model. The dependent variable was the difference in the score between the current and the previous time point. The independent variables and covariates were the group, sex, age, illness duration, number of affective episodes during the last year, and centre (as a random factor). We used this model to predict the missing values, added a random residual of the model to preserve the variance, and limited the imputed score to the range of the scale (e.g., between 0 and 60 for BDRS). We conducted the imputations 50 times, resulting in 50 datasets.

We compared the symptoms and functioning between groups at 6, 12, and 24 months using mixed-effects repeated-measures ANOVAs. The dependent variable was the score (at baseline and at the follow-up time point). The primary independent variables were the group, time, and their interaction. The covariates of interest were sex, age, illness duration, number of affective episodes in the previous year, centre (as a random factor), and individual (as a random factor nested within the centre). We conducted these ANOVAs separately for each imputed dataset and then combined the results using Rubin's rules.

Where there were no significant between-group differences, a paired samples t-test was applied to compare the baseline and post results, and baseline and 12-month results, of the variable across the whole sample.

Comparison of the dropout rates

We calculated the proportion of patients lost to follow-up at 6, 12, and 24 months separately for the two groups and compared the proportions using chi-square tests.

We used the "survival" and "coxme" packages for R to fit the mixed-effects Cox proportional hazards models and the "lme4" and "lmertTest" packages for R to fit the mixed-effects repeated-measures ANOVAs. The analyst was blind to which group was EMDR.

Results

Recruitment took place between 19th May, 2016 and 13th February, 2020; 102 patients were screened for the study and 82 invited to a baseline evaluation (see Fig. 1). Three patients later withdrew

informed consent, and two did not meet inclusion criteria during the baseline visit due to acute symptoms, meaning 77 patients were randomised to the two treatment conditions (39 to EMDR, and 38 to ST). Of these, 24 of the EMDR group and 26 of the ST group completed the intervention; 17 of the EMDR group and 17 of the ST group completed the 12-month follow-up; and 9 of the EMDR group and 11 of the ST group completed the 24-month follow-up.

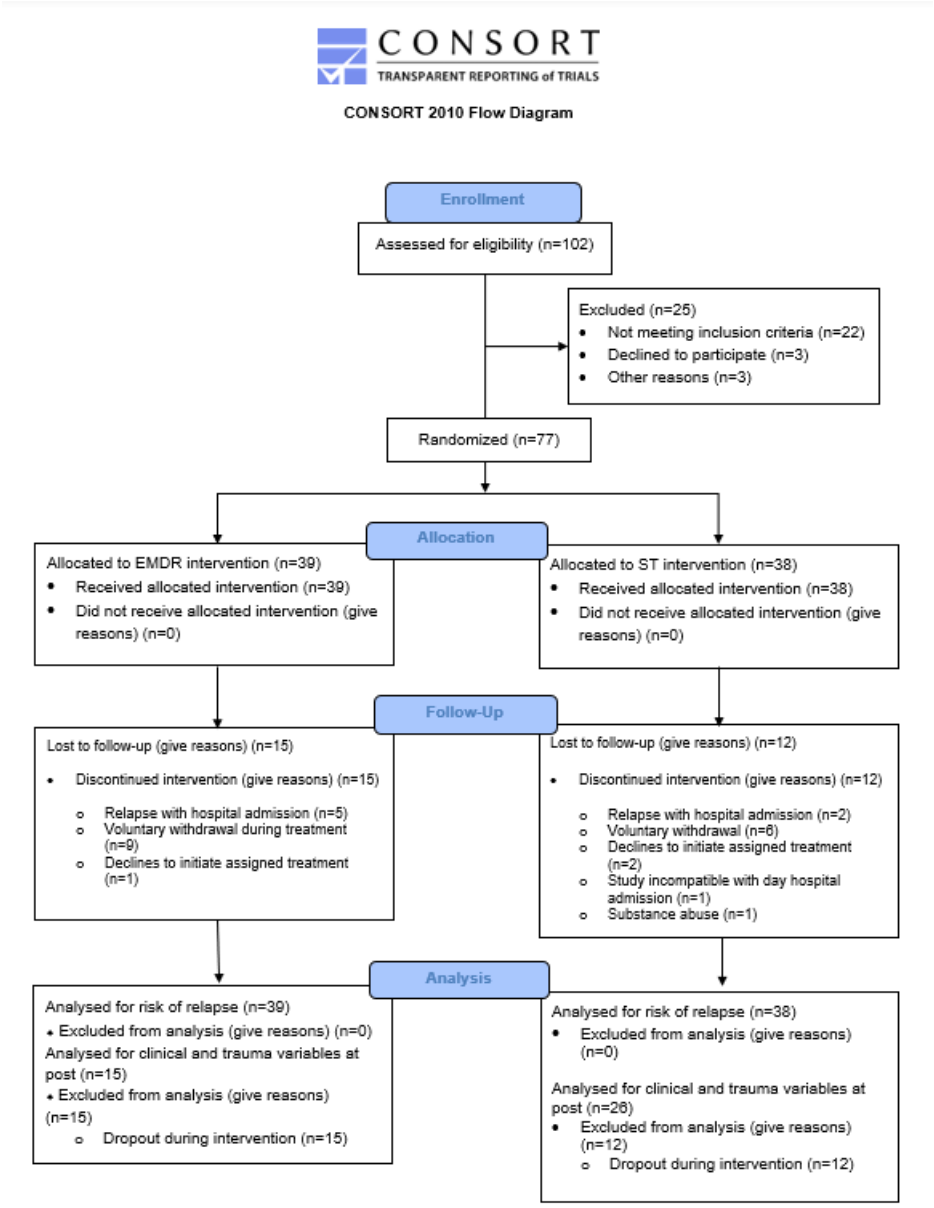


Figure 1. CONSORT Flow Diagram.

An overview of sociodemographic and clinical variables of the overall sample at baseline has previously been reported (Hogg *et al.*, 2022). A comparison of each group in terms of clinical and sociodemographic variables can be seen in Table 1. There was no significant difference between groups on any variable except illness duration, where the mean average illness duration in the ST group was 19.3 years compared to 15.0 years in the EMDR group (t[-2.0654], df=73.46, p=0.042); this was adjusted for in the subsequent analyses.

Table 1. Sociodemographic and clinical data for EMDR and ST group

Variable	EMDR (n=39)	ST (n=38)	Sig difference	Total (n=77)
Sex *n* (%)				
Male	8 (20.5%)	10 (26.3%)	X^2=0.110, df=1 p=0.740	18 (23.4)
Female	31 (79.5%)	28 (73.7%)		59 (76.6)
Other	0 (0.0%)	0 (0.0%)		0(0.0%)
Mean age in years (SD)	46.3 (9.4)	47.3 (7.3)	t(-0.542), df=71.412 p=0.590	46.8 (8.4)
Ethnicity *n* (%)			X^2=0, df=1, p=1	
Caucasian	34 (87.2)	36 (94.5)		70 (90.9)
Latin-American	1 (2.6)	0 (0.0)		1 (1.3)
Asian	0 (0.0)	1 (2.6)		1 (1.3)
Not reported	4 (10.3)	1 (2.6)		5 (6.5)
Civil Status *n* (%)				
Single	15 (38.5)	16 (42.1)	X^2=1.304, df=3, p=0.728	31 (40.2)
Married	14 (35.9)	15 (39.5)		29 (37.7)
Widowed	1 (2.6)	0 (0.0)		1 (1.3)
Separated/Divorced	9 (23.1)	7 (18.4)		16 (20.8)
Mean years education (SD)	13.6 (4.0)	14.0 (3.8)	t(-0.363), df=53.947 p=0.718	13.8 (3.9)
Education *n* (%)				
Incomplete primary	2 (5.1)	1 (2.6)	X^2=2.916, df=6, p=0.819	3 (3.9)
Complete primary	2 (5.1)	3 (7.9)		5 (6.5)
Incomplete secondary	4 (10.3)	5 (13.2)		9 (11.7)
Complete secondary	10 (25.6)	9 (23.7)		19 (24.7)
Incomplete tertiary	8 (20.5)	9 (23.7)		17 (22.1)
Complete tertiary	13 (33.3)	11 (28.9)		24 (31.2)
Work status *n* (%)				
Employed full-time	5 (12.8)	8 (22.9)	X^2=7.062, df=8, p=0.530	13 (16.9)
Employed part-time	2 (5.1)	1 (2.9)		3 (3.9)
Temporary sick leave	16 (41.0)	15 (42.9)		31 (40.3)
Permanent disability for mental health	7 (17.9)	7 (20.0)		14 (18.2)
Permanent disability for other reasons	1 (2.6)	0 (0.0)		1 (1.3)
Student	4 (10.3)	0 (0.0)		4 (5.2)
Homemaker	0 (0.0)	1 (2.9)		1 (1.3)
Unemployed	3 (7.7)	2 (5.7)		5 (6.5)
Other	1 (2.6)	1 (2.9)		2 (2.6)
Not reported	0 (0.0)	3 (7.9)		
Clinical variables				
Mean age of onset (SD)	31.3 (12.0)	28.8 (11.1)	t(1.184), df=73.988, p=0.240	30.1 (11.5)
Mean illness duration in years (SD)	15.0 (9.8)	19.3 (11.2)	t(-2.065), df=73.462, p=0.042	17.1 (10.7)
Mean number of hospital admissions (SD)	4.2 (7.0)	2.5 (3.5)	t(1.077), df=1, p=0.299	3.3 (5.6)
Mean number of episodes past year (SD)	2.4 (0.8)	2.6 (1.1)	X^2=0.105, df=1, p=0.746	2.5 (0.9)
History of psychotic symptoms *n* (%)				
No	22 (56.4)	20 (52.6)	X^2=0, df=1, p=1	42 (54.5)
Yes	17 (43.6)	17 (44.7)		34 (44.2)
Not reported	0 (0.0)	1 (2.6)		1 (1.3)
Comorbidity *n* (%)				
Axis I	8 (20.5)	9 (23.7)	X^2=0.113, df=1, p=0.952	17 (22.1)
Axis II	3 (7.7)	8 (21.1)	X^2=2.806, df=1, p=0.177	11 (14.3)
Axis III	22 (59.5)	25 (65.8)	X^2=0.321, df=1, p=0.743	47 (62.7)
BD Type *n* (%)				
BD-I	29 (74.4)	27 (71.1)	X^2=0.005, df=1, p=0.944	56 (72.7)
BD-II	10 (25.6)	11 (28.9)		21 (27.3)
Suicide *n* (%)				
History suicidal ideation	33 (84.6)	29 (76.3)	X^2=0.845, df=1, p=0.528	62 (80.5)
History suicide attempts	18 (46.2)	12 (31.2)	X^2=1.496, df=1, p=0.323	30 (39.0)
Mean number of suicide attempts (SD)	1.2 (2.9)	0.5 (0.8)	t(1.559), p=0.062)	0.9 (2.2)
Medication *n* (%)				
Mood stabilisers	36 (92.3)	32 (84.2)	X^2=4.235, df=1, p=0.123	68 (88.3)
Antipsychotics	29 (74.4)	26 (68.4)	X^2=0.693, df=1, p=0.579	55 (71.4)
Anxiolytics	15 (38.5)	17 (44.7)	X^2=0.225, df=1, p=0.813	32 (41.6)
Antidepressants	13 (33.3)	17 (44.7)	X^2=0.914, df=1, p=0.473	30 (39.0)
Other	6 (15.4)	9 (23.7)	X^2=0.758, df=1, p=0.562	15 (19.5)

