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REVIEW

Survival, Attachment, and Healing: An Evolutionary Lens on Interventions for Trauma-Related Dissociation

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Purpose: Dissociation is a necessary part of our threat response system, common to all animal species, normally temporarily activated under conditions of extreme or inescapable threat. Pathological dissociation, however, continues to occur after the initial threat has passed, in response to reminders or inaccessibility of safety and security. Present across the spectrum of psychiatric diagnoses, recurrent dissociative symptoms are linked to severe trauma exposure, insecure attachment, treatment non-response, and maladaptive coping behaviors such as substance use, suicidality, and self-harm. However, empirical studies testing treatments specific to dissociative processes remain scarce. This narrative review summarizes existing studies and provides theoretical, neurobiological, and evolutionary perspectives on dissociative processes and treatments for pathological dissociation.

Methods: A systematic search of five databases (MEDLINE, EMBASE, APA PsycINFO, CINAHL plus, Scopus) was conducted on April 13, 2023. Peer-reviewed clinical studies with adult participants, assessing intervention effects on dissociative symptoms, were included. Results were thematically analyzed and summarized.

Results: Sixty-nine studies were identified, mainly focused on posttraumatic stress disorder, trauma-exposed populations, and borderline personality disorder. Psychotherapy was studied in 72.5% of studies; other interventions included medications and neurostimulation. The majority reported positive outcomes, despite the heterogeneous spectrum of interventions. However, treatment of dissociative symptoms was the primary objective in only a minority.

Conclusion: Pathological dissociation is a complex phenomenon involving brain and body systems designed for perceiving and responding to severe threats, requiring an individualized approach. A literature is emerging regarding potentially evidence-based treatments to help those impacted by recurrent dissociative symptoms. When contextualized within a neurobiological and evolutionary perspective, these treatments can be understood as facilitating an internal and/or relational sense of safety, resulting in symptom reduction. Further studies are needed to explore effective treatments for dissociative symptoms.

Keywords: derealization, depersonalization, posttraumatic stress disorder, psychotherapy, psychopharmacology, transcranial magnetic stimulation

Introduction

Overview

For over 130 years, researchers and clinicians have explored the connection between trauma, dissociation, and mental health disorders.[1,2] Current research indicates that chronic dissociative symptoms are related to an interplay between genetic vulnerability, attachment disruptions, early life adversity and traumatic experience and are associated with significant mental health burden, including psychiatric comorbidity, disruptions in self-organization, emotional dysregulation, self-injurious behaviors, and suicide attempts.[2–10] Furthermore, dissociation is frequently associated with

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disturbances in cognitive, executive, and interpersonal function, which can adversely impact treatment.[11–13] Dissociation is a diagnostic feature of specific, often difficult-to-treat disorders associated with trauma, including dissociative disorders (DD), Borderline Personality Disorder (BPD), the dissociative subtype of Posttraumatic Stress Disorder (PTSD-DS), and complex PTSD (cPTSD).[5,14] In treatment, dissociation can hinder emotional engagement and learning;[11] however, few treatments exist that specifically focus on alleviating dissociative episodes. For these reasons, there continues to be intense interest in addressing the impact of dissociation.

This review has several aims: 1) to explore trauma-related dissociation through an evolutionary lens, as a neurobiologically driven survival response to severe threat, including relational disruption, 2) to summarize existing empirical studies on interventions impacting dissociation, focusing on depersonalization and derealization, and 3) to place these results within the context of clinical practice and relevance for future research.

A Brief History

Over the last century, dissociation has been categorized and understood as various states and processes, with ongoing debates as to what the term "dissociation" truly entails.[2] Normal and pathological, state versus trait, and drug-induced (eg, ketamine) dissociation are examples of such categories, each implying different mechanisms, duration, stability, and relationship to psychopathology. Dissociation is described as a disruption in the usual integration of mental processes, including consciousness, memory, emotions, identity, perception, motor control, body awareness, or behavior, with wide-ranging phenomenology.[2,14] For the purpose of this review, a useful distinction is one of normative (ie, non-pathological) versus pathological dissociation. Normative dissociation includes states like absorption, daydreaming, auto-pilot experiences, and hypnosis,[15] such as driving home and not remembering details of the journey. Alternatively, pathological dissociation is understood as a sequelae of traumatic or overwhelming experience. In this case, dissociation occurs recurrently long after the original trauma is over, in response to implicit or explicit reminders of those experiences.[6,8,9] Such states are accompanied by changes in brain neurochemistry, electricity, and activity patterns, distinct from those accompanying normative dissociation in neutral or safe situations, and serve to avoid the pain of fear and overwhelm.[6]

Understanding of trauma-related dissociation has significantly evolved since its recognition in the late 1800s. Janet's observations of individuals diagnosed with hysteria revealed that traumatic experiences could impact thoughts and behaviors, even if not consciously accessible.[2,16] For example, a sexual assault survivor may be unable to recall parts of the event, or may be numb to associated emotions and physical sensations. Influenced by this work, dissociation became historically viewed as a defense against intolerable affect or inner conflict.[1,2,14,16] Freud, for example, proposed that anxiety provoking material such as traumatic memories could be repressed, preventing conscious awareness.[2,16] Thus, 20th century theories of dissociation tended to focus on psychological processes.

Subsequent studies on early life stress and effects of psychological trauma clearly demonstrate, however, impacts on both brain and body. Pathological dissociation, intertwined with attachment and development, is associated with multiple structural and functional brain changes.[1,6,7,9,10,17] There is a particular association with prolonged inescapable threat, such as captivity, prolonged torture, child maltreatment or chronic parental misattunement or inconsistency.[2,6–9] Such experiences trigger an intense, whole-body survival response, coordinated by the brainstem, involving cognitive, limbic, perceptual, pain, motoric, and hormonal systems that work together to alter information processing and consciousness.[6,17] When experienced repeatedly during critical periods of brain development, the induced altered states of consciousness disrupt normal development of memory, cognition, and learning processes, emotional regulation, executive functioning, personality and identity formation, which increases risk for later psychiatric disorders, including PTSD, BPD, and DD.[1,2,6,7,10,18,19]

Categorizations of Trauma-Related Dissociation

Given the multiform nature of dissociation, multiple clinical classifications and theories on traumatic dissociation exist to aid clinicians. Common categorizations include primary, secondary, and tertiary dissociation,[20] state and trait dissociation,[21] functional and multiplicity dissociation,[22] structural dissociation,[23] and phenotypical dissociation.[24] These describe distinct but overlapping patterns of symptoms, levels of functioning, and comorbid psychopathology, with more severe forms often encompassing symptoms of milder categories. While a full exposition of these theories is

beyond the scope of this review, some general principles are relevant, including differentiating between state-related changes and more complex patterns involving identity self-states.

State dissociation represents transiently altered states of consciousness in response to stress or trauma, occurring during and immediately after a stressor or traumatic reminder. This can be classified as either primary or secondary dissociation. Primary dissociation refers to distressing trauma memory content intruding into conscious awareness, often in visual, olfactory, auditory, or kinesthetic sensory form, such as re-experiencing symptoms of PTSD.[20,25] Secondary dissociation, on the other hand, involves distancing from traumatic re-experiencing. This may include mental "leaving" of the body, accompanied by decreased arousal and awareness.[20] Subjectively, this can be experienced as disconnection, physical or emotional numbing, altered senses, or zoning out. Depersonalization, marked by a sense of separation from oneself, and derealization, characterized by a sense of detachment from the external world, are frequently encountered, transdiagnostic secondary dissociative symptoms, occurring in the peritraumatic context or in a range of psychiatric diagnoses, including anxiety disorders, trauma-related disorders such as PTSD and dissociative disorders.[2,6,14]

Chronic secondary dissociative symptoms are generally considered more severe than primary dissociation. Like more severe forms, they are linked to pervasive threats during childhood and chronic or repeated inescapable threats such as captivity or domestic violence.[6] Secondary dissociation has been conceptualized as a state of helplessness, wherein

> The individual has seemingly concluded that escape is extremely unlikely, and thus has made no efforts toward that end [and] the mind reflexively relinquishes executive control to a lower-order survival mechanism.

[20] Secondary dissociation is a common feature of cPTSD, PTSD-DS, and BPD and frequently associated with heightened suicidality, non-suicidal self-injury, and other potentially destructive coping behaviors.[1,2]

The most severe forms of dissociation include Unspecified or Other Specified Dissociative Disorder (U/OSDD) or Dissociative Identity Disorder (DID), as described in trait, tertiary, structural and multiplicity dissociation models.[2,20–24] This is generally believed to result from severe, recurrent early childhood harm, and reflect the impact of chronic and unrelenting fear in the absence of consistent parental care.[2,8] Personality development is disrupted, evolving into multiple ego or self-states with distinct cognitive, affective, and behavioral patterns, often accompanied by partial or full amnesia in between states.[25] This category is associated with profound changes in nervous system development and function, serious functional impairment due to amnesia and altered consciousness, emotion dysregulation, and a confusing array of symptoms disconnected from awareness of trauma cues.[12,22,23] It also carries a high risk of suicidality, self-harm, and psychiatric comorbidity.[2,12,14]

While trauma-related dissociation is a complex topic, basic dissociative processes are firmly rooted in our biology. In the next sections, dissociation will be discussed from an evolutionary lens, highlighting its role in our threat response system, intersections with attachment and neurobiology, and implications for clinical care.

