

# Neural responses to emotional stimuli across the dissociative spectrum: Common and specific mechanisms

Marco Cavicchioli, PhD <sup>1\*</sup>, Anna Ogliari, MD, PhD,<sup>1,2</sup> Cesare Maffei, MD,<sup>1</sup> Clara Mucci, PhD,<sup>3</sup> Georg Northoff, MD, PhD <sup>4,5,6</sup> and Andrea Scalabrini, PhD<sup>3\*</sup>

**Aim:** Departing from existing neurobiological models of dissociation, the current study aims at conducting a quantitative meta-analytic review of neural responses to emotional stimuli among individuals ascribed to the dissociative spectrum (DS). Accordingly, the study explored common and specific brain mechanisms across borderline personality disorder, conversion/somatoform disorders, posttraumatic stress disorder, posttraumatic stress disorder related to repeated interpersonal traumatic experiences, and dissociative disorders.

**Methods:** The meta-analysis included studies that administered emotional stimuli during functional magnetic resonance imaging acquisition among individuals included in the DS. There were two conducted meta-analytic procedures: (i) a Bayesian network meta-analysis for a region-of-interest-based approach; and (ii) robust voxel-based approach.

**Results:** Forty-four independent studies were included for a total of 1384 individuals (DS = 741 patients). The network meta-analysis showed specific patterns of neural activity considering an extended brain network involved in emotion

regulation for each condition ascribed to the DS. The voxel-based meta-analysis highlighted an increased activity of dorsal anterior cingulate cortex as a common neurological signature of the DS.

**Conclusion:** The common neural feature of the DS captures an implicit appraisal of emotion-eliciting stimuli as threatening and/or noxious for mental and physical integrity of the individual together with painful subjective experiences associated with physiological emotional reactions. Specific brain responses across the DS suggested the engagement in different mechanisms to address emotional stimuli, including implicit avoidance reactions and attempts to overcontrol of affective states together with a disruption of integrative processes of emotional mind-body features.

**Keywords:** dissociation, dissociative spectrum, emotion regulation, meta-analysis, neural responses.

<http://onlinelibrary.wiley.com/doi/10.1111/pcn.13547/full>

One of the first descriptions of dissociation was provided at the end of 19th century by Pierre Janet,<sup>1</sup> who described dissociative processing as a dysfunction of coordination and integration of psychological functions. Departing from his first attempts to systematize these complex clinical phenomena,<sup>1,2</sup> several operationalizations of dissociation have been provided.<sup>3</sup> Psychopathological approaches<sup>4,5</sup> have operationalized dissociation emphasizing the loss of high-order integrative and regulative capacities. Specifically, it captures “unbidden intrusions into awareness and behavior, with accompanying losses of continuity in subjective experience” (e.g., fragmentation of identity, depersonalization, derealization) and/or “inability to access information or to control mental functions that normally are readily amenable to access or control” (e.g., amnesia).<sup>4</sup>

Clinical frameworks<sup>6–8</sup> have referred to dissociation as a constellation of symptoms. On the one hand, *positive dissociative symptoms* include intrusive phenomena (e.g., flashbacks, reexperiencing and traumatic memories). On the other hand, *negative symptoms* refer to “apparent losses” of mental experiences (e.g., amnesia and loss of motor control). A further categorization identifies *psychoform*

*dissociative symptoms* that predominantly involve the mind (e.g., depersonalization) and *somatoform dissociation* that phenomenologically refers to the body (e.g., analgesia).

Some authors have also conceptualized dissociation as a structural pathology of personality.<sup>9,10</sup> Accordingly, it has been assumed a loss of integration between parts usually mediated by daily life action systems (i.e., activities of daily life and survival of the species) and defensive action systems (i.e., a range of subsystems dedicated to the survival of the individual in the face of threat) as a result of the insurgence of a threat to bodily integrity and/or life.