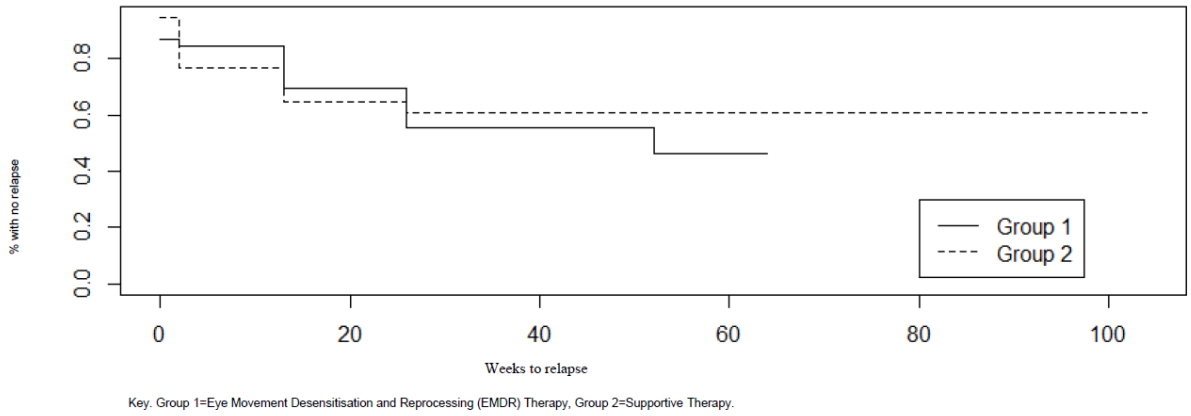
Table 1 (cont.)

Variable	EMDR (n=39)	ST (n=38)	Sig difference	Total (n=77)
Mean BDRS baseline score (SD)	9.1 (4.5)	9.0 (5.2)	t(0.069), df=73.018, p=0.946	9.1 (4.8)
Mean YMRS baseline score (SD)	2.0 (2,4)	2.5 (2.5)	t(-0.855), df=74.846, p=0.396	2.3 (2.4)
Mean IES-R baseline score (SD)	36.5 (27.0)	40.2 (24.4)	t(-0.620), df=70.981, p=0.537	38.3 (25.7)
Mean DES baseline score (SD)	11.5 (6.4)	14.7 (11.8)	t(-1.415), df=53.745, p=0.163	13.1 (9.6)
Mean FAST baseline score (SD)	29.5 (14.0)	28.5 (13.4)	t(0.317), df=73.854, p=0.752	29.0 (13.7)
Mean SCIP-S baseline score (SD)	69.1 (12.1)	68.2 (11.2)	t(0.332), df=69.961, p=0.741	68.7 (11.6)
PTSD Diagnosis *n* (%)				
Current	12 (30.7)	8 (21.1)	X^2=0.582, df=1, p=0.446	20 (26.0)
Lifetime	20 (51.3)	19 (50.0)	X^2=0, df=1, p=1	39 (50.6)

Key: EMDR=Eye Movement Desensitization and Reprocessing; ST=Supportive Therapy; SD=Standard Deviation; PTSD=post-traumatic stress disorder; df=degrees of freedom.

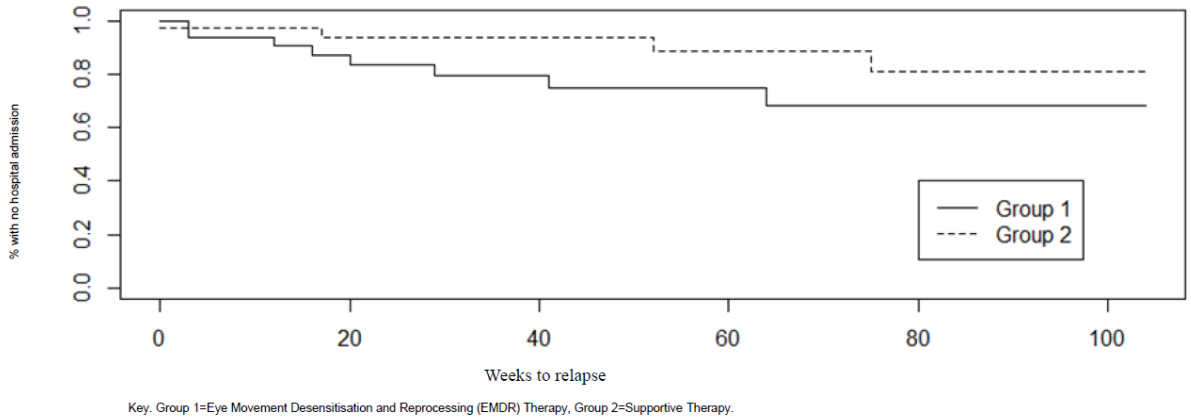
Primary outcomes: Relapse rates

For the primary outcome, all 77 participants were included in the analysis. Overall, 35.1% (n=27) of the sample had a relapse of any type, and 15.6% of the sample (n=12) had a relapse resulting in a hospital admission during the course of the study. The average time to hospital admission in the sample was 45.0 weeks, while the average time to any affective relapse was 27.3 weeks. There was no significant difference between groups in terms of risk of affective relapse (z(-0.04), p=0.97) or hospitalization (z(-1.50, p=0.13); see figures 2 and 3.



Key. Group 1=Eye Movement Desensitisation and Reprocessing (EMDR) Therapy, Group 2=Supportive Therapy.

Figure 2. Risk of an affective relapse of any type (with or without hospitalization).



Key. Group 1=Eye Movement Desensitisation and Reprocessing (EMDR) Therapy, Group 2=Supportive Therapy.

Figure 3. Risk of an affective relapse with hospitalization.

Secondary outcomes: Affective and trauma-related symptoms

Due to the high dropout rate for our primary outcome at 24-month (74%), available data were not representative for the whole sample, and therefore not reported in the main results but can be seen in Supplementary Table 1, along with the statistics for all time points for all affective and trauma-related variables.

In terms of affective symptoms, EMDR was significantly more effective in reducing depressive symptoms (t=4.252, p=0.00006, Cohen's d=0.969) and manic symptoms (t=2.248, p=0.027, Cohen's d=0.513) than ST at the 12-month follow-up; there were no significant differences at 6 months. The results for BDRS remained significant following the application of multiple corrections.

In terms of trauma related symptoms, there was a significant reduction across the whole sample as measured by the IES-R between baseline and post (t=5.139, df=44, p=<0.001), maintained at 12-months (t=4.911, df=30, p=<0.001), but no significant between-group differences at either 6- or 12-month time points. In addition, there were no significant between-group differences in the DES at either comparison.

Secondary outcomes: Functioning and cognitive impairment

Regarding functioning, scores improved at all time points as compared to baseline in both groups, but the only significant between-group difference was found at 12 months, where significantly improved FAST scores were observed in the EMDR group compared to the ST group (t=2.118, p=0.038, Cohen's *d*=0.486).

There were no significant between-group differences in cognitive impairment according to the SCIP at any time point, although there was a significant improvement between baseline and 6-months (t=-2.615, df=42, p=0.006), which was maintained at 12 months (t=-2.723, df=25, p=0.006) across the sample.