An Evolutionary Perspective on Trauma-Related Dissociation

Understanding the close connection between dissociation and threat responses requires an evolutionary perspective dating back to the emergence of predator–prey relationships around 500 million years ago.[26–28] In the beginning, primitive life forms had two survival mechanisms—movement and immobility—for pursuing and consuming other creatures for sustenance, fleeing from or confronting predators, or freezing in place when escape was impossible (ie, fight, flight or freeze).[6,26] From these origins, every organism with a central nervous system retained and elaborated upon these highly conserved, instinctual defensive responses to prolong existence and ensure the continuation of their species. Mediated by limbic, brainstem and physiological stress response structures, such as the amygdala, hypothalamic-pituitary -adrenal axis, and autonomic nervous system, they involve fixed action patterns and release of neurotransmitters, hormones, and pain and inflammatory mediators.[6,29]

Freeze responses, a form of dissociation, occur when stillness, disconnection, or energy conservation is perceived as the most effective survival strategy, varying from tonic immobility to vasovagal collapse. Tonic immobility involves both sympathetic and parasympathetic arousal, immobility and opioid-mediated analgesia while maintaining muscle tone.[6,29] With greater threat, there is progressive loss of sympathetic tone, and the dorsal vagus predominates, with decreased heart rate, respiration, and muscle tone, altered consciousness, and additional release of opioids.[6,29] In the animal world,

this is analogous to the opossum "playing dead" in response to imminent threat. These "shutdown" states are theorized to conserve energy, induce anesthesia, and potentially diminish predatory instincts elicited by movement, increasing likelihood of survival if a predator is distracted or loses interest. Thus, it is the defense of last resort during inescapable threat, employed when other options appear futile.[29]

Humans possess a complex nervous system that models, predicts, avoids, and responds to potential threat, building upon these active (eg, fight or flight) and inactive (eg, immobility or "freeze") animal defensive responses.[29] Depersonalization and derealization, for example, are considered to be inactive defenses akin to such freeze responses; associated altered states of consciousness are thought to be a product of altered brain function and the impact of associated opioid release.[6] The type and intensity of response exist on a continuum, depending on the degree, imminence, and controllability or escapability of the threat, often related to physical capacities and proximity to safety. These involve multiple brain circuits, coordinated by the brainstem periaqueductal gray, and modified by the prefrontal and other cortical inputs.[29] Imagination, mental simulation, predictive coding, and associated problem solving rely on complex cortical brain systems that integrate past and present sensory information. Extreme threat induces an intense response that inhibits the cortex and elicits fixed, primal emotional and behavioral responses (see Mobbs et al for a review).[29]

Humans also elaborated upon animal social defenses, including attachment and social learning, enabling care and protection of offspring and transmission of advantageous adaptations.[30] Social defenses involved multiple modifications to the nervous system, including prefrontal, limbic and brainstem areas involved in mammalian sexuality and behavioral flexibility, and development of the ventral branch of the vagus nerve, allowing prolonged close proximity needed for social engagement, play, and nurturing young.[19,31–33] This includes the attachment cry, which elicits a vigorous visceral urge to take immediate action, ensuring proximity for physical protection and assistance in ameliorating unmet needs, important for human infants given their prolonged dependence and defenselessness.[19,29,31,34,35] This response persists throughout life, induced by separation or loss, prompting caretaking and other relational responses.[30,34,35] Additionally, adaptations to oxytocin and vasopressin systems also motivate affiliative-nurturing behavior and aggressive-defensive behavior to maintain attachment bonds; these connect social information to pain, reward, anxiety and homeostatic mechanisms, including opioids, dopamine, serotonin, and stress responses.[19,36]

In humans, social evolution, in the form of group protection and co-regulation, became our primary strategy for both survival and well-being, likely due to our particular physical vulnerabilities to predators and environmental dangers in early hunter-scavenger-gatherer environments.[29,37] This evolutionary pressure to intensify social bonding capacities needed for long-term social protection likely promoted behaviors and adaptations to understand others, manage within-group aggression and keep individuals in the good graces of other group members.[29,37–39] Strong connections, both within and beyond close attachment relationships, facilitated the social and cultural transmission of these and other adaptive behaviors.[30] Moreover, because humans can vividly remember danger and mentally time travel, evoking strong stress responses, seeking reassurance from others likely buffered such stresses.[7,19,29] Therefore, human neurobiological systems are oriented towards seeking others not only for life-threatening situations but also for regulation of distress.

Securefulness likely evolved as a consequence of this social evolution.[40] Arising from neurobiological processes responsible for awareness, self-regulation, and co-regulation, securefulness refers to prolonged states of attuned mindfulness within attachment relationships.[40] This allows caregivers to anticipate and sensitively respond to infants and children, not only ensuring survival but also facilitating the child's capacity to regulate distress, experience a sense of safety and care, and understand self and others, important for cooperative relationships.[7–9,19,40,41] Secureful attachment includes bodily experiences of play, movement (eg, rocking), soft vocalizations and eye gaze, and safe, appropriate touch; this sensory input facilitates development of subcortical pathways necessary for integration of sensory and emotional information.[7,18,19,42] Affective touch is also calming and elicits oxytocin, enhancing bonding, relieving pain, and influencing development of associated neurohormonal systems, with potentially epigenetic and intergenerational consequences.[7,19,43–45] In summary, early securefulness experiences are the building blocks of a capable, valued, and connected sense of self within the world.[8,9,18,19] In many ways, securefulness is the opposite of dissociation,[40,46] a concept further explored below.

Dissociation as a Response to Primal Isolation Anguish

Just as attachment and belonging are vital to human well-being, social detachment and isolation are profoundly threatening. In this paper, we use the term primal isolation anguish to describe the neurobiological state of aloneness and terror that might accompany an infant without attachment, defenseless against predation or starvation. This state of separation involves the same neural wiring as pain, "akin to opioid withdrawal";[45] social contact eases this pain through endorphin or oxytocin release, depending on context.[7,45,47] This applies to adults as much as infants, especially in hunter-scavenger-gatherer societies, where disconnect from the tribe meant almost certain death. Intense states of primal anguish, therefore, often evoke a sense of helplessness, hopelessness, or loss of control in humans, activated not only by intense threat or social isolation but also intense physical or relational pain or entrapment.[7,9,45,47] We propose that this neurobiological state registers biologically as a life threat and is deeply connected with the phenomenon of dissociation.

In the evolutionary context, dissociation offers the ultimate escape for an infant or child in primal anguish. Ill-equipped to face a life threatening situation alone, a serious threat prompts a robust, all-encompassing attachment cry.[31,34,35] If help is not forthcoming, dissociation is the only remaining survival response; it detaches the child from helpless terror[6,8,9,19,29] Empirical research supports this, suggesting dissociation is employed as a coping mechanism when infants are left alone or are exposed to harm.[8,9] Studies also confirm a strong association between early life abuse, neglect, and trauma, as well as more subtle attachment disruptions like emotional unavailability or repetitive contradictory, inconsistent or role reversal behaviors in parenting, thus implicating repeated neurobiological states of primal anguish in the development of dissociative symptoms.[8,9,19]

Even when dissociation becomes a repetitive response to disrupted attachment, the drive for attachment remains. Intense threat elicits a painful and inflammatory stress response that activates attachment needs, prompting relationship seeking behaviors for regulation.[19,29,31,34,35] Securely attached individuals can seek support, or use internal resources to cope. However, if attachment is disrupted or pain is overwhelming, especially in situations of isolation, dissociation can occur. Severe childhood neglect or abuse forces the developing brain to mature under neurohormonal conditions of chronic terror and insecurity, with profound and often long-term impacts on brain function,[10,18] including right-brain cognition related to processing faces and social cues.[48] Maintaining connection with the source of physical danger also necessitates suppression of natural, active defense responses, and awareness of certain experiences.[8,9,19,49] This can create cycles where attempts to communicate distress are not met and there is no regulatory outlet, prompting dissociation.[8,9] A child who is a victim of sexual abuse by their parent, for instance, may alternate between dissociation induced by terror and moments of connection that ensure continuous provision of care, nourishment, and shelter. After repeated failed attempts at connection or repeated abuse, an individual may learn to avoid others altogether or incorporate the experiences as evidence of not being worthy of care, creating trauma-related states of shame.[49] Such shame is itself associated with inflammation, helplessness, withdrawal, depressive and dissociative symptoms, and altered information processing.[49–54] Thus, dissociation can become the default, or there may be oscillation between states of feeling out of control and states of feeling disconnected, robotic or unalive.

Neurobiology of Dissociation

Brain changes during dissociation reflect its function to reduce awareness and protect against the psychological and neurophysiological overwhelm and anguish that accompanies intense threat. Trauma-related dissociation occurs when this response persists long after the original threat is over, when reminders reactivate pathogenic memories storing intense trauma-related content. Sensory and emotional processing, the capacity to register, organize, and modulate incoming sensory and affective information, integration capacities, and brainstem areas modulating arousal and movement are key.[1,6,10,18] Studies demonstrate altered activity or structure of multiple areas involved in perceiving and processing internal and external sensations (ie, sensorimotor information), pain, and emotions, memory, and awareness, such as the hippocampus, amygdala, thalamus, insula, anterior cingulate cortex, prefrontal cortex (PFC), basal ganglia and posterior association areas.[1,6,18] The PFC and cingulate cortex become hyperactivated, preserving cognitive functions and overregulating the amygdala, insula, and periaqueductal gray (PAG), components of the salience network regulating attention, importance assigned to stimuli, and functioning of other networks.[1,6,18,55] The brainstem coordinates release of opioids, anesthetizing pain and altering consciousness, and inhibits motor responses.[6,29] Therefore, while the body

continues to experience the physiological impact of stress and anguish, the mind's awareness is blunted. While this may preserve global brain functioning, the emotional and sensory "shutdown" suppresses perception of and appropriate responses to safety and danger. Patients may appear passive or inattentive, or report symptoms of numbing, hypoarousal, or paralysis.[2,6]

Although initially adaptive, these states or traits have long-term functional consequences, as whole-brain integration of multisensory data is needed for higher-order brain functions, including social capacities.[7,18] Widespread brain functional hyperconnectivity has been reported in those with chronic dissociative symptoms, as well as altered connectivity in the Default Mode Network (DMN), frontoparietal control networks, networks related to sensorimotor processing, and areas involved in arousal, consciousness, attention, awareness, proprioception and movement.[1,18,56] Epigenetic mechanisms may also be impacted, including altered oxytocin and attachment reward responses.[1,7,19] Given the involvement of the DMN, involved in self-referential processing, it is not surprising that sufferers frequently report altered sense of self and relationship to others and the world.[7,10,19,55] Repeated states of clouded consciousness and variable degrees of sensory and affective information loss can lead to challenges related to memory, learning, and discontinuous personal narratives, contributing to a fragmented sense of self.[19] The following section describes how these early adaptations can become maladaptive patterns in the context of psychotherapy, impairing therapeutic processes.

Dissociation in the Context of Psychotherapy

Engaging in psychotherapy requires the capacity to tolerate sensory and emotional experiences within a safe enough relationship. Individuals with chronic dissociation often struggle to feel safe, especially in relationships, making psychotherapy challenging or even terrifying. Positive and attuned interactions with therapists may evoke feelings of fear, shame, primal anguish or grief, as individuals become aware of painful past experiences. Factors like insecure attachment, shame, amnesia for events, and fear of authenticity and vulnerability can hinder engagement in psychotherapy.[49,52,57] Relatively mild relational misattunements, symbolic reminders of abandonment, or states of entrapment or distress activated by internal conflict can serve as trauma cues, evoking viscerally intense threat responses. These issues may manifest in various ways, including missed appointments, distress, excessive compliance, passivity, and unexpected reactions in the therapeutic relationship.[57] Additionally, it may be difficult to recognize needs, goals, values, or even the extent of their own fear. Further, dissociation-related memory impairment and sense of incapacity can make tasks like homework challenging.

The fawning response may also impact psychotherapeutic processes and impair recognition of dissociation. When humans dissociate, they often appear alive rather than dead, as attachment needs are activated by perceived threat, stirring security seeking from others.[8,9,19,29] This is often expressed as a fawning response designed to maintain connection, accepting whatever is available within the relationship. In this state, patients may appear "normal", calm, agreeable, and quiet. By mimicking attachment, they may submit to actions they believe will lead to care or connection. This complicates authentic interaction and ability to recognize wants, feelings, and thoughts – essential for establishing clear boundaries. Fawning may therefore enable people to remain attached to unhealthy or abusive relationships, saving them from the terror of aloneness or primal anguish. This can go unnoticed and people-pleasing behavior, unconsciously performed to avoid relational distress, may be misconstrued as authentic, slowing therapeutic progress.