Furthermore, dissociative phenomena have been also conceptualized considering two key underlying processes: *compartmentalization* (i.e., inability to bring normally accessible information into the field of consciousness) and *detachment* (i.e., alterations of the quality of consciousness).<sup>11,12</sup> Compartmentalization processes could underpin different dissociative symptoms such as dissociative amnesia, conversion symptoms, other somatoform dissociative symptoms, and “body memories” (i.e., reexperiencing traumatic pain in the body).<sup>13</sup> Detachment mechanisms might be linked to a wide range of dissociative

<sup>1</sup> Department of Psychology, University “Vita-Salute San Raffaele”, Milan, MI, Italy

<sup>2</sup> Child in Mind Lab, University “Vita-Salute San Raffaele”, Milan, MI, Italy

<sup>3</sup> Department of Human and Social Science, University of Bergamo, Bergamo, Italy

<sup>4</sup> Mental Health Centre, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China

<sup>5</sup> Centre for Cognition and Brain Disorders, Hangzhou Normal University, Hangzhou, Zhejiang Province, China

<sup>6</sup> The Royal’s Institute of Mental Health Research & University of Ottawa. Brain and Mind Research Institute, Centre for Neural Dynamics, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada

\* Correspondence: Email: [cavicchioli.marco.psicologo@gmail.com](mailto:cavicchioli.marco.psicologo@gmail.com); [andrea.scalabrini@unibg.it](mailto:andrea.scalabrini@unibg.it)

phenomena including absorption, derealization, and depersonalization, together with the absence or alteration of emotional experience (e.g., numbing).<sup>12</sup> However, a clear separation between these dissociative mechanisms and related phenomena is complex and not always recognizable. For instance, dissociative amnesia is mainly viewed as a compartmentalization phenomenon. Nevertheless, the same dissociative phenomenon could be a consequence of an altered state of consciousness linked to detachment mechanisms, which interfere with the encoding and storage of information (e.g., deficit of encoding and storage of traumatic material).

In addition to the previous approaches, dissociative phenomena have also been considered as a psychological dimension<sup>14,15</sup> that range from milder forms with no or minimal interference on adaptation (e.g., absorption, daydreaming, and trance-like behaviors<sup>16–18</sup>) to pathological and more pervasive ones (e.g., dissociative amnesia, derealization, and depersonalization). Dissociation is also considered a transdiagnostic factor that underpins different psychopathological conditions.<sup>19,20</sup> Specifically, Lyssenko and colleagues<sup>19</sup> have shown a dissociative continuum featured by the highest severity of dissociative phenomena within dissociative disorders (DDs), followed by post-traumatic stress disorder (PTSD), borderline personality disorder (BPD), conversion disorder (CD), and somatoform disorders (SDs). According to a hierarchical approach to psychopathology,<sup>21</sup> these disorders might represent a spectrum (i.e., dissociative spectrum [DS]), namely a constellation of syndromes that share latent psychopathological mechanisms (i.e., dissociation). Whereas, the severity of dissociation linearly decreases across other psychiatric conditions, including eating disorders, substance-related and addictive disorders, schizophrenia, obsessive-compulsive disorder, anxiety, and affective disorders.

### Clinical features of dissociation across the dissociative spectrum

Despite dissociation capturing latent mechanisms shared by different conditions ascribed to the DS, some functional and phenomenological differences might be discussed across these disorders. Looking at BPD, there is consistent evidence<sup>4,5,22–24</sup> that has demonstrated a key role of transient stress-related derealization and depersonalization symptoms as extreme forms of avoidance of emotion-eliciting stimuli and/or related internal responses.<sup>25,26</sup> Brown and colleagues<sup>27</sup> suggested that both CD and SDs could be viewed as DDs referring to a revision of clinical studies focused on somatoform dissociation (e.g., anesthesia, seizures, paralysis, and dysphagia). Furthermore, provisional considerations suggested that compartmentalization should be viewed as the key mechanism underlying somatoform dissociative symptoms among individuals with CD and SDs.<sup>12</sup> PTSD shows a constellation of dissociative phenomena, including positive dissociative symptoms (e.g., reexperiencing) and negative dissociative symptoms (e.g., emotional numbing).<sup>28,29</sup> Referring to PTSD linked to repeated interpersonal traumatic experiences (PTSD-IT) and DDs (e.g., dissociative identity disorder [DID]), clinical literature posits at the base of these conditions a key role of a “structural dissociation.”<sup>30,31</sup> This kind of structural dissociation is sustained by a complex system of dissociative symptoms including negative psychoform dissociative symptoms (e.g., amnesia and numbing), negative somatoform dissociative symptoms (e.g., anesthesia and sensory loss), positive psychoform dissociative symptoms (e.g., traumatic memories and nightmares), and positive somatoform dissociative symptoms (intrusions of sensorimotor aspects of traumatic reexperiences and pain).<sup>31,32</sup>