Dropout

Dropout rates were similarly high in both groups (38.5% at 6 months, 56.4% at 12 months and 76.9% at 24 months in the EMDR group, and 31.2% at 6 months, 55.3% at 12 months and 71.1% at 24 months

in the ST group) without statistically significant differences between the two groups (see supplementary table 2).

A univariate analysis was carried out which found no significant association between clinical and sociodemographic variables at baseline and risk of dropout (see supplementary table 3).

Discussion/Conclusion

To our knowledge, these are the results of the first multicentre RCT investigating the efficacy of a trauma-focused therapy in reducing affective relapses in BD. Although there was no significant difference between EMDR and ST in terms of this primary outcome, EMDR was significantly more effective than ST in the secondary outcomes of improving symptoms of depression, mania, and psychosocial functioning at the 12-month time point. Surprisingly, trauma symptoms reduced significantly in both the EMDR and ST groups.

The majority of previous studies aiming at a reduction of BD relapses have compared the intervention with a waitlist control group (Swartz and Swanson, 2014; Miklowitz *et al.*, 2021), whereas we compared EMDR with ST, an active control condition which is often as effective as the therapies it is compared with in non-BD populations (Markowitz, 2014). A previous study comparing CBT with ST in reducing relapses in BD similarly found no significant difference between treatment arms (Meyer and Hautzinger, 2012), which was attributed to shared therapeutic components. In our study, shared characteristics between EMDR and ST include psychoeducation and emotional support and alliance. BD patients tend to have low levels of social support (Studart *et al.*, 2015), so the therapeutic alliance may be especially beneficial. Future research could include the presence of a third group receiving pharmacological treatment only to clarify non-specific therapeutic benefits.

Preventing relapses in BD remains a challenge, with a recent meta-analysis estimating the risk of relapse at 44% in the first year following a BD mood episode, and at 70% within five years (Radua *et al.*, 2017). It is difficult to put the relapse rates from our study into context, due to the inclusion criteria of current trauma symptoms, which impact negatively on BD's clinical course (Aas *et al.*, 2016), and a minimum of two affective episodes in the previous year, which is important as a high number of previous episodes and shorter intervals between affective episodes are both associated with a higher risk of relapse (Altman *et al.*, 2006). Also of note is that we applied a strict intention-to-treat rule in our analysis, meaning dropouts who abandoned the study early for reasons other than relapse were included in the analysis, contributing to shorter relapse rates. The lack of hospitalisation prevention in the EMDR group contradicted our main hypothesis, but resembled findings from other studies in severe mental disorder (Robinson *et al.*, 2019).

A meta-analysis into the efficacy of adjunctive psychotherapy for reducing BD relapses indicates that non-euthymic patients with 13 or more lifetime affective episodes respond poorly to adjunctive psychotherapy (Scott *et al.*, 2007). The participants in our study had subsyndromal depression (BDRS = 9.1), and the mean number of previous episodes was 14.75 (SD 17.2), and thus may have been prone to a reduced treatment response. However, at the 12-month time point, EMDR was significantly superior to ST for reducing symptoms of depression (p=0.0006) and mania (p=0.027), which means that positive effects of EMDR appear to have been maintained for at least six months following the

end of therapy. A much larger effect size was observed for the effects of EMDR on depression severity than on mania scores (d=0.969 compared to 0.513). This may partly be due to the 'ceiling effect' of the low hypomania scores at the baseline in our study.

The significant improvement in subsyndromal depressive symptoms is especially encouraging, given not only the high burden of illness and the increased risk of suicide associated with these symptoms, but also the important clinical challenge of successfully treating depressive episodes in BD (Baldessarini *et al.*, 2020; Levenberg and Cordner, 2022). Untreated (subsyndromal) depressive symptoms can have an important negative impact on quality of life, psychosocial functioning, and cognition (Wingo *et al.*, 2010; Khafif *et al.*, 2021; Matsuo *et al.*, 2021), and the improvement in these symptoms may partially explain the significant improvement in our study in psychosocial functioning at 12 months in the EMDR group (p=0.038) (Moreno-Alcázar *et al.*, 2017). Psychosocial functioning tends to deteriorate in BD patients following multiple affective episodes (Rosa *et al.*, 2012), and subsyndromal depressive symptoms should be targeted early in the disease course to improve functional outcomes (Kauer-Sant'Anna *et al.*, 2009), so the improvement in the EMDR treatment condition in a sample of patients with a long history of affective episodes and subsyndromal depressive symptoms is promising. Poor psychosocial functioning is also associated with cognitive impairment (Martínez-Arán *et al.*, 2004) related to a worse disease course (Robinson and Ferrier, 2006). In our study, cognitive impairment scores improved significantly across conditions (t=2.615, df=42, p=0.006), although there were no between-group differences.

As this was the first multicentre RCT on trauma-focused psychotherapy, an important aim was to investigate the safety and tolerability of EMDR. Trauma-focused treatments are safe in patients with PTSD with no comorbid psychiatric disorder (Larsen *et al.*, 2015), but patients with severe mental disorder are usually excluded from PTSD trials, and a major concern of addressing trauma in BD patients is that it may destabilise affective symptoms (Grubaugh *et al.*, 2011). Our findings of comparable relapse and dropout rates for EMDR and ST support EMDR as a safe and acceptable adjunctive psychotherapy for BD with sequelae from psychological trauma, and support the results of our pilot trial (Novo *et al.*, 2014). As trauma symptoms and diagnosis of PTSD are associated with a poorer prognosis in BD (Aas *et al.*, 2016), it may be counter-productive to leave these unaddressed for fear of destabilising the patient.

Interestingly, there was a significant reduction in trauma symptoms in both EMDR and ST conditions. This was unexpected in the ST condition, and unlikely to be due to spontaneous remission as the average interval between the traumatic event and study enrolment in our sample was 22.4 years. In non-BD populations, EMDR and trauma-focused CBT are more effective treatments for PTSD than supportive and present-centred therapies (Bisson *et al.*, 2013). However, ST can be superior to a waitlist condition (Ehlers *et al.*, 2014) and can be as effective as CBT in chronic PTSD among those who complete all the sessions (Cottraux *et al.*, 2008). Thus, ST may include elements which alleviate trauma symptoms despite not directly focusing on traumatic events. Again, the social support factor may contribute to the efficacy of EMDR and ST, as social support has been shown to moderate PTSD symptoms (Price *et al.*, 2013, 2018). Similarly, difficulties in emotion regulation, often experienced in PTSD (Tull *et al.*, 2020), may be ameliorated by ST. Furthermore, the evaluation and reappraisal of prior traumatic events during study assessments is likely to have impacted trauma-related symptoms, as re-telling trauma narratives can have therapeutic effects (Jongedijk, 2014; Kaminer, 2016). Finally, it is of

note that the EMDR Bipolar protocol only focused on traumatic memories once BD symptoms were stabilised: given the severe clinical profile of participants, many only began to process traumatic memories in the final therapy sessions.

This study's strengths include, firstly, being the first multicentre RCT investigating a trauma-focused psychotherapy in comparison with an active control condition (i.e. ST) in trauma exposed BD patients. Secondly, the EMDR intervention followed a strict protocol facilitating replication of the study interventions in future research as well as its implementation in clinical practice. Third, our study included both BD-I and BD-II patients which allows us to generalize findings to the bipolar spectrum. In this respect, EMDR appears to be promising for male and female BD-I and BD-II patients with trauma symptoms, who are either in a euthymic state or show subsyndromal affective symptoms.

However, there are also several limitations: firstly, our primary endpoint (relapse rates over 24 months) may have been too ambitiously chosen, not considering the putative high dropout rate in a potentially severe mental health condition as BD. Secondly, the final stages of the trial coincided with the first wave of the COVID-19 pandemic, meaning four subjects received part of the treatment online. We could not find any research comparing online and face-to-face psychotherapy in BD patients, but EMDR has been shown to be effective delivered online (McGowan *et al.*, 2021), and the pandemic affected both treatment arms equally. A third limitation is the concomitant pharmacotherapy which may have had confounding effects, although there were no significant between-group differences in pharmacological treatment. Moreover, although raters were blind to treatment allocation, patients were not blind to treatment modality because of the nature of the interventions. Finally, comorbid psychiatric disorders were not diagnosed by standardized interviews, but rather assessed by reviewing the medical history together with the patient.

In summary, the specific EMDR protocol for BD shows promise in treating affective symptoms, but was not superior to ST in reducing relapses. This study provides valuable data supporting the safety and tolerability of trauma-focused EMDR in trauma-exposed patients with BD. Future RCTs should focus on exploring the therapeutic effects of EMDR on affective symptoms observed in this study. These findings pave the way for future research in treating comorbid trauma in BD, which is often associated with less favorable outcomes and chronicity.

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Statement of Ethics

This study was carried out in accordance the World Medical Association Declaration of Helsinki (World Medical Association, 2013). Ethical approval for this study was received from the Ethics Committee of each institution: Hospital Benito Menni (ref.: PR-2014-15), Hospital Clínic of Barcelona (ref.: HCB/2015/1005) and Hospital del Mar (ref.: 2015/6502/I). Informed consent was signed by all participants prior to enrolment in the study. The study was explained to all participants and written informed consent prior to enrolment in the study was obtained.