Further, therapy can break down when stress triggers intense fight or flight responses, threatening the therapeutic relationship. When overwhelmed, human capacities such as empathy, attunement, intuition, and self and other regulation can falter, and we may revert to animal defenses, sabotaging the essential need for safe human connection.[19] In these moments, relying on social connections for co-regulation, including within therapy, becomes even more crucial. However, persistent trauma-induced nervous system dysregulation perpetuates a sense of enduring threat,[5] impeding access to calmer states needed for attunement and development of healthy relationships fundamental for healing.[33]

Trauma-focused psychotherapies may be particularly challenging for dissociative individuals, as they often require direct attention to the dissociated threatening experiences. Due to experiencing recurrent, frightening states of overwhelm, emotion itself may become a trauma cue, resulting in exquisite avoidance of emotion.[58] Dissociation can block access to and therefore processing of the affectively charged trauma memory network emphasized in trauma therapies.[59] Since we learn to self-regulate within relationships with attuned caregivers, childhood trauma survivors face a dual challenge: inability to access necessary content and difficulty utilizing self or co-regulation to facilitate trauma

processing.[7,10,18,19] Further, dissociation-related amnesia and attentional changes make it harder to acquire skills that would reduce reliance on dissociation.[11,13]

Given the clear importance of dissociation for clinical care, an understanding of available interventions is crucial for improving outcomes. This review examines both psychological and biological interventions for dissociative symptoms such as derealization and depersonalization; further, results will be discussed in light of the previously presented evolutionary perspective, including the view that interventions may act by enhancing an inner sense of safety.

Methods

While this is a narrative review, we used a systematic search for literature on treatment strategies for dissociative episodes. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines for scoping reviews process to enhance rigor, embedding results within a conceptual, narrative frame informed by clinical experience.[60] MEDLINE (Ovid Interface 1946–2023), EMBASE (Ovid Interface 1974–2023), APA PsycINFO (Ovid Interface 1806–2023), CINAHL plus with Full Text (EBSCOhost Interface 1937–2023), and Scopus (1970–2023) databases were searched on April 13, 2023, for published peer-reviewed studies. The search strategy combined subject headings and keywords for three main concepts: dissociation or dissociative episodes, treatments, and mental disorders frequently comorbid with dissociation (see Supplementary Materials). Peer-reviewed clinical studies were included if they assessed the effect of a treatment on dissociative episodes in adults and were written in English or French. A dissociative episode was defined as the presence of functional, stress or trauma-related dissociation (eg, depersonalization, derealization) that was not induced by a drug, medical condition, or intervention (eg, hypnosis). We explicitly excluded tertiary dissociation, such as DID, as this represents an exceptionally complex disorder for which treatment is highly individualized, often long term, and typically carried out by those with special training and experience. Therefore, most studies are not designed for this population. Further, it would be challenging to integrate studies on tertiary dissociation and still present a coherent synthesis of these complexities within the space available.

The research team met regularly to ensure quality data screening, selection, extraction, and synthesis procedures. Covidence software (https://www.covidence.org) was used to remove duplicates and facilitate article screening and full-text review. The team created a data extraction form using Google Forms, which included: population characteristics (age, sex and gender, ethnicity, country, trauma type, dissociation characteristics), study design, intervention, dissociation measurement instruments, sample size, main results, dropout rate, and study limitations. Each article was reviewed independently; however, the extracted information was verified by a senior author and collated. A thematic qualitative analysis followed.[61] During this process, key references known to authors with subject matter expertise were considered, with iterative literature searches as needed during manuscript development.

Results

Study and Sample Characteristics

Our search yielded 4873 articles; after duplicate removal, 2838 articles were screened, and 69 met eligibility criteria for inclusion (Tables 1–3, Figure 1). These studies included a total of 3710 participants, mostly females; no studies reported on gender identity. Most studies were conducted in either Europe (n = 37; 53.6%) or the United States (n = 28; 40.6%), and in the civilian (n = 66; 95.0%) population. Most studies were randomized controlled trials (RCT; n = 33; 47.8%) or a pre/post study design (n = 25; 36.2%), typically with 60 or fewer participants (n = 51; 73.9%). All were published between 1990 and 2023, approximately half since 2014. The impact of treatment on dissociative symptoms was the primary aim of only 15 (21.7%) studies, mostly within the context of Depersonalization Disorder (DPD). Most studies focused on either PTSD, trauma-exposed populations (n = 38; 55.1%) or BPD (n = 10; 14.5%), with dissociative symptoms as a secondary outcome. DPD studies more often focused on medications or repetitive Transcranial Magnetic Stimulation (rTMS), in contrast to PTSD and BPD studies, which included both psychotherapy and medications. Dissociation was usually measured using validated, dissociation-specific rating scales (n = 52; 75.4%), most often the Dissociative Experiences Scale (DES; n = 37; 53.6%) or Cambridge Depersonalization Scale (CDS; n = 11; 15.9%) (Table 4).

Table 1 Psychotherapy Intervention Studies and Impact on Dissociation

Author, Year (Country)	Study Design	Study Objectives	Population	Sample Size (n); Mean Age [SD or Range]	Intervention	Control	Impact on Dissociation	Measure Used
MINDFULNESS AND BODY-BASED THERAPIES								
Millman et al, 2023[62] (UK)	Pre/post design	Effect on D/D, interoceptive awareness, mindfulness, and body vigilance	DDD; recruited worldwide	n=60 (DDD group=31); 33.0 [12.1]	Twelve weeks of daily online BA/DE vs DE alone	Healthy controls	Improved in DDD groups	*CDS
Nidich et al, 2016[63] (USA)	RCT	Effect on perceived stress, trauma related anxiety, depression, sleep, and dissociation symptoms	Male prison inmates	n=181; TM group= 28.6 [7.2]	Five sessions of group TM plus practice	TAU	Improved	Modified TSC
Price, 2005[64] (USA)	RCT	Effect on PTSD symptoms, dissociation, psychological distress, physical symptoms, and body awareness	Women with CSA in therapy	n=24; Median age= 41.0 [26–56]	Eight weeks MABT	Massage +psychotherapy	Improved	*DES
Price, 2006[65] (USA)	RCT; Mixed Methods	Effect on PTSD symptoms, dissociation, psychological distress, and physical symptoms	Women with CSA in therapy	n=8; 38.0 [28–52]	Eight weeks MABT	Waitlist	No change	*DES
Price et al, 2012[66] (USA)	RCT	Effect on symptoms of SUD, PTSD, eating disorder, distress, physical symptoms, dissociation, emotion regulation, bodily connection, and awareness	Recently hospitalized women with SUD	n=46; 39.0 [19–58]	Eight weeks MABT + TAU	TAU: 12-week CBT approach	Improved	*DES
Price et al, 2017[67] (USA)	Pre/post design	Effect on PTSD and dissociative symptoms	Women with chronic PTSD in therapy	n=9; 40.7 [25–55]	Twenty, twice weekly yoga practice	None	Improved	*DES
Schoenberg et al, 2012[68] (UK)	RCT	Effect on DPD and associated depression symptoms	DPD diagnosis and CDS score of >70	n=32; Biofeedback= 36.8 [7.7]	Eight, 20min biofeedback sessions over four weeks	Sham	No change	*DES *CDS
Willy-Gravley et al, 2021[69] (USA)	RCT	Effect on substance relapse, body awareness, dissociation, and emotion regulation	Incarcerated women with substance abuse history	n=114; NR	Six weeks of twice weekly EMBER yoga	Therapeutic Community	Improved	*SBC
CBT, SKILLS-BASED OR PSYCHOEDUCATION (PRESENT-FOCUSED)								
Cognitive behavioral based interventions								
Davis et al, 2011[70] (USA)	RCT	Effect on chronic nightmares and associated symptoms	Trauma-exposed individuals with nightmares	n=47; 47 [38.5]	Two hours per week for three weeks of ERRT	Waitlist	Improved as a function of time, not ERRT	TSI-Dissociation subscale

Guillen Botella et al, 2021[71] (Spain)	NRCT	Effect on symptoms of BPD, depression, impulsivity, dissociation, anxiety, suicide risk, state-trait anger expression, emotion regulation, resilience, quality of life, and reasons for living	Inpatients with BPD	n=72; 32.1 [8.8]	Manualized DBT vs STEPPS	None	Equally improved in DBT and STEPPS	*DES
Hunter et al, 2005[72] (UK)	Pre/post design	Effect on dissociation, depression, anxiety, and function	DPD outpatients	n=21; 38.0 [12.0]	Four to twelve weeks of CBT	None	Improved	*CDS-S *DES
Klein et al, 2010[73] (Australia)	Pre/post design	Effect on symptoms of PTSD, depression, anxiety, quality of life, dissociation, anger, thought control, treatment credibility and satisfaction, and therapeutic alliance	PTSD	n=22; M= 51.0 [11.0], F= 40.6 [11.7]	Ten weeks of online CBT with asynchronous therapist support	None	Improved	*DES
Sachse et al, 2011[74] (UK)	Pre/post design	Effect on mindfulness, and symptoms of anxiety, depression, dissociation, and impulsiveness	BPD at a specialist clinic	n=22; 39.0 [7.5]	Eight week MBCT group	None	No change	*DES
Schweden et al, 2016[75] (Germany)	RCT	Effect on depersonalization symptoms during an acute social stressor	Social Anxiety Disorder	n=92; CBT= 24.6 [5.2]	Up to 25 CBT sessions	Waitlist and healthy controls	Improved	*CDS
Schweden et al, 2020[76] (Germany)	RCT	Effect on depersonalization in the context of performance anxiety; changes in trait test anxiety, emotion regulation, and depressive symptoms	University students with high levels of test anxiety	n=49; CBT= 26.5 [8.0]	One 4.5 hour group CBT session	Waitlist	Improved	*CDS-S
Skills or psychoeducational interventions								
Karatzias et al, 2016[77] (Scotland)	Case series	Effect on subjective well-being, mental health symptoms, function, and PTSD and dissociative symptoms	Women with interpersonal trauma	n=71; 40.4 [10.6]	Eighteen TREM group sessions	None	Improved	*DES
Lubin et al, 1998[78] (USA)	Pre/post design	Effect on PTSD, dissociation, depression, and other general psychiatric symptoms	Women victims/ witnesses of serious trauma	n=29; 41.5 [10.5]	Sixteen week Interactional Psychoeducation Group Therapy	None	No change	*DES
Najavits et al, 2013[79] (USA and Canada)	Pre/post design	Effect on PTSD and pathological gambling, and symptoms of anxiety, depression, somatization, substance use disorders, coping skills, and function	PTSD + pathological gambling	n=7; 45.9 [10.6]	Six months of weekly SS (max 25 sessions)	None	Improved dissociation and somatization	TSC-40 BSI-18
Najavits & Johnson et al, 2014[80] (USA)	Pre/post design	Effect on psychiatric symptoms including trauma, coping, aggressive and suicidal behaviors	PTSD + SUD; victims of domestic violence or sexual assault	n=7; 45.1 [10.5]	Seventeen weeks of the Creating Change program	None	Improved	TSC-40
Protopopescu et al, 2022[81] (Canada)	RCT	Effect on cognitive functioning, PTSD, anxiety, and depression, dissociation, and emotion regulation	Current or former military or public safety personnel with PTSD or trauma	n=40; 44.25 [7.5]	Nine weeks of group GMT	TAU	Improved	*MDI

(*Continued*)

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Table 1 (Continued).