### Manifestation of dissociation in emotional contexts

Dissociation affects different domains of human mental functioning (e.g., time perception, body representation, and identity),<sup>4</sup> including the emotional one. Specifically, experimental and clinical research suggest that dissociation might affect each stage of emotion generation. For instance, emotional-eliciting events might be dissociated

from memory facilitating the onset of automatic and intense affects that are manifested in a chaotic and incongruous form.<sup>33</sup> Dissociative symptoms and mechanisms might also interfere with a coherent encoding of salient events<sup>34,35</sup> leading to an unintegrated experience where different aspects of the event such as its sensory, affective, and cognitive features are separately encoded and disintegrated automatically.<sup>36–38</sup> Stressful affects, especially those associated with emotional pain, are consequently not experienced in consciousness nor integrated within the self, leading to what Bromberg<sup>39</sup> terms “not-me” self-states. Furthermore, dissociation might facilitate the unexpected and nonvoluntary onset of overwhelming affects due to alterations of integration processes.<sup>33,40–45</sup>

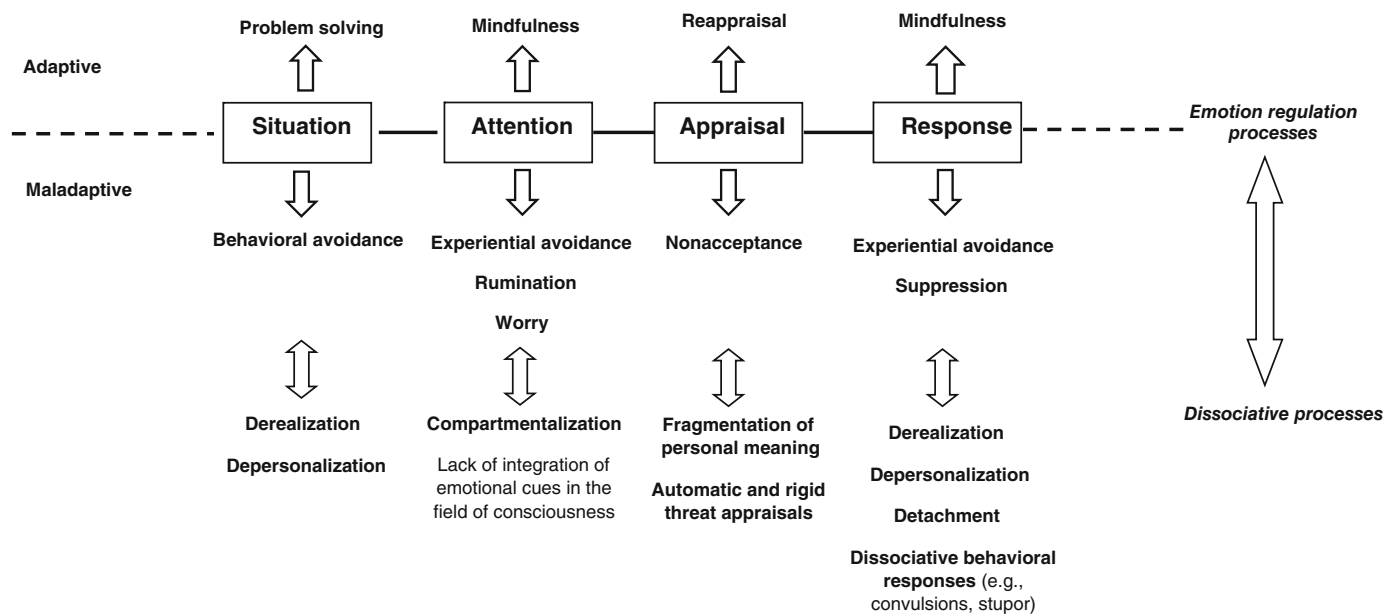
Trying to integrate this evidence with empirical literature on emotion regulation (ER), which focuses on all processes involved in influencing positive and negative emotions in terms of intensity, duration, and/or quality, consciously or automatically,<sup>46</sup> dissociation could be viewed as an ER strategy (ERS) – “an escape before there is no escape.”<sup>47</sup> In this regard, Cavicchioli and colleagues<sup>48</sup> conducted a meta-analytic review to further investigate the relationship between dissociation and adaptive and maladaptive ERSs that individuals use to alter emotional reactions. Meta-analytic findings showed significant associations between dissociation and maladaptive domains of ER, suggesting to view dissociation as a constellation of automatic mechanisms with two main maladaptive functions within the context of ER: (i) escape reactions from internal-external emotion-eliciting situations and related affective responses; and (ii) attempts of overmodulation of affective states (see Fig. 1a,b for a graphical summary).