Author Contributions

BLA conceived the idea for the study and led the study. BLA and WL (with others) developed the EMDR Bipolar protocol. AMA coordinated the study. BH, AV, IG, WL, EJ, MM, LB, MR, RC, RSG, AMR, and JC were involved in the recruitment and evaluation of patients and data collection. BH, IGS, MF and AMA prepared the data for analysis. JR carried out the statistical analysis. BH worked on the first draft of the paper with BLA, AMA, and JR. All authors contributed to the interpretation of results and the final draft and approved the final draft.

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Supplementary Tables

Supplementary table 1: results at all time points

	Post-treatment		12-month follow-up		24-month follow-up	
	Estimate* (SD)	**Statistics**	**Estimate* (SD)**	**Statistics**	**Estimate* (SD)**	**Statistics**
BDRS	2.382 (1.58)	t(1-507), df=75, p=0.136	7.475 (1.76)	**t(4.252), df=75, p=0.0006, Cohen's d=0.969**	4.454 (3.37)	t(1.322), df=79, p=0.190
YMRS	0.577 (0.71)	t(0.808), df=75, p=0.422	1.973 (0.88)	**t(2.249), df=75, p=0.027, Cohen's d=0.513**	-0.138 (0.82)	t(-0.168), df=144, p=0.867
FAST	3.558 (4.40)	t(0.809), df=74, p=0.421	8.061 (3.81)	**t(2-118), df=74, p=0.038, Cohen's d=0.486**	-1.502 (3.54)	t(-0.424), df=74, p=0.673
SCIP-S	-1.865 (2.68)	t(-0.695), df=65, p=0.490	-2.458 (2.60)	t(-0.946), df=71, p=0.348	-1.319 (5.27)	t(-0.250), df=70, p=0.803
IES-R	-3.267 (5.99)	t(-0.545), df=72, p=0.587	-2.807 (6.02)	t(-0.466), df =71, p=0.642	-9998 (6.99)	t(-1.431), df=74, p=0.157
DES	1.789 (2.39)	t(0.749), df=70, p=0.456	-1.619 (2.02)	t(-0.800), df=70, p=0.427	-0.560 (2.03)	t(-0.276), df=70, p=0.783

Key. SD=Standard Deviation; BDRS: Bipolar Depression Rating Scale; YMRS: Young Mania Rating Scale; FAST: Functioning Assessment Short Test; SCIP-S: The Screen for Cognitive Impairment in Psychiatry; IES-R: Impact of Event Scale-Revised; DES: Dissociative Experiences Scale.

* Estimate: estimated difference between ST and EMDR adjusted for age, sex, illness duration and number of affective episodes over the previous 12 months.

Supplementary Table 2: Dropout rates per treatment condition

% Dropout	**EMDR**	**ST**	**Statistics**
Post-treament	38.5%	31.6%	X^2(0.155), df=1, p=0.694
12-month follow-up	56.4%	55.3%	X^2(0), df=1, p=1
24-month follow-up	76.9%	73.7%	X^2(0.004), df=1, p=0.948

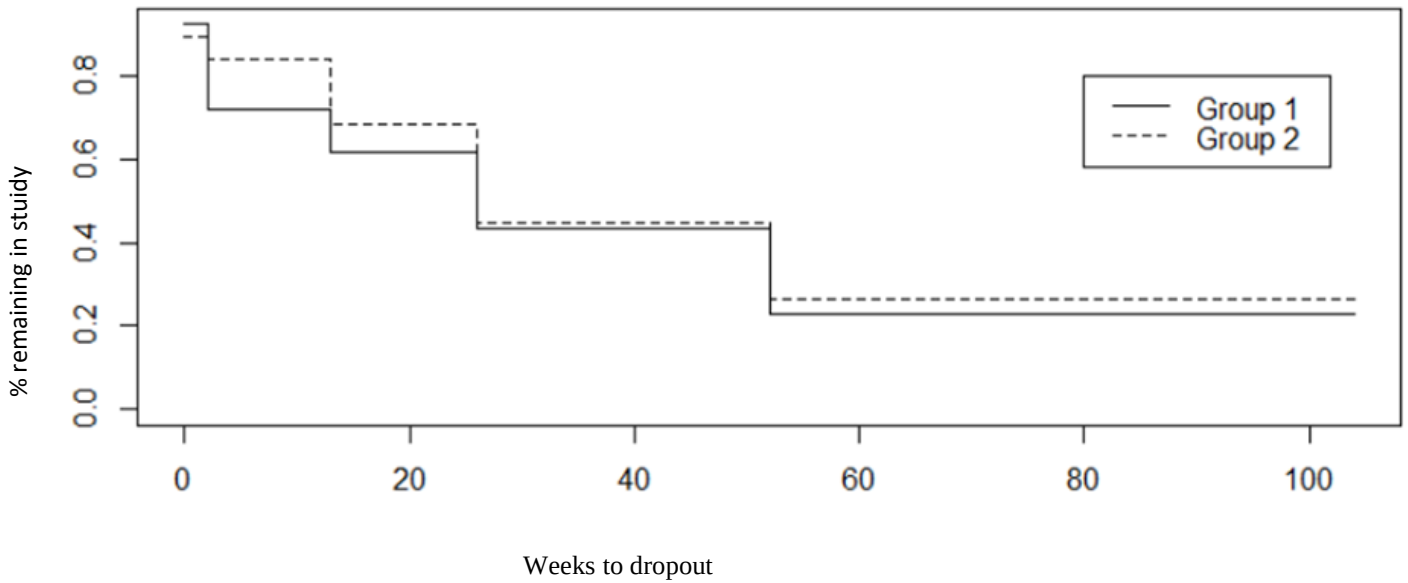
Key: EMDR=Eye Movement Desensitization and Reprocessing therapy; ST=Supportive Therapy.

Supplementary Table 3 Analysis of dropout rates by baseline variables

Variable	**Statistic**
Sex	z=-0.123, p=0.902
Age	z=-1.375, p=0.169
Years of education	z=0.055, p=0.956
Age of onset	z=0.527, p=0.598
Illness duration	z=-1.923, p=0.054
Number of hospital admissions	z=1.802, p=0.072
History of psychotic symptoms	z=0.528, p=0.597
BD Type	z=-0.993, p=0.321
Number of suicide attempts	z=0.837, p=0.403
Current PTSD diagnosis	z=1.181, p=0.238
Lifetime PTSD diagnosis	z=0.249, p=0.803
BDRS score	z=-0.773, p=0.44
YMRS score	z=-1.216, p=0.224
FAST score	z=-0.07, p=0.944
SCIP-S score	z=0.592, p=0.554
IES-R score	z=0.148, p=0.883
DES score	z=-1.366, p=0.172

Key: BD=Bipolar Disorder; PTSD=post-traumatic stress disorder; BDRS: Bipolar Depression Rating Scale; YMRS: Young Mania Rating Scale; FAST: Functioning Assessment Short Test; SCIP-S: The Screen for Cognitive Impairment in Psychiatry; IES-R: Impact of Event Scale-Revised; DES: Dissociative Experiences Scale.

Supplementary Figure 1. Risk of dropout per treatment arm.



Key: Group 1 = Eye Movement Desensitisation and Reprocessing (EMDR) therapy; Group 2 = Supportive Therapy.

5. Discussion

5. Discussion

This thesis covers the role of psychological trauma in mental disorder, from assessing the possibility of it being a transdiagnostic risk factor across a range of mental disorders, through to investigating its characteristics and treatment in people with a specific disorder, BD. In accordance with the first hypothesis, the first part of this thesis demonstrates robustly, through an umbrella review, that there is highly suggestive evidence that psychological trauma is a transdiagnostic risk factor for mental disorder, nearly tripling the risk (OR=2.92). Prior to this umbrella review, there was a range of evidence linking psychological trauma with different mental disorders (7,61,82), but no overarching synthesis to understand its role as a general risk factor in psychiatric disorder, which may explain why the evaluation and treatment of psychological trauma is not systematically implemented in psychiatric services. Therefore, the results of this first part of the thesis have important implications in terms of prevention, early intervention, and treatment.

In terms of prevention, the umbrella review demonstrates the need for child maltreatment to be conceptualised as a public health issue (135). The World Health Organisation advocates employing prevention strategies at the individual, family, community, and society levels (136). However, child maltreatment rates are still high, and have been exacerbated by global events such as the COVID-19 pandemic (137,138), war (139,140), and the consequences of climate change (141). The results of the thesis point to the urgent need to prioritise measures to protect vulnerable children.

Regarding early intervention, it is key for trauma to be correctly screened for and identified. If a child's trauma history is overlooked, their trauma symptoms may be misdiagnosed as other psychiatric diagnoses such as ADHD, mood, or anxiety disorders (142,143), which can delay necessary treatment. Furthermore, even if PTSD is screened for, symptoms of trauma in

children may include biopsychosocial dysregulation not covered in the standard PTSD diagnosis (144). A proposed diagnosis called Developmental Trauma Disorder (DTD) (145) provides a broader understanding of trauma symptoms than the standard PTSD diagnosis in children, which can support improved identification and treatment of trauma in children and adolescents.

The transdiagnostic mechanisms model proposed by McLaughlin and colleagues (109) suggests mechanisms which link psychological trauma with a range of different psychopathologies. Intervention strategies focused on transdiagnostic mechanisms, such as social support, or emotional regulation, or on the biological substrates, could provide innovative new approaches for prevention and early intervention in a range of mental disorders.