Author, Year (Country)	Study Design	Study Objectives	Population	Sample Size (n); Mean Age [SD or Range]	Intervention	Control	Impact on Dissociation	Measure Used
Roe-Sepowitz et al, 2014[82] (USA)	Pre/post design	Effect on trauma symptoms	Incarcerated women with trauma	n=320; 33.8 [9.8]	Twelve weeks of a psychoeducation group	None	Improved	TSI
Rudstam et al, 2022[83] (Sweden)	RCT	Effect on trauma symptoms and associated anxiety, distress, depression, dissociation, and function	Women with PTSD or CPTSD	n=45; 43.7 [9.9]	Twelve weeks of group music and imagery	Waitlist control	No change	*SDQ-5 *DES-Taxon *DES
Zlotnick et al, 1997[84] (USA)	RCT	Effect on PTSD and trauma symptoms; dissociation	Women with PTSD + CSA	n=48; 39.0 [9.6]	Fifteen weeks of affect management group	Waitlist control	Improved	*DES
TRAUMA-FOCUSED THERAPIES (INCLUDES MEMORY PROCESSING)								
Trauma focused psychotherapies								
Abramowitz et al, 2010[85] (Israel)	Pre/Post design	Effect on PTSD and associated depressive and dissociative symptoms	Military members with PTSD symptoms	n=37; 41.2 [12.2]	Six weekly hypnotherapeutic olfactory conditioning sessions	None	Improved	*DES
Carletto et al, 2018[86] (Italy)	Pre/post design	Effect on relapse and symptoms of PTSD, anxiety, depression, and dissociation	SUD	n=40; EMDR= 32.0 [8]	Twenty-four weeks of EMDR	TAU: addiction specialist, medication	Improved	*DES
Covers et al, 2021[87] (Netherlands)	RCT	Effect on PTSD and associated symptoms of anxiety, depression, and dissociation	PTSD symptoms, recent rape	n=57; 25.8 [8.2]	Two EMDR sessions (3.5 hours total)	TAU	Improved	*DSS
Gonzalez-Vazquez et al, 2018[88] (Spain)	Case-control	Effect on dissociation, general health, and well being	Severe traumatization	n=31; 28.0 [20–59]	Group bilateral stimulation (EMDR-based intervention)	Psychoeducation	No change	*DES
Mauritz et al, 2022[89] (Netherlands)	Pre/post design	Effect on symptoms of PTSD, dissociation, psychiatric symptoms, care needs, quality of life, global functioning, and care consumption	PTSD + severe mental illness and interpersonal trauma	n=23; 49.9 [9.8]	Weekly individual NET (five-sixteen sessions)	None	Improved	*DES

Pabst et al, 2014[90] (Germany)	RCT	Effect on BPD, PTSD, depression, and dissociation symptoms	Women with BPD + chronic PTSD due to rape	n=22; NET= 30.4 [8.6]	Individual weekly or biweekly NET sessions	TAU by BPD experts	Improved	*DES
Rothbaum et al, 2005[91] (USA)	RCT	Effect on PTSD and associated mood, anxiety, SUD, and dissociation symptoms	Women with Chronic PTSD due to rape	n=74; 33.8 [11.0]	Nine bi-weekly PE vs EMDR sessions	Waitlist Control	Improved in PE and EMDR	*DES-II
Combination trauma-focused interventions								
Beck et al, 2021[92] (Denmark)	RCT	Effect on trauma symptoms, well-being, somatoform and psychoform dissociation, and attachment	Refugees with personality change after catastrophic experiences or PTSD	n=74; 42.0 [NR]	Sixteen week trauma focused guided music and imagery treatment	TAU: PTSD specific individual psychotherapy	Improved on DSS-20 but not SDQ-20	*SDQ-20*DSS-20
Bowen et al, 2010[93] (Australia)	Pre/post design	Efficacy of disclosure in therapy for reducing anxiety, depression, and frequency and severity of dissociation.	Male military veterans with PTSD enrolled in a PTSD program	n=72; 51.0 [10.4]	PTSD program, encouraged to disclose trauma in group and individual therapy (twenty-four days).	None; comparing high to low trauma disclosure	Improved; disclosures > non-disclosures	CAPS dissociation items
Classen et al, 2001[94] (USA)	RCT	Effect on trauma-related symptoms and associated anxiety, depression, dissociation, sleep, and sexual and interpersonal problems	Women with PTSD due to CSA	n=58; 38.4 [11.7]	Twenty-four weekly trauma focused group vs present focused group	Waitlist	Improved	TSC-40
Cloitre et al, 2012[59] (USA)	RCT	Impact of sequential treatment on dissociation and PTSD symptoms	Women with PTSD related to CSA or physical abuse	n=104; 36.3 [9.7]	Sixteen weeks of either STAIR+ NST, STAIR +SC, or SC/NST	Active control	Improved in all groups; STAIR/ NST better for high dissociation group	TSI Dissociation subscale
Görg et al, 2016[95] (Germany)	Pre/post design; mixed methods	Effect on state dissociation and trauma specific emotional experiences	PTSD diagnosis and enrolled in the DBT-PTSD program	n=26; 42.2 [9.4]	Twelve weeks residential DBT-PTSD program plus MORPHEUS two to five times per week.	None	Improved	DSS-4
Harned et al, 2014[96] (USA)	RCT	Effect on PTSD symptoms, NSSI, trauma related guilt cognitions, and symptoms of dissociation, anxiety, and depression	Suicidal and self-injuring women with BPD + PTSD	n=26; 32.6 [12.0]	One year of DBT+PE	DBT without PE	Improved; DBT-PE > DBT	*DES Taxon

(*Continued*)

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Table 1 (Continued).

Author, Year (Country)	Study Design	Study Objectives	Population	Sample Size (n); Mean Age [SD or Range]	Intervention	Control	Impact on Dissociation	Measure Used
Kleindienst et al, 2021[97] (Germany)	RCT	Effect on PTSD and BPD symptoms, NSSI, high-risk behaviors, suicide attempts, dissociative and depressive symptoms, and function	Women with BPD + PTSD	n=93; 33.5 [10.6]	Forty-five weekly sessions of DBT-PTSD vs CPT followed by three booster sessions	Active comparator	Improved in both groups	*DSS
McDonagh et al, 2005[98] (USA)	RCT	Effect on PTSD and associated anxiety, depression, dissociation, hostility, anger symptoms, and quality of life	Women with PTSD + CSA	n=74; CBT=39.8 [9.9], PCT= 39.6 [9.6]	Fourteen weekly sessions of CBT+PE+CR vs PCT	Waitlist	No change in either group	*DES
Raabe et al, 2022[99] (Netherlands)	RCT	Effect on PTSD symptoms and co-occurring depression, dissociation, emotion regulation, shame/guilt, and interpersonal problems	PTSD due to multiple events of childhood abuse (CA-PTSD)	n=61; 35.9 [10.7]	Sixteen trauma ImRs sessions vs 8 STAIR sessions followed by sixteen ImRs	Waitlist control	Improved; ImRs=ImRs/ STAIR	*DIS-Q
Steil et al, 2018[100] (Germany)	Pre/post design	Effect on PTSD, BPD, depression, trauma related symptoms, and behavioral dyscontrol difficulties	Women with PTSD related to CSA and ≥ 4 BPD symptoms	n=21; 34.0 [9.3]	Twenty-four weekly DBT-PTSD sessions	None	Improved	*DES
Intensive trauma programs								
Steele et al, 2018[101] (USA)	Pre/post design	Effect on PTSD, dissociation, depression symptoms, moral injury, and relational attachment	Military members with PTSD	n=85; 42.9 [11.6]	Seven days (Ten EMDR sessions +equine therapy, yoga, and narrative writing)	None	Improved	*DES
Steuwe et al, 2016[102] (Germany)	Pre/post design	Effect on symptoms of PTSD, BPD, depression, dissociation, and quality of life	Specialty ward inpatients with BPD	n=11; 34.9 [9.7]	Twice weekly NET (four-fifteen sessions); art or music, body therapy and movement	None	Improved	*DES
Zoet et al, 2018[103] (Netherlands)	Pre/post design	Determine the impact of dissociative subtype of PTSD on treatment response	PTSD	n=168; PTSD-DS= 36.1 [11.3], PTSD= 38.8 [10.8]	Eight days of EMDR + PE, physical activity, and group psycho- education	None	Improved	CAPS
Zoet et al, 2021[104] (Netherlands)	Pre/post design	Effect of treatment on PTSD and somatoform dissociative symptoms	PTSD	n=219; 39.7 [12.3]	Eight days of EMDR + PE, physical activity, and group psycho- education	None	Improved	*SDQ-20 *SDQ-5
OTHER PSYCHOTHERAPEUTIC INTERVENTIONS								
Damsa et al, 2014[105] (Switzerland)	Pre/post design	Effect on lipid levels in DD as primary focus; effect on general psychiatric symptoms, dissociation, depression, and alliance	DD diagnosis on SCID-IV and DES≥30	n=32; 38.1 [9.8]	Eight weekly psychodynamic therapy sessions	None	Improved	*DES

Gregory et al, 2008[106] (USA)	RCT	Effect on BPD and SUD symptoms, parasuicidal behavior, depression, and dissociation	BPD + Alcohol Use Disorder	n=30; 28.7 [7.7]	Twelve to eighteen weeks psychodynamic group	TAU	Improved	*DES
Hodgdon et al, 2021[107] (USA)	Pre/post design	Effect on PTSD, depression, dissociation, affect dysregulation, somatization, and disrupted self-perception	PTSD + depression; childhood traumas	n=17; 46.0 [NR]	Sixteen weekly internal family systems therapy	None	Improved	SIDES-SR
Kellett et al, 2013[108] (UK)	Case series	Effect on BPD symptoms, distress, identity, and dissociation	BPD diagnosis	n=19; M= 38.0 [1.7], F= 28.3 [8.7]	Twenty-four CAT sessions	None	Improved	*DES
Weiner & McKay, 2013[109] (USA)	Pre/post design	Effect on D/D, anxiety and PTSD symptoms	Undergraduates with high anxiety sensitivity and/or PTSD symptoms	n=352; 20.1 [NR]	Three weekly Interoceptive exposure sessions	None	Improved on DDDS but not DES	*DDDS *DES
Wildgoose et al, 2001[110] (UK)	Case series	Effect on dissociative processes and personality fragmentation in BPD, and general symptomatology	BPD	n=5; 39.4 [7.1]	Sixteen weekly CAT sessions	None	Improved	*DIS-Q

Notes: *Dissociation specific questionnaire.