### Brain networks involved in ER

Psychological processes involved in ER have also found robust support from neuroscience data. Referring to adaptive ERSs (i.e., mindfulness, distraction, reappraisal), neuroimaging research has identified an extended brain network—middle frontal gyrus (MFG), parahippocampal gyrus, hippocampus, insula, bilateral inferior frontal gyrus (IFG)/ventrolateral prefrontal cortex (VLPFC), bilateral superior frontal gyrus (SFG)/dorsal prefrontal cortex (DLPFC), supplementary motor area (SMA), and pre-SMA—that show a heightened activity when individuals use these ERSs (for a meta-analysis see Morawetz et al.<sup>49</sup>). Furthermore, the use of adaptive ERSs, such as mindfulness, was linked to reduced amygdala activation in association with increased activity of DLPFC, MFG, anterior cingulate cortex (ACC) parahippocampal gyrus, hippocampus, and insula.<sup>50,51</sup> The involvement of this extended brain network was also replicated for several maladaptive ERSs including suppression (i.e., greater activation of IFG/VLPFC),<sup>49</sup> rumination (i.e., decreased activation in the left amygdala, hippocampus, ACC, and orbitofrontal cortex),<sup>52</sup> worry (i.e., increased activity of MFG, IFG, and anterior insula) (for a meta-analysis see reference 53), and experiential avoidance (i.e., reduced activation in the left MFG and bilateral amygdala).<sup>54</sup> Figure 2 graphically summarizes brain regions involved in ER processes.

### Neurobiological models of dissociation: strengths and limitations

The first proposal for a neurobiological model of dissociation linked to the emotional functioning was provided by Lanius and colleagues.<sup>28,55</sup> Consistently, dissociative reactions (e.g., disengagement from the emotional content of the traumatic memory through depersonalization or derealization symptoms) among patients with PTSD has been associated with an abnormal increased activation of dorsal ACC (dACC) and the medial PFC together with a concurrent shutdown of limbic regions (e.g., amygdala). Recently, Chiba and colleagues<sup>29</sup> have been provided a partial revision of the previous model based on a meta-analytic review of neuroimaging and behavioral studies. The authors have suggested a reciprocal inhibition between the amygdala and ventromedial PFC that generates dynamic alternations between states of emotional undermodulation (i.e., hyperarousal, hypervigilance, reexperiencing) and overmodulation (i.e., hypoarousal,

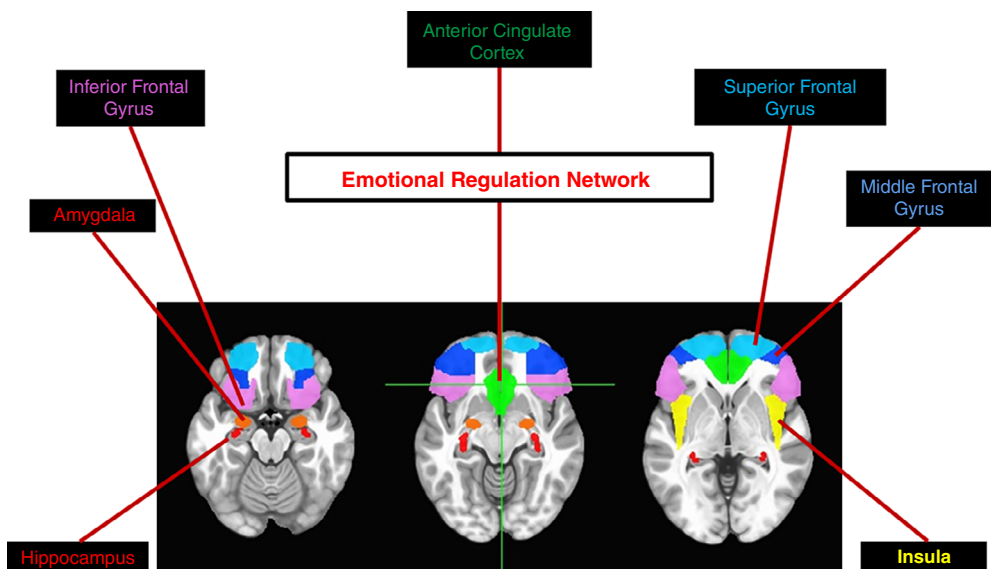


**Fig. 1** (a) An integrative model of dissociation within emotion generation and regulation processes. (b) The relationships between dissociative mechanisms and emotion regulation.

avoidance, dissociation) within the same individual affected from a trauma-related condition.