Regarding specific abuse types, physical and sexual abuse were both shown to be implicated in a range of diagnostic categories. However, the umbrella review search only uncovered studies investigating the association between emotional abuse and one diagnostic spectrum, anxiety disorders. This reflects the fact that emotional abuse is under-researched and often not included as a category in major studies (5,7), despite evidence showing that emotional abuse is the most prevalent form of childhood trauma worldwide (146). Another overlooked form of maltreatment is emotional and physical neglect, which were not specifically assessed in any of the studies included in our review, and which are frequently overlooked (8,147), despite their widespread prevalence: a meta-analysis of a large number of children across 13 independent samples has estimated the prevalence of emotional neglect to be 18.4% and physical neglect to be 16.3% (147). A major study in Lancet suggests that the health outcomes of neglect can be as serious as the health outcomes of other forms of abuse (148).

Future research must start to systematically include the concepts of emotional abuse, and emotional and physical neglect, to provide further data regarding this area.

The results of the umbrella review also highlight the importance of screening for trauma history in adult psychiatric services. Screening for trauma has been recommended in mental health and substance use patients in order to improve treatment adherence and disease course, reduce relapse rates, and to contribute to appropriate diagnosis and treatment plans (149), although this is not systematically implemented across health services.

Even where trauma is identified, there is a lack of evidence base for the clinical treatment of comorbid trauma in psychiatric disorders. The remaining objectives of the thesis aimed to address some of these gaps in a specific disorder, BD. The second objective of the thesis was to describe the clinical and sociodemographic characteristics of a sample of patients with BD and a history of psychological trauma and to compare the trauma profiles of BD-I and BD-II, while the third objective was to analyse the impact of a lifetime PTSD diagnosis, physical abuse, and sexual abuse on the clinical course of BD. It was hypothesised that a PTSD diagnosis, a history of sexual abuse, and a history of physical abuse would each be associated with a worse disease course, but there would be no difference in symptom profile across BD subtypes. The second part of this hypothesis was proven, with our results supporting earlier evidence (90) which demonstrates that the presentation of BD symptoms does not change across BD type. However, the hypothesis that PTSD diagnosis and specific abuse types within a traumatised sample would lead to a worse clinical profile was largely disproven. The only significant difference between participants with a lifetime PTSD diagnosis and those without was an increased risk of having ever experienced psychotic symptoms. However, it is important to highlight that the non-PTSD group showed a high level of subsyndromal symptoms. Therefore, although the results must be interpreted with caution in light of the

lack of a control group of BD patients without psychological trauma, one explanation of the results is that subsyndromal trauma symptoms have a significant clinical impact similar to PTSD, which could have important implications in terms of how trauma is addressed in a clinical setting.

The initial hypothesis of physical abuse being related to a worse clinical BD course was disproved, and in the case of sexual abuse, the hypothesis was only proven in relation to rapid cycling. These results suggest that in a traumatised sample, specific effects of each type of abuse may be hard to detect. To build on these findings, further research should screen for emotional abuse and emotional and physical neglect, in addition to sexual and physical abuse. Furthermore, when this study was launched, CPTSD was not yet an official diagnosis in the ICD-11 and CPTSD was not included as a study variable. However, evaluating the presence of CPTSD, in addition to PTSD and subsyndromal PTSD symptoms, and including a control group of BD patients without trauma, would be an important avenue for future research to determine the impact of different trauma diagnoses on BD disease course and quality of life, in order to optimise screening programmes and treatment plans for people with comorbid BD and trauma.

Of note in this study, the results provided important preliminary evidence that experiences related to BD itself can be traumatic. Examples from this study included risky behaviours and interactions with the police related to manic episodes, and involuntary hospital admissions. Similar to how psychotic episodes are now understood to be potentially traumatic events (87,150,151), these results point to the need for more research into the possibility of traumatic events directly related to BD.

Regarding the complementary analyses aimed at understanding gender differences in a traumatised BD sample, there was only one difference by gender, where females in our

sample had a significantly higher age of onset than males, which is in contrast to previous research which has found no gender difference in age of onset (152,153), although men may have an earlier onset with first-episode mania than women (154). However, to the author's knowledge, there is a lack of research regarding the intersection of gender and trauma history and its impact on age of onset, and our results also showed a surprising trend towards a PTSD diagnosis being associated with a later age of onset, contrary to expectations. Further research can help clarify how gender interacts with trauma to influence age of onset.

The final two specific objectives of the thesis were to assess the efficacy of an adjunctive trauma-focused therapy, EMDR, in BD, as compared to an adjunctive non-trauma-focused therapy, ST, in terms of reducing affective relapses and hospital admissions, and in improving clinical symptoms, psychosocial functioning, cognition, and trauma symptoms. The initial hypothesis was only partially proven. EMDR therapy was shown to be superior to ST in terms of reducing affective symptoms and improving functioning at six months post-intervention, with a particularly strong impact on subsyndromal depressive symptoms, which are hard to treat in BD and represent a high illness burden (64,155). However, EMDR was not superior to ST in reducing affective relapses, which is in line with similar research demonstrating the difficulty in achieving a reduction in relapse rates (156,157). However, this result, combined with there being no significant difference in dropout rates or hospital admissions between the two groups, points to the EMDR Bipolar protocol being a safe psychosocial adjunctive treatment, with no risk of destabilising symptoms as a result of focusing on trauma.

Moreover, and surprisingly, EMDR was not more effective than ST in reducing trauma symptoms, which significantly reduced at post-intervention compared to baseline in both the EMDR and the ST group. This raises interesting questions regarding whether therapeutic

support and emotional regulation were able to reduce PTSD symptoms without specifically addressing traumatic events, or whether there was a therapeutic benefit to the trauma evaluations. An additional possibility is that only a few EMDR sessions were dedicated to processing traumatic events, as the bipolar EMDR manual focuses on stabilising symptoms before processing trauma, and many participants had a severe disease course with an important number of current adverse events.

This research demonstrates the feasibility of addressing comorbid trauma in a severe mental disorder, BD, showing that trauma can be safely addressed in this population, and that there is the potential to also have a positive impact on disease course. While future research can focus on identifying the optimal duration and method, and on assessing the cost-effectiveness of a trauma-focused psychotherapy, these results refute concerns about applying trauma-focused therapies in severe mental disorders for fear of destabilising symptoms, and support the use of trauma-informed care in psychiatric services, and further research into this area.

The overarching theme of the thesis is to understand psychological trauma's role as a transdiagnostic risk factor for mental disorder, and within the context of BD, provide evidence as to the treatment of comorbid trauma through EMDR. The results highlight the need for a greater emphasis on preventing and early intervention in childhood trauma, and the need for further research in treating comorbid trauma in adult psychiatric services, with the EMDR Bipolar protocol showing potential as a feasible and safe adjunctive psychosocial treatment for BD patients with comorbid trauma.

5.1 Limitations

The limitations of each individual study have been outlined in the discussion section of each manuscript. However, there are some limitations which apply across the thesis. It was not

possible to include a gender perspective across the work as, in the case of the umbrella review, the systematic reviews and meta-analyses did not differentiate results by gender. Regarding the second paper, the small number of men in the sample (n=18) impeded the inclusion of an analysis by gender in the main paper. Supplementary analyses showed no significant differences between gender on any variables except age of onset, although there was a tendency towards worse clinical scores in women, which may be significant with a larger sample size. Regarding the final paper, the randomisation procedure ensured a balanced number of men and women in each study arm, and the number of men in each arm was too small to identify if there were differences in treatment response. Future research could focus on clarifying this point across all genders.

Another limitation across the thesis is the reliance on subjective, retrospective data for trauma assessment, both in the bipolar study and in the umbrella review, where only two of the 106 individual studies included in the umbrella review used prospective data. Research has indicated that prospective and retrospective measures of child abuse cannot be used interchangeably as they detect different groups of people (158). Retrospective data has been associated more closely with psychopathology than objective measures of trauma (159). Furthermore, although retrospective data is subjective and based on recall, there are also difficulties with objective measures of childhood maltreatment, which rely on abuse and neglect being detected. There is strong evidence that many types of abuse and trauma are under reported: a Lancet study showed that official rates of sexual abuse were less than a tenth of those estimated to have occurred (148). It is important to interpret the results of this thesis in the context of subjective reports of trauma.

A further limitation is the lack of data on emotional abuse and emotional and physical neglect. In the case of the umbrella review, this reflected a lack of prior research including

these abuse types. In the bipolar study, data regarding trauma exposure was collected through the gold standard CAPS trauma sheet, which does not include emotional abuse, or emotional or physical neglect. It was decided to use the gold standard CAPS scale due to extensive research on its validity, and this was not supplemented with a further interview to detect other types of childhood trauma because of the risk of tiring and overwhelming patients with the already long trauma evaluation. However, emerging evidence on the importance of emotional abuse and neglect (8,160–162), including the results of our umbrella review, point to the importance of including measures for this, such as the Childhood Trauma Questionnaire (CTQ), or the use of other tools to measure PTSD which include emotional abuse or neglect.

Finally, CPTSD was not included in this thesis as it was not an official diagnosis when this work began; CPTSD was newly included in the ICD-11 when it was published in 2019, and is still not included in the DSM-5. Although its inclusion would have been interesting given recent research indicating its prevalence in severe mental illness (17), and the indications that CPTSD is associated with more frequent and severe abuse, and with greater functional impairment (163), recent research has suggested CPTSD is less common in BD patients than in other psychiatric patients (94), which may to some extent mitigate this limitation.