Abbreviations: BA/DE, Body Awareness and Dance Exercise; BPD, Borderline Personality Disorder; BSI, Brief Symptom Inventory; CAPS, Clinician-Administered PTSD Scale; CAT, Cognitive Analytic Therapy; CBT, Cognitive Behavioral Therapy; CDS-S, Cambridge Depersonalization Scale-Situational; CDS, Cambridge Depersonalization Scale; CPT, Cognitive Processing Therapy; CPTSD, Complex Posttraumatic Stress Disorder; CR, Cognitive Restructuring; CSA, Childhood Sexual Abuse; D/D, Depersonalization/Derealization Symptoms; DBT-PTSD, Dialectical Behavior Therapy for Posttraumatic Stress Disorder; DBT, Dialectical Behavior Therapy; DD, Dissociative Disorder; DDD, Depersonalization Derealization Disorder; DDDS, Degree of Depersonalization and Derealization Scale; DE, Dance Exercise; DES-Taxon, Dissociative Experiences Scale-Taxon; DES, Dissociative Experiences Scale; DIS-Q, Dissociation Questionnaire; DPD, Depersonalization Disorder; DSS, Dissociative Tension Scale; EMBER, Embodied Mindfulness Based Emotional Resilience; EMDR, Eye Movement Desensitization and Reprocessing; ERRT, Exposure, Relaxation, and Rescripting Therapy; F, Female; GMT, Goal Management Training; ImRs, Imagery Rescripting; M, Male; MABT, Mindful Awareness in Body-Oriented Therapy (Formerly "Body-Oriented Therapy"); MBCT, Mindfulness Based Cognitive Therapy; MDI, Multi-Scale Dissociation Inventory; MORPHEUS, A computer program that supports in sensu self-Exposure exercises; n, Sample Size; NET, Narrative Exposure Therapy; NR, Not Reported; NRCT, Non-Randomized Controlled Trial; NSSI, Non-Suicidal Self-Injury; NST, Narrative Story Telling; PCT, Present Centered Therapy; PE, Prolonged Exposure; PTSD-DS, Dissociative Subtype Of Posttraumatic Stress Disorder; PTSD, Posttraumatic Stress Disorder; RCT, Randomized Controlled Trial; SBC, Scale of Body Connectedness; SC, Supportive Counseling; SCID-IV, Structured Clinical Interview for the Diagnostic And Statistical Manual of Mental Disorders-IV; SD, Standard Deviation; SDQ, Somatoform Dissociation Questionnaire; SIDES-SR, Structured Interview for Disorders Of Extreme Stress-Self Report Version; SS, Seeking Safety; STAIR, Skills Training In Affective And Interpersonal Regulation; STEPPS, Systems Training for Emotional Predictability and Problem Solving; SUD, Substance Use Disorder; TAU, Treatment As Usual; TM, Transcendental Meditation; TREM, Trauma Recovery and Empowerment Model; TSC, Trauma Symptom Checklist; TSI, Trauma Symptom Inventory; UK, United Kingdom; USA, United States of America.

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Table 2 Medication Intervention Studies and Impact on Dissociation

Author, Year (Country)	Study Design	Study Objective	Population	Sample Size (n); Mean Age [SD or Range]	Medication, Dose, and Treatment Duration	Control	Effect on Dissociation	Dissociation Measure
Bellino et al, 2008[111] (Italy)	Pre/post design	Efficacy and tolerability of adjunctive aripiprazole; BPD, trait impulsiveness, depression, anxiety, social occupational function, and general psychiatric symptoms	BPD + Sertraline non-response (100–200 mg)	n=21; 26.3 [4.6]	Aripiprazole augmentation 10–15 mg/day for 12 weeks	None	Improved	BPDSI
Bozzatello et al, 2017[112] (Italy)	RCT	Efficacy of asenapine compared to olanzapine in BPD; symptoms of BPD, trait impulsiveness, aggression, NSSI, depression, global improvement, and function	BPD from Personality Disorders Clinic	n=51; 24.7 [5.3]	Asenapine (5–10 mg/day) or Olanzapine (5–10 mg/day) for 12 weeks	Comparison of active treatments	Improved	BPDSI
Davis et al, 2004[113] (USA)	RCT	Efficacy of nefazodone for PTSD; monitoring symptoms of PTSD, anxiety, depression, dissociation as well as drug side effects	Chronic PTSD	n=42; 53.8 [8.7]	Nefazodone twice daily for 12 weeks (mean= 435 mg/d; max= 600mg/d)	Placebo	Improved	*CADSS
Hollander et al, 1990[114] (USA)	Case series	Describe cases of DPD or D/D; test if comorbid OCD or PD predicts response to SSRI treatment	DPD or D/D	n=8; 32.14 [10.6]	SSRI at various doses/durations. Fluoxetine (5–80mg/day; n=7) Fluvoxamine (300mg/d; n=1)	None	Improved	Narrative symptom description
Marshall et al, 2007[115] (USA)	RCT	Efficacy of paroxetine on symptoms of PTSD, general psychiatric symptoms, interpersonal problems, anxiety, depression, and dissociation	Chronic PTSD	n=52; 39.8 [11.2]	Paroxetine 60mg/day for 10 weeks	Placebo	Improved	*DES
Marshall et al, 1998[116] (USA)	Pre/post design	Efficacy of paroxetine for symptoms of chronic PTSD, depression, anxiety, dissociative symptoms, and general psychiatric symptoms	Chronic PTSD	n=17; 38.0 [NR]	Paroxetine daily for 12 weeks (mean= 42.5mg/d; max= 60mg/d)	Placebo	Improved	SCL-90 (modified)

Nuller et al, 2001[117] (Russia)	Single blinded cross over design, NRCT	Efficacy of Naloxone for depersonalization symptoms and corticoid secretion	DPD or D/D	n= 50 (naloxone= 14); 32 [NR]	IV naloxone: single dose (1.6–4 mg) or multiple doses (6–50 mg total)	Placebo and healthy volunteer controls for corticoid secretion tests)	Improved	*Depersonalization scale and subjective responses
Philipsen et al, 2004[118] (Germany)	RCT	Effect of clonidine for NSSI urges during acute aversive states	Women with NSSI + BPD in a DBT Program	n=22; 28.7 [6.4]	Clonidine: one 75µ dose and one of 150µg while in an acute state in each participant	No	Improved	*DSS + 20 SDQ items
Philipsen et al, 2004[119] (Germany)	Cross-over RCT	Effect of single dose naloxone for acute dissociative states	Women with BPD	n=9; 34.9 [6.7]	IV naloxone 0.4 mg	Saline placebo	No difference from placebo	*DSS *CADSS
Roullet et al, 2022[120] (France)	RCT	Efficacy of propranolol for reducing PTSD and MDE symptom, comparing high (DES≥30) and low dissociation (DES<30) groups	Chronic PTSD; PCL-5≥45	n=63; 39.2 [35.7–42.1]	Propranolol prior to six weekly NET (0.67 mg/kg then 1.0 mg/kg of long-acting propranolol 90 min later)	Placebo	Improved; propranolol +NET>placebo +NET; greater improvement in DES≥30 group	*DES
Schmahl et al, 2012[121] (Germany)	Two RCT's; cross over design	Anti-dissociative efficacy of naltrexone compared in highly dissociative BPD.	Women with BPD and DES≥18	n=29; RCT 1= 28.3 [8.0] RCT 2= 29.2 [8.9]	RCT 1: naltrexone 50 mg/day for three weeks RCT 2: naltrexone 50 mg/day or 200mg/day	Placebo	No change	*DSS *DES
Sierra et al, 2003[122] (UK)	RCT; cross over	Effect of Lamotrigine on depersonalization disorder	DPD	n=14; 35.2 [3.4]	Lamotrigine for 6 weeks (max= 250 mg/day)	Placebo	No change	*CDS *DES
Sierra et al, 2006[123] (UK)	Case Series	Effect of Lamotrigine on dissociative symptoms, mainly D/D	DPD in specialty clinic	n=32; 37.1 [18–73]	Lamotrigine: mean 209.8 mg/day (range 25–600 mg/day); 13.7 months (range 6–21 months)	None	Improved on CDS but not DES	*CDS *DES

(*Continued*)

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Table 2 (Continued).

Author, Year (Country)	Study Design	Study Objective	Population	Sample Size (n); Mean Age [SD or Range]	Medication, Dose, and Treatment Duration	Control	Effect on Dissociation	Dissociation Measure
Simeon et al, 2004[124] (USA)	RCT	Efficacy of fluoxetine for depersonalisation in DPD, symptoms of anxiety, depression, obsessive compulsive disorder, and panic attacks	DPD	n=50; Fluoxetine group= 34.5 [11.4]	Fluoxetine over 10 weeks (max= 60 mg/day)	Placebo	No change	*DSS *DES-DPS
Simeon & Knutelska, 2005[125] (USA)	Case series	Efficacy of naltrexone for depersonalisation in DPD and symptoms of PTSD	DPD	n=14; 30.9 [8.5]	Naltrexone: 100 mg daily for six weeks (n=6); 250 mg daily for 10 weeks (N=7)	None	Improved	*CADSS *DES-DPS *CDS
Uguz & Sahingoz, 2014[126] (Turkey)	Case series	Report on effect of aripiprazole on depersonalization and changes in symptoms of MDD and OCD	Women with DPD + MDD + OCD	n=3; 33.0 [7.0]	Aripiprazole for 6–10 weeks (5 mg/ day and increased to 10 mg/day)	None	Improved	Subjective patient report

Notes: *Dissociation specific measure.

Abbreviations: BPD, Borderline Personality Disorder; BPDSI, Borderline Personality Disorder Severity Index; CADSS, Clinician Administered Dissociative States Scale; CDS, Cambridge Depersonalization Scale; D/D, Depersonalization/Derealization Symptoms; DBT, Dialectical Behavior Therapy; DES-DPS, Dissociative Experiences Scale Depersonalization Subscale; DES, Dissociative Experiences Scale; DPD, Depersonalization Disorder; DSS, Dissociative Tension Scale; IV, Intravenous; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; n, Sample Size; NET, Narrative Exposure Therapy; NR, Not Reported; NRCT, Non-randomized Controlled Trial; NSSI, Non-suicidal Self-Injury; OCD, Obsessive Compulsive Disorder; PCL, Post Traumatic Stress Disorder Checklist; PD, Panic Disorder; PTSD, Post Traumatic Stress Disorder; RCT, Randomized Control Trial; SCL-90, Symptom Checklist-90 Revised; SD, Standard Deviation; SDQ, Somatoform Dissociation Questionnaire; SSRI, Selective Serotonin Reuptake Inhibitor; UK, United Kingdom; USA, United States of America.

Table 3 rTMS Intervention Studies and Impact on Dissociation

Author, Year (Country)	Study Design	Study Objective	Population	Sample Size (n); Mean age, [SD]	Medication, Dose, and Treatment Duration	Control	Effect on Dissociation	Dissociation Measures
Jay et al, 2014[127] (UK)	RCT	Test if low frequency (inhibitory) rTMS to the right VLPFC would decrease autonomic arousal and DPD symptoms	Medication resistant DPD in males	VLPFC: n=8; 34.9 [5.2] TPJ: n=9; 39.3 [14.6]	Single rTMS session; 15 min to right VLPFC or right TPJ at 1 Hz (900 pulses/session)	Healthy controls (n=20)	Improved for both rTMS sites	*CDS
Jay et al, 2016[128] (UK)	Case series	Test rTMS protocol for D/D, depression, and anxiety symptoms	DPD	n=7; 36.1 [12.7]	Twenty rTMS sessions over ten weeks; 15 min to right VLPFC at 1 Hz (900 pulses/session)	No	Improved for CDS; no change in DES	*CDS *DES
Mantovani et al, 2011[129] (USA)	Pre/post design	Test low frequency TPJ rTMS in DPD and associated depression and anxiety symptoms	DPD	n=12; 33.6 [12.9]	Three weeks of right TPJ rTMS (1Hz; 1800 pulses/day), followed by three weeks of either right or left rTMS	No	Improved	*CDS, *CADSS, *DES

Notes: *Dissociation specific measure.
Abbreviations: CADSS, Clinician-Administered Dissociative States Scale; CDS, Cambridge Depersonalization Scale; D/D, Depersonalization/Derealization Symptoms; DES, Dissociative Experiences Scale; DPD, Depersonalization Disorder; n, Sample Size; RCT, Randomized Control Trial; rTMS, repetitive Transcranial Magnetic Stimulation; SD, Standard Deviation; TPJ, Temporoparietal Junction; UK, United Kingdom; USA, United States of America; VLPFC, Ventrolateral Prefrontal Cortex.

Study Interventions

Study interventions included psychotherapy (n = 50; 72.5%), medication (n = 16; 23.1%), and rTMS (n = 3; 4.3%) approaches (Tables 1–3). Psychotherapy interventions were nearly evenly divided between those employing trauma-specific therapies and non-trauma focused approaches, which will be expanded upon below.

Psychotherapeutic Interventions

Mindfulness and Body Awareness-Based Psychotherapies

Mindfulness and body-based therapy studies (n = 8) reported overall positive but mixed results, with heterogeneous designs. Six were RCTs, but some enrolled participants with modest baseline dissociative symptom scores, and only two were specifically designed to assess dissociative conditions (eg, DPD).[62,68] The remaining six studies measured dissociation as an associated feature of trauma exposure or psychopathology (Table 1).

Interventions included transcendental meditation[63] and body-based interventions that encouraged bodily awareness via directed attention to bodily sensations, such as Mindful Awareness in Body-oriented Therapy (MABT),[64–66] Body Awareness and Dance Exercise (BA/DE),[62] modified yoga,[67,69] or biofeedback.[68] All studies except electrodermal biofeedback reported promising results.[68] This study involved altering skin conductance to manipulate an arcade game interface, facilitating awareness and control of this physiologic measure previously found to be low in DPD.[68] Study participants had higher baseline dissociative symptom scores compared to many of the other studies, a possible confounder. MABT involved massage, body awareness exercises and inner body focus, whereas BA/DE involved the addition of guided body awareness to a dance exercise. Interestingly, while the BA/DE study was positive, authors noted that the most significant reduction in dissociation scores occurred immediately after dance exercise, regardless of whether directed bodily awareness was added,[62] an unexpected finding.

Cognitive Behavioral, Skills-Based, and Psychoeducation Interventions

Interventions based upon Cognitive Behavioral Therapy (CBT) or Dialectical Behavior Therapy (DBT) were also common; five of seven reported improvements in dissociation. These included group and individual formats, single and multiple session interventions, and in-person and asynchronous online interventions tested for PTSD, social- or test-related anxiety, and DPD.[72,73,75,76] DBT and Systems Training for Emotional Predictability and Problem Solving (STEPPS) both equally improved dissociative symptoms in BPD,[71] but Mindfulness-based CBT (MCBT) did not,[74] despite very similar, moderately severe baseline DES scores (26.02[SD = 14.13] vs 25.0[SD = 20.2]). Dissociation was

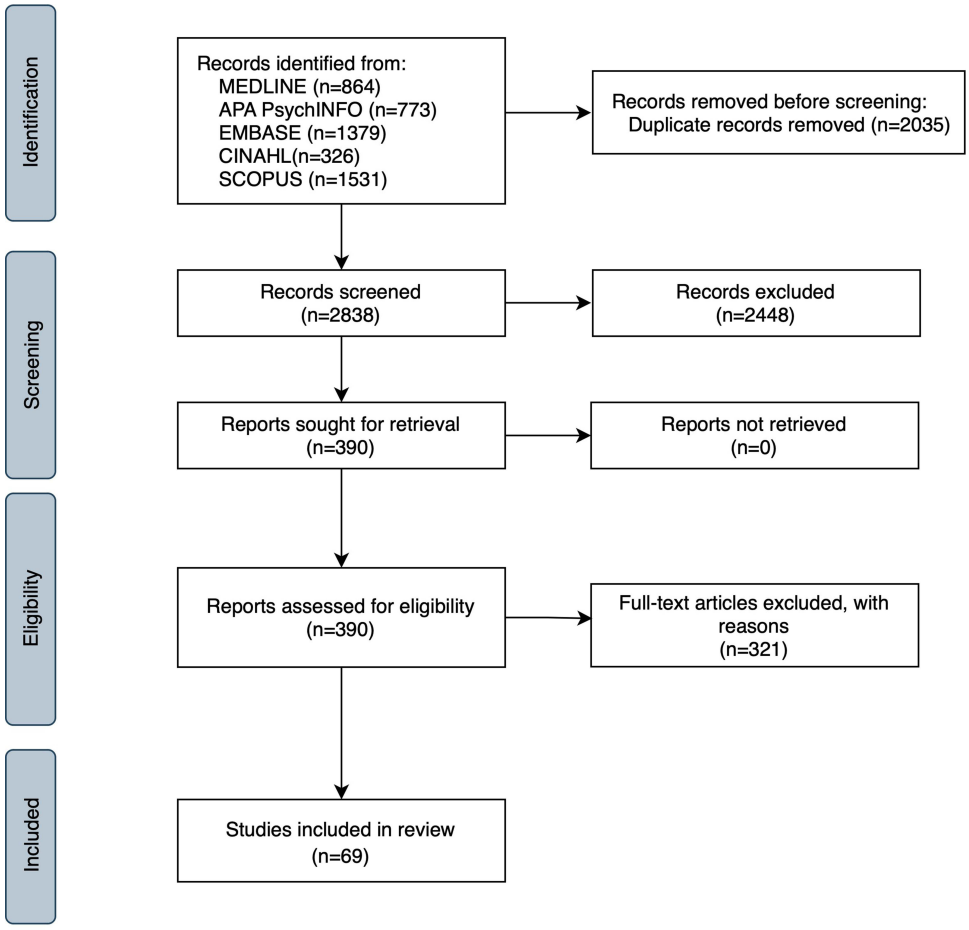

Figure 1 Flow diagram.

a secondary objective in all but two studies: one focused on DPD,[72] and the other on depersonalization induced by test anxiety in university students.[76]

Other skills-based interventions, incorporating psychoeducation and cognitive approaches, with or without coping skills, were described in an additional eight studies, improving dissociation in six (Table 1). These treatments were usually delivered in a group format (n = 6) and often included psychoeducation pertaining to symptoms of trauma and/or PTSD and an interactive component between group members. Populations studied included those with PTSD or trauma exposure, including interpersonal,[77,78,80,82–84] or military trauma.[81] Comorbidity with Substance Use Disorder (SUD) or pathological gambling was present in two studies.[79,80] None of these studies were primarily designed to address dissociation, and one study specifically excluded those with more severe dissociative symptoms.[83]

Trauma-Focused Psychotherapies

Many interventions included either a specific trauma-focused therapy (n = 7), such as Eye Movement Desensitization and Reprocessing (EMDR), or a trauma-focused therapy in combination with another intervention (n = 14), including within an intensive trauma program (n = 4). Studies with a single, specific trauma-focused therapy included EMDR (n = 4),[86–88,91] Narrative Exposure Therapy (NET) (n = 2),[89,90] Prolonged Exposure (PE) (n = 1),[91] and Hypnotherapeutic Olfactory Conditioning (HOC) (n = 1);[85] all but a group-based bilateral stimulation intervention reported dissociation improvement. This study enrolled participants with severe dissociative symptoms from a specialty trauma and dissociation clinic.[88] Other populations studied included PTSD or trauma exposure (n = 5),[85–87,89,91] including those with comorbid BPD[90] and severe mental illness with repeated interpersonal trauma.[89]