5.2 Future lines of research

The results of this thesis opens the avenue to a range of future lines of research, including the following:

1. Investigate innovative methods for the prevention, early intervention and treatment of trauma.
2. Identification of the underlying processes through which psychological trauma leads to mental disorder.

3. Research to understand the association between mental disorder and emotional abuse, emotional neglect, and physical neglect, in order to gain a better understanding of these to-date under-researched types of trauma.
4. Research to elucidate the different impact of subsyndromal PTSD, PTSD, CPTSD on clinical BD symptoms, in comparison with no trauma symptoms, to identify patients who are vulnerable to a worse disease course.
5. Trials to replicate the current results of the efficacy of EMDR in BD, and new trials with other trauma-focused psychotherapies such as TF-CBT.
6. Investigation into addressing comorbid trauma in other severe mental disorders.

6. Conclusions

6. Conclusions

1. Psychological trauma is a transdiagnostic risk factor which nearly triples the risk of any mental disorder (OR = 2.92).
2. The association between emotional abuse, emotional neglect, and physical neglect and mental disorders is under-researched.
3. A lifetime PTSD diagnosis in BD is associated with a significant increase of having ever experienced psychotic symptoms but is not associated with any other indicator of a worse disease course, as compared to BD patients with subsyndromal trauma symptoms.
4. Sexual abuse in BD patients may be specifically associated with rapid cycling, but it is hard to detect specific effects of sexual and physical abuse in a traumatised sample.
5. There is no difference in trauma symptom profile between BD-I and BD-II.
6. There was no significant difference between the EMDR and ST treatment arms in terms of affective relapses, hospital admissions, or dropout rates.
7. The EMDR condition was significantly superior to ST at 6 months post-intervention follow-up in reducing subsyndromal depressive symptoms, hypomanic symptoms, and in improving psychosocial functioning.
8. There was no significant improvement in cognition in either the EMDR and ST treatment conditions.
9. EMDR was not significantly superior to ST in improving trauma-related symptoms, but in both groups there was a significant improvement at six months as compared to baseline.

10. The EMDR Bipolar protocol appears to be an acceptable adjunctive psychotherapy to treat BD patients with comorbid psychological trauma, and may be superior to ST in reducing affective symptoms and in improving psychosocial functioning.

7. Bibliography

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8. Appendix

8. Appendix.

8.1 List of studies excluded from the umbrella review following full-text screening

Appendix. List of studies excluded from the umbrella review following full-text screening.

First author	Year	Title	Journal	Volume	Issue	Pages
Aaby	2020	The associations of acceptance with quality of life and mental health following spinal cord injury: a systematic review.	Spinal cord	58	2	130-148
Abbey	2015	A meta-analysis of prevalence rates and moderating factors for cancer-related posttraumatic stress disorder.	Psycho-oncology	24	4	371-381
Agius	2016	The co-existence of depression, anxiety and posttraumatic stress symptoms in the perinatal period: A systematic review.	Midwifery	36		70-79
Al Falasi	2021	Prevalence and Determinants of Immediate and Long-Term PTSD Consequences of Coronavirus-Related (CoV-1 and CoV-2) Pandemics among Healthcare Professionals: A Systematic Review and Meta-Analysis.	International journal of environmental research and public health	18	4	
Alcantara	2013	Conditional risk for PTSD among Latinos: a systematic review of racial/ethnic differences and sociocultural explanations.	Clinical psychology review	33	1	107-119
Alisic	2015	Children's Mental Health and Well-Being After Parental Intimate Partner Homicide: A Systematic Review.	Clinical child and family psychology review	18	4	328-345
Al-Modallal	2008	Impact of physical abuse on adulthood depressive symptoms among women.	Issues in mental health nursing	29	3	299-314
Alvarez-Segura	2014	Are women with a history of abuse more vulnerable to perinatal depressive symptoms? A systematic review.	Archives of women's mental health	17	5	343-357
Ayers	2016	The aetiology of post-traumatic stress following childbirth: a meta-analysis and theoretical framework.	Psychological medicine	46	6	1121-1134
Ba	2017	Physical, mental and social consequences in civilians who have experienced war-related sexual violence: a systematic review (1981-2014).	Public health	142		121-135
Bailey	2018	Childhood trauma is associated with severity of hallucinations and delusions in psychotic disorders: A systematic review and meta-analysis	Schizophrenia Bulletin	44	5	1111-1122
Baranyi	2018	Prevalence of Posttraumatic Stress Disorder in Prisoners.	Epidemiologic reviews	40	1	134-145
Barazzone	2019	The links between adult attachment and posttraumatic stress: A systematic review.	Psychology and psychotherapy	92	1	131-147
Beaglehole	2019	A systematic review of the psychological impacts of the Canterbury earthquakes on mental health.	Australian and New Zealand journal of public health	43	3	274-280
Beaglehole	2018	Psychological distress and psychiatric disorder after natural disasters: systematic review and metaanalysis.	The British journal of psychiatry : the journal of mental science	213	6	716-722
Beaudry	2021	An Updated Systematic Review and Metaregression Analysis: Mental Disorders Among Adolescents in Juvenile Detention and Correctional Facilities.	Journal of the American Academy of Child and Adolescent Psychiatry	60	1	46-60
Berger	2012	Rescuers at risk: a systematic review and metaregression analysis of the worldwide current	Social psychiatry and psychiatric epidemiology	47	6	1001-1011

		prevalence and correlates of PTSD in rescue workers.				
Bernhard	2018	Association of trauma, Posttraumatic Stress Disorder and Conduct Disorder: A systematic review and meta-analysis.	Neuroscience and biobehavioral reviews	91		153-169
Birkley	2016	Posttraumatic Stress Disorder Symptoms, Intimate Partner Violence, and Relationship Functioning: A Meta-Analytic Review.	Journal of traumatic stress	29	5	397-405
Blackmore	2020	Systematic Review and Meta-analysis: The Prevalence of Mental Illness in Child and Adolescent Refugees and Asylum Seekers.	Journal of the American Academy of Child and Adolescent Psychiatry	59	6	705-714
Bloch	2017	Literature review and meta-analysis of risk factors for delayed post-traumatic stress disorder in older adults after a fall.	International journal of geriatric psychiatry	32	2	136-140
Brewin	2000	Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults.	Journal of consulting and clinical psychology	68	5	748-766
Brosbe	2011	Predicting posttraumatic stress following pediatric injury: a systematic review.	Journal of pediatric psychology	36	6	718-729
Bruce	2006	A systematic and conceptual review of posttraumatic stress in childhood cancer survivors and their parents.	Clinical psychology review	26	3	233-256
Buswell	2021	A systematic review of PTSD to the experience of psychosis: prevalence and associated factors.	BMC psychiatry	21	1	09-Sep
Cenat	2021	Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: A systematic review and meta-analysis.	Psychiatry research	295		113599-113599
Cenat	2020	Symptoms of posttraumatic stress disorder, depression, anxiety and other mental health problems following the 2010 earthquake in Haiti: A systematic review and meta-analysis.	Journal of affective disorders	273		55-85
Carmassi	2020	Post-Traumatic Stress Reactions in Caregivers of Children and Adolescents/Young Adults with Severe Diseases: A Systematic Review of Risk and Protective Factors.	International journal of environmental research and public health	18	1	
Carmassi	2020	Risk and Protective Factors for PTSD in Caregivers of Adult Patients with Severe Medical Illnesses: A Systematic Review.	International journal of environmental research and public health	17	16	
Carroll	2016	The prevalence of women's emotional and physical health problems following a postpartum haemorrhage: a systematic review.	BMC pregnancy and childbirth	16		261-261
Charlson	2012	Predicting the impact of the 2011 conflict in Libya on population mental health: PTSD and depression prevalence and mental health service requirements.	PloS one	7	7	e40593e40593
Chen	2015	The Incidence of Posttraumatic Stress Disorder After Floods: A Meta-Analysis.	Disaster medicine and public health preparedness	9	3	329-333

Chen	2020	Prevalence of Post-Traumatic Stress Disorder Following Caesarean Section: A Systematic Review and Meta-Analysis.	Journal of women's health (2002)	29	2	200-209
Christiansen	2017	Posttraumatic stress disorder in parents following infant death: A systematic review.	Clinical psychology review	51		60-74
Cividanes	2019	Revictimization as a high-risk factor for development of posttraumatic stress disorder: a systematic review of the literature.	Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)	41	1	82-89
Clarner	2015	Work-related posttraumatic stress disorder (PTSD) and other emotional diseases as consequence of traumatic events in public transportation: a systematic review	International Archives of Occupational and Environmental Health	88	5	549-564
Cnossen	2017	Predictors of Major Depression and Posttraumatic Stress Disorder Following Traumatic Brain Injury: A Systematic Review and Meta-Analysis.	The Journal of neuropsychiatry and clinical neurosciences	29	3	206-224
Colledge	2020	Depression, post-traumatic stress disorder, suicidality and self-harm among people who inject drugs: A systematic review and metaanalysis.	Drug and alcohol dependence	207		107793-107793
Conard	2014	Deployment and PTSD in the female combat veteran: a systematic review.	Nursing forum	49	1	01-Oct
Cook	2011	Older women survivors of physical and sexual violence: a systematic review of the quantitative literature.	Journal of women's health (2002)	20	7	1075-1081
Cooke	2020	Prevalence of posttraumatic and general psychological stress during COVID-19: A rapid review and meta-analysis.	Psychiatry research	292		113347-113347
Corsi	2021	PTSD in parents of children with severe diseases: a systematic review to face Covid-19 impact.	Italian journal of pediatrics	47	1	08-Aug
Coventry	2020	Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis.	PLoS medicine	17	8	e1003262e1003262
Cox	2008	A meta-analysis of risk factors that predict psychopathology following accidental trauma.	Journal for specialists in pediatric nursing : JSPN	13	2	98-110
Cruz	2020	Effect of Extreme Weather Events on Mental Health: A Narrative Synthesis and Meta-Analysis for the UK.	International journal of environmental research and public health	17	22	
Dai	2016	The incidence of post-traumatic stress disorder among survivors after earthquakes:a systematic review and meta-analysis.	BMC psychiatry	16		188-188
Dai	2018	Prevalence of acute stress disorder among road traffic accident survivors: a meta-analysis.	BMC psychiatry	18	1	188-188
Daugirdaite	2015	Posttraumatic stress and posttraumatic stress disorder after termination of pregnancy and reproductive loss: a systematic review.	Journal of pregnancy	2015		646345-646345
Davydow	2008	Posttraumatic stress disorder in general intensive care unit survivors: a systematic review.	General hospital psychiatry	30	5	421-434
Davydow	2015	Posttraumatic stress disorder in organ transplant recipients: a systematic review.	General hospital psychiatry	37	5	387-398

De Bellis	2019	Depression in Maltreated Children and Adolescents	Child and Adolescent Psychiatric Clinics of North America	28	3	289-302
Debell	2014	A systematic review of the comorbidity between PTSD and alcohol misuse.	Social psychiatry and psychiatric epidemiology	49	9	1401-1425
d'Ettorre	2021	Post-Traumatic Stress Symptoms in Healthcare Workers Dealing with the COVID-19 Pandemic: A Systematic Review.	International journal of environmental research and public health	18	2	
D'Ettorre	2020	Post-traumatic stress disorder symptoms in healthcare workers: a ten-year systematic review.	Acta bio-medica : Atenei Parmensis	91	12	e2020009e2020009
Dimitry	2012	A systematic review on the mental health of children and adolescents in areas of armed conflict in the Middle East.	Child: care, health and development	38	2	153-161
Djelantik	2020	The prevalence of prolonged grief disorder in bereaved individuals following unnatural losses: Systematic review and meta regression analysis.	Journal of affective disorders	265		146-156
Dube	2018	Health Outcomes for Children in Haiti Since the 2010 Earthquake: A Systematic Review.	Prehospital and disaster medicine	33	1	77-88
Dworkin	2017	Sexual assault victimization and psychopathology: A review and meta-analysis.	Clinical psychology review	56		65-81
Edmondson	2012	Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review.	PloS one	7	6	e38915e38915
Edmondson	2013	Prevalence of PTSD in Survivors of Stroke and Transient Ischemic Attack: A Meta-Analytic Review.	PloS one	8	6	e66435e66435
Frias	2015	Comorbidity between post-traumatic stress disorder and borderline personality disorder: a review.	Psychopathology	48	1	01-Oct
Fulton	2015	The prevalence of posttraumatic stress disorder in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans: a meta-analysis.	Journal of anxiety disorders	31		98-107
Furr	2010	Disasters and youth: a meta-analytic examination of posttraumatic stress.	Journal of consulting and clinical psychology	78	6	765-780
Furuta	2012	A systematic review of the relationship between severe maternal morbidity and post-traumatic stress disorder.	BMC pregnancy and childbirth	12		125-125
Guenak	2020	Post-traumatic stress disorder as a risk factor for dementia: systematic review and meta-analysis.	The British journal of psychiatry : the journal of mental science	217	5	600-608
Garton	2017	Poststroke Post-Traumatic Stress Disorder: A Review	Stroke	48	2	507-512
Giannoni-Pastor	2016	Prevalence and Predictors of Posttraumatic Stress Symptomatology Among Burn Survivors: A Systematic Review and Meta-Analysis.	Journal of burn care & research : official publication of the American Burn Association	37	1	e79-89
Gradus	2017	Prevalence and prognosis of stress disorders: A review of the epidemiologic literature	Clinical Epidemiology	9		251-260

Greene	2016	Prevalence, Detection and Correlates of PTSD in the Primary Care Setting: A Systematic Review.	Journal of clinical psychology in medical settings	23	2	160-180
Grekin	2014	Prevalence and risk factors of postpartum posttraumatic stress disorder: a meta-analysis.	Clinical psychology review	34	5	389-401
Griffiths	2007	The prevalence of post traumatic stress disorder in survivors of ICU treatment: a systematic review.	Intensive care medicine	33	9	1506-1518
Guest	2016	Psychological distress following a motor vehicle crash: A systematic review of preventative interventions.	Injury	47	11	2415-2423
Hong	2016	Systematic Review on Post-Traumatic Stress Disorder Among Survivors of the Wenchuan Earthquake.	Trauma, violence & abuse	17	5	542-561
Hou	2020	Everyday life experiences and mental health among conflict-affected forced migrants: A metaanalysis.	Journal of affective disorders	264		50-68
Ireland	2020	Psychopathy and trauma: Exploring a potential association.	International journal of law and psychiatry	69		101543-101543
Kapfhammer	2018	Acute and long-term mental and physical sequelae in the aftermath of traumatic exposure. Some remarks on “the body keeps the score”	Psychiatria Danubina	30	3	254-272
Keynejad	2020	Psychological interventions for common mental disorders in women experiencing intimate partner violence in low-income and middle-income countries: a systematic review and meta-analysis.	The lancet. Psychiatry	7	2	173-190
Kim	2020	The Effectiveness of Psychological Interventions for Women Traumatized by Sexual Abuse: A Systematic Review and Meta-Analysis.	Issues in mental health nursing	41	5	385-394
Kimuli Balikuddembe	2020	Health-Related Rehabilitation after the 2008 Great Wenchuan Earthquake in China:A Ten Year Retrospective Systematic Review.	International journal of environmental research and public health	17	7	
Kitzmann	2003	Child witnesses to domestic violence: a metaanalytic review.	Journal of consulting and clinical psychology	71	2	339-352
Kline	2021	The Effect of Concurrent Depression on PTSD Outcomes in Trauma-Focused Psychotherapy: A Meta-Analysis of Randomized Controlled Trials.	Behavior therapy	52	1	250-266
Kok	2012	Posttraumatic stress disorder associated with combat service in Iraq or Afghanistan: reconciling prevalence differences between studies.	The Journal of nervous and mental disease	200	5	444-450
Kokou-Kpolou	2020	Correlates of grief-related disorders and mental health outcomes among adult refugees exposed to trauma and bereavement: A systematic review and future research directions.	Journal of affective disorders	267		171-184
Kyron	2021	Prospective risk and protective factors for psychopathology and wellbeing in civilian emergency services personnel: a systematic review.	Journal of affective disorders	281		517-532

Ladds	2017	Systematic review: Predicting adverse psychological outcomes after hand trauma.	Journal of hand therapy : official journal of the American Society of Hand Therapists	30	4	407-419
Lee	2018	Trauma exposure, posttraumatic stress, and preventive health behaviours: a systematic review.	Health psychology review	12	1	75-109
Lee	2020	Occupational post-traumatic stress disorder: an updated systematic review.	BMC public health	20	1	768-768
Liang	2019	Posttraumatic stress disorder following the 2008 Wenchuan earthquake: A 10-year systematic review among highly exposed populations in China.	Journal of affective disorders	243		327-339
Lin	2018	Prevalence of posttraumatic stress disorder among road traffic accident survivors: A PRISMAcompliant meta-analysis.	Medicine	97	3	e9693e9693
Machtinger	2012	Psychological trauma and PTSD in HIV-positive women: a meta-analysis.	AIDS and behavior	16	8	2091-2100
Marie	2020	Anxiety disorders and PTSD in Palestine: a literature review.	BMC psychiatry	20	1	509-509
McDonnell	2017	Anxiety Among Adolescent Survivors of Pediatric Cancer.	The Journal of adolescent health : official publication of the Society for Adolescent Medicine	61	4	409-423
McFarlane	1998	Epidemiological evidence about the relationship between PTSD and alcohol abuse: the nature of the association.	Addictive behaviors	23	6	813-825
Mehta	2012	Prevalence of post-traumatic stress disorder among children and adolescents who survive road traffic crashes: a systematic review of the international literature.	Journal of paediatrics and child health	48	10	876-885
Meyerson	2011	Posttraumatic growth among children and adolescents: a systematic review.	Clinical psychology review	31	6	949-964
Misiak	2017	Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings	Neuroscience and Biobehavioral Reviews	75		393-406
Mitchell	2011	Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies.	The Lancet. Oncology	12	2	160-174
Mitchell	2017	Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder.	General hospital psychiatry	47		48-60
Mohwinkel	2018	Gender differences in the mental health of unaccompanied refugee minors in Europe: a systematic review.	BMJ open	8	7	e022389e022389
Morina	2018	Prevalence of depression and posttraumatic stress disorder in adult civilian survivors of war who stay in war-afflicted regions. A systematic review and meta-analysis of epidemiological studies.	Journal of affective disorders	239		328-338