Table 4 Dissociation Measures Used in the Included Studies

Measure of Dissociation	Main Focus	Number (%) of References	References
Dissociation specific measures			
DES/FDS	State and trait dissociation: D/D, gaps in awareness or memory, identify dissociation	37 (53.6%)	Price, 2005;[64] Price, 2006;[65] Price et al, 2012;[66] Price et al, 2017;[67] Schoenberg et al, 2012;[68] Guillen Botella et al, 2021;[71] Hunter et al, 2005;[72] Klein et al, 2010;[73] Sachse et al, 2011;[74] Karatzias et al, 2016;[77] Lubin et al, 1998;[78] Rudstam et al, 2022;[83] Zlotnick et al, 1997;[84] Abramowitz et al, 2009;[85] Carletto et al, 2018;[86] Gonzalez-Vazquez et al, 2018;[88] Mauritz et al, 2022;[89] Pabst et al, 2014;[90] Rothbaum et al, 2005;[91] Harned et al, 2014;[96] McDonagh et al, 2005;[98] Steil et al, 2018;[100] Steele et al, 2018;[101] Steuwe et al, 2016;[102] Damsa et al, 2014;[105] Gregory et al, 2008;[106] Kellett et al, 2013;[108] Weiner & McKay, 2013;[109] Marshall et al, 2007;[115] Roullet et al, 2022;[120] Schmahl et al, 2012;[121] Sierra et al, 2003;[122] Sierra et al, 2006;[123] Simeon et al, 2004;[124] Simeon & Knutelska, 2005;[125] Jay et al, 2016;[128] Mantovani et al, 2011[129]
CDS	State dissociation: D/D	11 (15.9%)	Millman et al, 2023;[62] Schoenberg et al, 2012;[68] Hunter et al, 2005;[72] Schweden et al, 2016;[75] Schweden et al, 2020;[76] Sierra et al, 2003;[122] Sierra et al, 2006;[123] Simeon & Knutelska, 2005;[125] Jay et al, 2014;[127] Jay et al, 2016;[128] Mantovani et al, 2011[129]
DSS/DSS-4	State dissociation: D/D, gaps in awareness or memory, sensory alterations	8 (11.9%)	Beck et al, 2021;[92] Covers et al, 2021;[87] Görg et al, 2016;[95] Kleindienst et al, 2021;[97] Philipsen et al, 2004;[118] Philipsen et al, 2004;[119] Schmahl et al, 2012;[121] Simeon et al, 2004[124]
SDQ-20/SDQ-5	State and trait dissociation: predominantly somatoform dissociation, also two D/D items	4 (5.8%)	Rudstam et al, 2022;[83] Beck et al, 2021;[92] Zoet et al, 2021;[104] Philipsen et al, 2004[118]
CADSS	State dissociation: D/D, identity dissociation, memory gaps	4 (5.8%)	Davis et al, 2004;[113] Philipsen et al, 2004;[119] Simeon & Knutelska, 2005;[125] Mantovani et al, 2011[129]
DIS-Q	State and trait dissociation: mainly D/D and identify dissociation, also memory gaps.	2 (2.9%)	Raabe et al, 2022;[99] Wildgoose et al, 2001[110]
SBC	State dissociation: awareness and dissociation from bodily sensations, D/D	1 (1.4%)	Willy-Gravley et al, 2021[69]
DDDS	Study task-induced state dissociation	1 (1.4%)	Weiner & McKay 2013[109]
MDI	State and trait dissociation: D/D, memory gaps, identity dissociation, emotional constriction, disengagement	1 (1.4%)	Protopopescu et al, 2022[81]
DS	Depersonalization symptoms	1 (1.4%)	Nuller et al, 2001[117]
Subjective report	Participant or clinician report on change in dissociative symptoms	4 (5.8%)	Uguz & Sahingoz, 2014;[126] Nuller et al, 2001;[117] Görg et al, 2016;[95] Hollander et al, 1990[114] (clinician narrative report)
Non-dissociation specific measures			
TSC	Trauma symptoms; Three dissociation items pertaining to D/D	4 (5.8%)	Nidich et al, 2016;[63] Najavits et al, 2013;[79] Najavits & Johnson et al, 2014;[80] Classen et al, 2001[94]
TSI	PTSD and associated symptoms; Dissociation subscale	3 (4.3%)	Davis et al, 2011;[70] Roe-Sepowitz et al, 2014;[82] Cloitre et al, 2012[59]

(*Continued*)

Table 4 (Continued).

Measure of Dissociation	Main Focus	Number (%) of References	References
CAPS	PTSD symptoms; Two dissociation items pertaining to D/D	2 (2.9%)	Bowen et al, 2010;[93] Zoet et al, 2018[103]
BPDSI	Borderline personality symptoms; Two dissociation items pertaining to D/D	2 (2.9%)	Bellino et al, 2008;[111] Bozzatello et al, 2017[112]
SCL-90	Wide range of psychological symptoms; Dissociation items include: D/D, memory gaps, identity dissociation, and somatic symptoms	1 (1.4%)	Marshall et al, 1998[116]
SIDES-SR	Past and current functioning across multiple domains; Two dissociation items: amnesia and transient dissociation/depersonalization.	1 (1.4%)	Hodgdon et al, 2022[107]
BSI	Range of psychological symptoms; Somatization as the only dissociative symptom in the scale	1 (1.4%)	Najavits et al, 2013[79]

Abbreviations: BPDSI, Borderline personality disorder severity index; BSI; Brief Symptom Inventory; CADSS, Clinician Administered Dissociative states scale; CAPS, Clinician Administered PTSD scale; CDS, Cambridge Depersonalization Scale; D/D, Depersonalization/Derealization symptoms; DDDS, Depersonalization and Derealization Scale; DES/FDS, Dissociative Experiences Scale/ Fragebogen für dissoziative Symptome; DIS-Q, Dissociation questionnaire; DS, Depersonalization Scale; DSS, Dissociative Tension Scale; MDI, Multi-scale dissociation inventory; SBC, Scale of bodily connection; SCL-90, Symptom checklist; SDQ, Somatoform dissociation questionnaire; SIDES-SR, Structured Interview for Disorders of Extreme Stress, Self-report version; TSC, trauma symptom checklist; TSI, Trauma symptom Inventory.

Treatments that combined a trauma-focused modality with another therapy were also common (n = 14 studies); all but two reported improvements in dissociation. These studies used either EMDR, an exposure-based therapy, or trauma imagery rescripting therapy combined with another intervention such as CBT or DBT-based skills training, cognitive restructuring, movement (yoga, physical activity, or equine therapy), expressive art, music, writing, supportive therapy, or psychoeducation. These studies appeared to include more complex populations such as PTSD with a history of childhood sexual or physical abuse, BPD, other trauma-related personality changes,[92,96,97,100] or another Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis.[97] Treatment was often administered within trauma-specific specialty programs,[93,96,97,100–104] and four studies reported on intensive, daily therapy programming.[101–104]

Other Psychotherapeutic Interventions

Six studies described other intervention types, including psychodynamic, Internal Family Systems (IFS), Cognitive Analytic Therapy (CAT), or interoceptive exposure. These were small, overall positive studies.[105–110] All utilized dissociation-specific scales, and three focused on dissociation as the main treatment target in either DD, BPD, or PTSD.[105,109,110]

Pharmacological Interventions

Pharmacotherapy was the focus of 16 studies, and all but three reported positive effects on dissociative symptoms (Table 2 and Table 5). Studies reported positive results for nefazodone, clonidine, the selective serotonin reuptake inhibitors (SSRIs) paroxetine and fluvoxamine, and atypical antipsychotics asenapine, olanzapine and aripiprazole; there were mixed findings for fluoxetine, lamotrigine and opioid receptor antagonists naloxone and naltrexone (Table 5). Propranolol, when used prior to exposure therapy to augment response, was also reported as beneficial, especially in those with greater dissociative symptoms.[120] Studies typically lasted up to 12 weeks, focusing on diagnoses that included BPD, PTSD, or DPD. On occasion, baseline dissociation symptoms were low and could be considered normative.[115]

Four studies included opioid antagonists, with mixed results. Of the two naloxone studies, the larger, single blinded crossover study in DPD (n = 50 participants) demonstrated improvement,[117] while a smaller one with nine BPD participants did not.[119] Naloxone was delivered intravenously, as either a single dose ranging from 0.4 mg to 1.6 mg or in multiple increasing doses, from 2 to 10 mg, every 2–3 weeks.[117,119] Two negative randomized naltrexone studies

Table 5 Pharmacological Interventions Associated with Dissociative Symptom Improvement

Interventions	Number (%) of References	Medication	Reference
Intervention type	16 studies		
SSRI	4 (25%)	Paroxetine, Fluoxetine*, Fluvoxamine	Hollander et al, 1990;[114] Marshall et al, 2007;[115] Marshall et al, 1998;[116] Simeon et al, 2004[124]
SSRI augmentation	1 (6%)	Aripiprazole + sertraline	Bellino et al, 2008[111]
5-HT2 antagonist	1 (6%)	Nefazodone	Davis et al, 2004[113]
Atypical antipsychotics	2 (13%)	Asenapine, olanzapine, aripiprazole	Bozzatello et al, 2017;[112] Uguz & Sahingoz, 2014[126]
Anticonvulsant	2 (13%)	Lamotrigine*	Sierra et al, 2003;[122] Sierra et al, 2006[123]
Opioid antagonists	4 (25%)	Naloxone*, naltrexone*	Nuller et al, 2001;[117] Philipsen et al, 2004;[119] Schmahl et al, 2012;[121] Simeon & Knutelska, 2005[125]
α2-adrenergic agonists	1 (6%)	Clonidine	Philipsen et al, 2004[118]
Augmentation of exposure therapy	1 (6%)	Propranolol	Roullet et al, 2022[120]

Note: *Indicates mixed reports.
Abbreviations: SSRI, Selective Serotonin Reuptake Inhibitor; 5-HT, 5-hydroxytryptamine; α2, Alpha-2.

were reported together, which included participants with BPD; another DPD case series (n = 14) reported positive results.[121,125] Naltrexone doses ranged from 50 to 250 mg/day, over 3–10 weeks.

Atypical antipsychotics and the anticonvulsant lamotrigine, both with mood stabilizing properties, were studied for dissociative symptoms, for up to 12 weeks. Atypical antipsychotics included aripiprazole, asenapine, and olanzapine. Studies were small and heterogenous, mainly including participants with BPD.[111,112,126] One RCT (n = 51) compared asenapine to olanzapine 5–10 mg/day for 12 weeks in BPD, demonstrating improvement in BPD-related dissociation symptoms with both medications. The two small lamotrigine studies focused on DPD with mixed results; the positive case series used up to 600 mg per day over 6–21 months.[122,123]

Finally, antiadrenergic medications propranolol, used as an adjunct to NET, and clonidine were the focus of two RCTs, both reporting positive results. Phillipsen et al (2004) studied clonidine for BPD patients with self-harm, enrolled within a DBT program,[118] and Roullet (2022) studied the impact of adding propranolol prior to NET treatment for chronic and severe PTSD.[120]

Neuromodulation Using rTMS

All neuromodulation studies (n = 3) examined the use of low-frequency rTMS (1 Hz) among participants with DPD.[127–129] The protocol varied across studies, ranging from a single rTMS session,[127] a variable protocol with up to 20 sessions over 10 weeks,[128] to an intensive regimen with three sessions per day for three weeks.[129] RTMS was applied to the right ventrolateral prefrontal cortex (VLPFC) or temporoparietal junction (TPJ)[127–129] In all studies, rTMS was noted to reduce DPD symptoms by the end of the treatment, specifically depersonalization measured with the DES and CDS (Table 3).