Musanabaganwa	2020	Burden of post-traumatic stress disorder in postgenocide Rwandan population following exposure to 1994 genocide against the Tutsi: A meta-analysis.	Journal of affective disorders	275		Jul-13
Muscatelli	2017	Prevalence of Depression and Posttraumatic Stress Disorder After Acute Orthopaedic Trauma: A Systematic Review and Meta-Analysis.	Journal of orthopaedic trauma	31	1	47-55
Neria	2008	Post-traumatic stress disorder following disasters: a systematic review.	Psychological medicine	38	4	467-480
Neria	2011	Posttraumatic stress disorder following the September 11, 2001, terrorist attacks: a review of the literature among highly exposed populations.	The American psychologist	66	6	429-446
Ng	2020	National and regional prevalence of posttraumatic stress disorder in sub-Saharan Africa: A systematic review and meta-analysis.	PLoS medicine	17	5	e1003090e1003090
Ni	2020	Mental health during and after protests, riots and revolutions: A systematic review.	The Australian and New Zealand journal of psychiatry	54	3	232-243
O'Driscoll	2016	Sexual problems and post-traumatic stress disorder following sexual trauma: A meta-analytic review.	Psychology and psychotherapy	89	3	351-367
Ophuis	2018	Prevalence of post-traumatic stress disorder, acute stress disorder and depression following violence related injury treated at the emergency department: a systematic review.	BMC psychiatry	18	1	311-311
Orth	2006	Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis.	Journal of consulting and clinical psychology	74	4	698-706
Ozer	2003	Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis.	Psychological bulletin	129	1	52-73
Palmisano	2016	Life adverse experiences in relation with obesity and binge eating disorder: A systematic review.	Journal of behavioral addictions	5	1	Nov-31
Paolucci	2001	A meta-analysis of the published research on the effects of child sexual abuse.	The Journal of psychology	135	1	17-36
Paredes Molina	2018	PTSD in civilian populations after hospitalization following traumatic injury: A comprehensive review.	American journal of surgery	216	4	745-753
Parikh	2015	Post-traumatic stress disorder and post-traumatic growth in breast cancer patients--a systematic review.	Asian Pacific journal of cancer prevention : APJCP	16	2	641-646
Parker	2015	Posttraumatic stress disorder in critical illness survivors: a metaanalysis.	Critical care medicine	43	5	1121-1129
Parker	2016	Mental health implications for older adults after natural disasters--a systematic review and metaanalysis.	International psychogeriatrics	28	1	Nov-20
Paz Garcia-Vera	2016	A Systematic Review of the Literature on Posttraumatic Stress Disorder in Victims of Terrorist Attacks.	Psychological reports	119	1	328-359
Peconga	2020	Post-traumatic stress disorder, depression, and anxiety in adult Syrian refugees: What do we know?	Scandinavian journal of public health	48	7	677-687
Petrie	2018	Prevalence of PTSD and common mental disorders amongst	Social psychiatry and psychiatric epidemiology	53	9	897-909

		ambulance personnel: a systematic review and meta-analysis.				
Pollock	2017	Posttraumatic stress following spinal cord injury: a systematic review of risk and vulnerability factors.	Spinal cord	55	9	800-811
Pompili	2013	Posttraumatic stress disorder and suicide risk among veterans: a literature review.	The Journal of nervous and mental disease	201	9	802-812
Porter	2001	Forced displacement in Yugoslavia: a metaanalysis of psychological consequences and their moderators.	Journal of traumatic stress	14	4	817-834
Qiu	2021	Prevalence of post-traumatic stress symptoms among people influenced by coronavirus disease 2019 outbreak: A meta-analysis.	European psychiatry : the journal of the Association of European Psychiatrists	64	1	e30-e30
Rafiq	2018	The relationship between childhood adversities and dissociation in severe mental illness: a metaanalytic review.	Acta psychiatrica Scandinavica	138	6	509-525
Robertson	2010	Institutionally based health care workers' exposure to traumatogenic events: systematic review of PTSD presentation.	Journal of traumatic stress	23	3	417-420
Rodrigues	2017	The traumatic experience of first-episode psychosis: A systematic review and meta-analysis.	Schizophrenia research	189		27-36
Rubonis	1991	Psychological impairment in the wake of disaster: the disaster-psychopathology relationship.	Psychological bulletin	109	3	384-399
Rytwinski	2013	The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis.	Journal of traumatic stress	26	3	299-309
Sage	2018	Factors associated with Type II trauma in occupational groups working with traumatised children: a systematic review.	Journal of mental health (Abingdon, England)	27	5	457-467
Salehi	2021	The prevalence of post-traumatic stress disorder related symptoms in Coronavirus outbreaks: A systematic-review and meta-analysis.	Journal of affective disorders	282		527-538
Sherr	2011	HIV infection associated post-traumatic stress disorder and post-traumatic growth - A systematic review	Psychology, Health and Medicine	16	5	612-629
Slade	2021	A systematic review of clinical effectiveness of psychological interventions to reduce post traumatic stress symptoms following childbirth and a meta-synthesis of facilitators and barriers to uptake of psychological care.	Journal of affective disorders	281		678-694
Slewa-Younan	2015	A Systematic Review of Post-traumatic Stress Disorder and Depression Amongst Iraqi Refugees Located in Western Countries.	Journal of immigrant and minority health	17	4	1231-1239
Smid	2009	Delayed posttraumatic stress disorder: systematic review, meta-analysis, and meta-regression analysis of prospective studies.	The Journal of clinical psychiatry	70	11	1572-1582
Souza	2011	Posttraumatic stress disorder in peacekeepers: a meta-analysis.	The Journal of nervous and mental disease	199	5	309-312
Steel	2009	Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass	JAMA	302	5	537-549

		conflict and displacement: a systematic review and metaanalysis.				
Stoddard Jr.	2014	Outcomes of Traumatic Exposure	Child and Adolescent Psychiatric Clinics of North America	23	2	243-256
Tang	2017	A Meta-Analysis of Risk Factors for PostTraumatic Stress Disorder (PTSD) in Adults and Children after Earthquakes.	International journal of environmental research and public health	14	12	
Tang	2020	Global estimate of the prevalence of posttraumatic stress disorder among adults living with HIV: a systematic review and meta-analysis.	BMJ open	10	4	e032435e032435
Tay	2019	The culture, mental health and psychosocial wellbeing of Rohingya refugees: a systematic review.	Epidemiology and psychiatric sciences	28	5	489-494
Trickey	2012	A meta-analysis of risk factors for post-traumatic stress disorder in children and adolescents.	Clinical psychology review	32	2	122-138
Valentine	2018	A systematic review of social stress and mental health among transgender and gender nonconforming people in the United States.	Clinical psychology review	66		24-38
van den Berk-Clark	2017	Mental Health Help Seeking Among Traumatized Individuals: A Systematic Review of Studies Assessing the Role of Substance Use and Abuse.	Trauma, violence & abuse	18	1	106-116
van Warmerdam	2019	Prevalence of anxiety, depression, and posttraumatic stress disorder in parents of children with cancer: A meta-analysis.	Pediatric blood & cancer	66	6	e27677e27677
Vardaxi	2018	Life events in schizoaffective disorder: A systematic review.	Journal of affective disorders	227		563-570
Vasileva	2018	Attachment, Development, and Mental Health in Abused and Neglected Preschool Children in Foster Care: A Meta-Analysis	Trauma, Violence, and Abuse	19	4	443-458
Vilchinsky	2017	Cardiac-disease-induced PTSD (CDI-PTSD): A systematic review.	Clinical psychology review	55		92-106
Vindegaard	2020	COVID-19 pandemic and mental health consequences: Systematic review of the current evidence.	Brain, behavior, and immunity	89		531-542
Visser	2017	The course, prediction, and treatment of acute and posttraumatic stress in trauma patients: A systematic review.	The journal of trauma and acute care surgery	82	6	1158-1183
von Werthern	2018	The impact of immigration detention on mental health: a systematic review.	BMC psychiatry	18	1	382-382
Wang	2021	Prevalence and risk factors of posttraumatic stress disorder among Chinese shidu parents: A systemic review and meta-analysis.	Journal of affective disorders	282		1180-1186
Wilder Schaaf	2013	Anxiety, depression, and PTSD following cardiac arrest: a systematic review of the literature.	Resuscitation	84	7	873-877
Williamson	2018	Occupational moral injury and mental health: systematic review and meta-analysis.	The British journal of psychiatry : the journal of mental science	212	6	339-346
Woolf	2016	Early Traumatic Stress Responses in Parents Following a Serious Illness in Their Child: A Systematic Review.	Journal of clinical psychology in medical settings	23	1	53-66

Xiong	2020	Impact of COVID-19 pandemic on mental health in the general population: A systematic review.	Journal of affective disorders	277		55-64
Xue	2015	A meta-analysis of risk factors for combat-related PTSD among military personnel and veterans.	PloS one	10	3	e0120270e0120270
Yildiz	2017	The prevalence of posttraumatic stress disorder in pregnancy and after birth: A systematic review and meta-analysis.	Journal of affective disorders	208		634-645
Zaat	2018	Posttraumatic stress disorder related to postpartum haemorrhage: A systematic review.	European journal of obstetrics, gynecology, and reproductive biology	225		214-220