Discussion

Summary

This paper summarized the empirical literature studying interventions for dissociative symptoms. This included 69 studies, overall reporting dissociative symptom reduction across a wide range of interventions, including psychotherapies, medications, and rTMS. Our results extend previous reviews reporting that both trauma-focused and non-trauma-focused treatments can reduce dissociative symptoms,[130] often with greater benefit for those with more severe symptomatology.[59]

While results are generally positive, multiple methodological issues impact interpretation of the findings. These include small sample sizes, heterogeneity, few RCTs and use of non-specific dissociation scales, or ones with limited breadth.[5,103,130,131] Many studies were not designed to assess dissociation but rather measured dissociation as a secondary outcome. Further, few studies differentiated between high and low dissociation subgroups, likely representing different psychopathology. Some reported statistically significant results that may not be clinically relevant, included participants with low baseline symptoms, or did not report on baseline scores.[65,66,115] Also, whether dissociation moderates treatment response remains difficult to ascertain from these results and may depend on contextual factors, associated psychopathology, and trial methodology.[5,12,59]

There is a clear need, in particular, to better understand the role of pharmacotherapies for dissociative symptoms. This review found studies reporting improvements in dissociative symptoms for the following medications: nefazodone, SSRIs (paroxetine and fluvoxamine), atypical antipsychotics (asenapine, olanzapine, and aripiprazole), the alpha$_2$ agonist clonidine, and the beta blocker propranolol, when used to augment NET. Mixed findings were reported for naloxone, naltrexone, fluoxetine, and lamotrigine. There were few studies overall, with modest rigor, which has been noted in previous reviews.[132,133] Sutar and Sahu (2019) reported only paroxetine and naloxone were supported by RCTs, with modest support.[132] A systematic review of opioid antagonists found only five small studies using naloxone or naltrexone for dissociative symptoms in BPD, PTSD, DD, or opioid use disorder.[133] Taken together, further high-quality studies are needed.

Pharmacological mechanisms and their relationship to dissociative processes remain to be fully elucidated. Clonidine and propranolol are commonly used adjunctively for PTSD due to their antiadrenergic effects.[5] Opioid antagonists may block opioid-mediated dissociative numbing and analgesia, mediated through the μ-opioid receptor, and κ-opioid receptor mediated dysphoria and alterations in consciousness.[5,6,133] SSRIs and antipsychotics, on the other hand, reduce agitation, anxiety and depressive symptoms.[5] In addition to D2 and 5-HT2 receptor antagonism, atypical antipsychotics have variable effects on adrenergic and other serotonin receptors.[134] SSRIs enhance both top-down control of negative emotion and modulate subcortical amygdala activity.[135] Over time, SSRIs can desensitize 5-HT1A autoreceptors in the dorsal raphe nucleus (DRN).[136] Serotonin release from the DRN to the PAG is implicated in passive defensive responding to inescapable threats and perception of powerlessness, with potential implications for dissociation;[137] a range of other neurotransmitters, including dopamine, opioids, cannabinoids, and oxytocin, are also implicated in associated PAG mediated threat responses.[138,139] Interestingly, ameliorating learned helplessness, a response to inescapable or uncontrollable threat, has also been explored as a common therapeutic mechanism for psychedelics and ketamine.[140] MDMA-assisted therapy, which facilitates a sense of safety and trust through oxytocin release, may be of particular interest to the field of dissociation.[141]

RTMS, which uses magnetic fields to excite or inhibit neurons in specific regions of the brain, is a novel option for DPD.[142] rTMS has been studied for other related psychiatric disorders, including depression and PTSD, usually with high frequency (ie, stimulatory) rTMS applied to the right or left DLPFC.[5,142] However, studies using rTMS for DPD targeted the right VLPFC or TPJ with low frequency (ie, inhibitory) protocols.[127–129] The TPJ is an integration area associated with social cognition, attention and self-awareness and implicated in neglect and depersonalization;[6,143,144] both the DLPFC and VLPFC are involved in emotion regulation, including in response to social pain.[144–146] This fits with the fronto-limbic inhibition model of dissociation, with PTSD-DS exhibiting PFC overregulation of amygdala activation, relative to classic PTSD.[6] Notably, rTMS effects are specific to the brain area targeted, theoretically allowing customization; in theory, further elucidation of neurobiology specific to dissociation subtypes may lead to greater rTMS protocol specificity.

Safety as Foundational for Dissociation Treatment

It is useful to consider that most, if not all, helpful interventions directly or indirectly modulate threat response systems, thereby promoting a sense of inner safety. For example, cognitive and emotional regulation interventions directly enhance a sense of safety by reducing physiological distress and improving self-efficacy, whereas trauma-focused interventions desensitize pathogenic memories perpetuating chronic threat responses. Medications and rTMS also impact neurobiological systems relevant to internal distress, such as autonomic reactivity, executive and emotional regulatory capacity, or dissociative processes.[5,6,127,129,133,134,142]

Dissociation stands in stark contrast to safety. This review frames dissociation as a defense response to primal isolation anguish, a state of terrifying helplessness and aloneness. Severe chronic dissociative symptoms are understood as a consequence of brain adaptations to environments devoid of reliable relational safety and often repeated or prolonged experiences of inescapable terror and abandonment.[7,8,18,19] Such circumstances not only result in insecure attachment but also profoundly impact the way the brain develops, adapting by shutting down somatosensory integration between cortical and subcortical areas.[18] While this allows survival, it inhibits development of a robust experiential template for safety, prevents the person from being able to tolerate and use interoceptive and exteroceptive information to accurately assess and respond to present danger, and robs the person of the capacity to feel a coherent sense of being an agentive self.[18,19] In summary, in general, attachment injury prevents those impacted from feeling safe and from being mindful of difficult bodily experiences on their own.

This has direct implications for mindfulness and psychotherapy in general. Mindfulness involves present moment awareness, with acceptance, including of somatosensory experience. However, many of those with dissociative symptoms missed the repeated, attuned attachment experiences necessary to internalize a sense of safety and comfortably be alone with internal experience.[40,46] When present, dissociated trauma-related content can flood awareness, prompting further dissociation.[40,58,147,148] Rather than expecting solo practice, in-session or within-group practices with mindful, relational co-regulation (ie, securefulness) may be needed to prevent overwhelm.[40] This principle also applies to helping patients tolerate painful content in treatment generally, regardless of modality.

The concept of securefulness adds to mainstream conceptualizations of therapeutic alliance, which is a consistent driver of therapeutic outcomes.[149] As it implies a neurophysiological state, securefulness may lend to physiological studies of therapist-patient dyads and more objective adjunctive measures of alliance and psychological safety. Such measures may be especially helpful for dissociative individuals, where fawning and reduced internal awareness can complicate assessment. Physiological measures, perhaps captured through wearable devices, may also help therapists identify triggers for dissociation, pace therapy and balance the need to support and the need to teach patients how to nurture themselves. As dissociation can disrupt emotional learning and slow progress, perhaps such tools could be used to recognize and mitigate such effects.[11]

Top-Down and Bottom-Up

Kearney and Lanius (2022) proposed that optimal treatment for traumatized patients combines "top-down" (eg, cognitive) with "bottom-up" (eg, body based) strategies, allowing for vertical integration of brain processing. They conceptualize trauma-related symptoms as foundationally

> Grounded in brainstem-level somatic sensory processing dysfunction and its cascading influences on physiological arousal modulation, affect regulation, and higher-order capacities.

[18] Such integrative treatment would facilitate the connections between brainstem, vestibular and cerebellar connections with the body, the reticular activating system that governs level of consciousness, limbic areas for memory, emotion and secure attachment, with sensory relay and integration areas (eg, thalamus, insula), and higher cortical functions. For example, therapies that include somatosensory and vestibular stimulation, such as play therapy, might facilitate such a process, especially if integrating safe relational experience. Such experiences not only build sensory distress tolerance, mindfulness, and attentional control but also help to build a sense of safety, connection, and agency in one's body and within the therapeutic relationship and differentiate safe from unsafe sensation.

Several current and novel interventions can be considered integrative, employing both top-down and bottom-up strategies. Examples from this review include EMDR,[86] dance,[62] MABT,[66] modified yoga,[67,69] biofeedback,[68] and interoceptive exposure.[109] Intensive trauma programs often added physical activities to trauma focused modalities.[103] Other examples include somatic trauma psychotherapies (eg, Somatic Experiencing and Sensorimotor Psychotherapy), Deep Brain Reorienting, and Multi-Modal Motion-Assisted Memory Desensitization and Reconsolidation (3MDR).[5,18,150] EMDR combines top-down activation of the PFC and attentional control with direct effects on the brainstem to engage sensory integration.[18] Somatic psychotherapies similarly engage attentional control, emotion regulation, and mindful experiencing of somatosensory states. Deep Brain Reorienting focuses on subcortical orienting,

shock, and PAG-based affective responses associated with traumatic memories, without discussing traumatic content.[150] Finally, 3MDR includes treadmill walking, somatosensory processing, and an eye movement task within a virtual reality exposure environment.[5] All emphasize co-regulation and safety of the therapeutic context, to titrate experience.

Other Opportunities for Research

This review raises research opportunities related to dissociation. Far from monolithic, dissociative symptoms may serve different functions, such as avoiding sensory experience, specific emotions, inner conflict, or vulnerability; further, there may be clinically important neurobiological subtypes. Research to improve matching of patients to therapies or therapy combinations, perhaps integrating top-down and bottom-up strategies, is indicated. Feasible clinical assessment and symptom measurement tools that assess dissociative symptoms over time would be helpful in this endeavor. Sixty percent of studies used the self-rated DES II screening measure, which has no set time frame, is vulnerable to subjective interpretation and can miss indicators of somatoform dissociation. Validated, practical tools for measuring felt sense of safety and securefulness could also facilitate research in this area, although this remains to be empirically tested.

Limitations

This review focused on empirical studies of interventions that reported an impact on trauma-related dissociation such as derealization and depersonalization, excluding severe forms of identity dissociation. Most studies did not explicitly exclude such disorders, however, which are under-recognized and could have been included in the reviewed studies.[12] There are few well-designed studies to guide treatment in this complex cohort, although literature demonstrates improvement in therapy.[2,12] Additionally, no qualitative studies were captured as part of our search, representing a potential research gap. This review is also limited to studies in English or French, potentially overlooking research from other regions or languages.

Conclusion

Trauma-related dissociation is a complex, transdiagnostic phenomenon involving brain and body systems designed for perceiving and responding to severe threats, including the primal isolation anguish of being alone and helpless. For humans, this is intertwined with attachment, the primary method we evolved for maintaining safety, especially during developmental years. Chronic or recurrent dissociative symptoms are associated with severe and often repeated inescapable threat, often in the form of attachment or interpersonal trauma. Therefore, we propose that relational safety and attunement, termed Securefulness, be prioritized in treatment, regardless of modality.

A range of interventions are associated with reduced dissociative symptoms, including pharmacotherapies, rTMS, and a variety of psychotherapy and behavioral approaches. However, many methodological issues and knowledge gaps remain to be addressed. When viewed through an evolutionary, relational and neurobiological perspective, these treatments promote an internal sense of safety through their action on threat and regulatory systems. Given the importance of relational safety, future studies should consider the quality of relationship within interventional trials, to further delineate this factor in trial outcomes and for clinical care.

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