Despite the relevance of these neurobiological approaches to dissociation in the context of emotion functioning, some limitations might be discussed. First, the previous models focus specifically on the activity of few brain areas (i.e., MFG, IFG, ACC, amygdala). These regions only partially overlap with a more extended and well-supported neural network involved in ER according to the recent literature. Second, these models exclusively refer to the explanation of dissociative responses of individuals with PTSD. This aspect is not sufficient in the understanding of dissociative phenomena in the context of ER, especially referring to empirical evidence that suggests the existence of a psychopathological spectrum (i.e., SDs, CD, BPD, PTSD, DDs)<sup>19,20</sup> characterized by latent dissociative mechanisms at the base of their clinical manifestations.

Most recently, Roydeva and Reinders<sup>56</sup> attempted to provide a comprehensive neurobiological model of dissociation. They conducted a comprehensive qualitative review of neurobiological markers of dissociation (e.g., neuroimaging, psychobiological, psychophysiological, and genetic) associated with clinical conditions ascribed to the DS. Referring to neuroimaging results, this review concluded that the hyperactivity of prefrontal regions, especially SFG, medial parts of IFG, and MFG, should be considered the key neurobiological marker of pathological dissociation. Moreover, the qualitative discussion of results highlighted an increased activity of ACC found across dissociative conditions. It was also discussed the impact of a heightened insula activity, especially during the administration of emotional stimuli. However, the authors did not definitely support the role of ACC and insula as core neurobiological markers of dissociation. Despite the systematic and extensive work of integration, their conclusions based on neuroimaging studies show some



**Fig. 2** Emotion regulation brain network.

limitations. First, the qualitative approach did not allow to precisely estimate whether and which brain region should be considered as key biological markers of dissociative reactions, especially referring to their regulatory functions of affective states. Furthermore, the qualitative approach did not allow to evaluate the heterogeneity of brain activities across studies and clinical conditions constituting the DS. Ultimately, this review did not evaluate whether specific patterns of neural activity associated with dissociation in the context of ER might differentiate each condition ascribed to the DS, which is characterized by distinct clinical manifestations (for diagnostic criteria see<sup>4,5</sup>).

### The present study

Extending findings of previous reviews and meta-analyses,<sup>28,29,56</sup> the current study aims at quantitatively defining the involvement of the ER brain network in the context of emotion-task functional magnetic resonance imaging (fMRI) among disorders constituting the DS. First, using a well-established ER network of interest (i.e. SFG, MFG, IFG, cingulate cortex, insula, parahippocampal gyrus, hippocampus, and amygdala, extracted by<sup>49–54</sup>), we aimed at exploring:

- 1 the ER network activity in response to the administration of emotional stimuli in task-fMRI across the whole DS (i.e., healthy patients with clinically relevant levels of dissociation, SDs/CDs, BPD, PTSD, DDs); and
- 2 specific patterns of neural responses to the presentation of emotional stimuli for each clinical condition constituting the DS.

Accordingly, a network meta-analysis using a Bayesian hierarchical framework<sup>57</sup> was used for two main reasons. First, this method allows to robustly compute effect sizes of between-group differences comprehensively considering the complexity of results<sup>58</sup> reporting brain activity of regions of interest (ROIs) across conditions. Furthermore, the network meta-analysis allows to quantitatively estimate which ROIs might be considered the most representative neural responses to the presentation of emotional stimuli across the whole DS and within each clinical condition ascribed to it.<sup>58</sup> These advantages might address limitations previously discussed concerning the clarification of key patterns of neural activity underlying the whole DS.<sup>56</sup> Moreover, this methodological approach might sustain extensions of existing neurobiological models of dissociative-related disorders<sup>28,29</sup> above and beyond the PTSD.

Ultimately, to further corroborate our investigation and to neuroscientifically support the validity of a psychopathological spectrum characterized by common latent mechanisms,<sup>21</sup> we used a whole brain robust voxel-based approach to explore and confirm the existence of a neural response to emotional stimuli shared by disorders included in the DS.

## Methods

### Criteria for selecting studies

The current meta-analytic review was conducted in line with MARS (Meta-Analysis Reporting Standards) of the American Psychological Association<sup>59</sup> and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.<sup>60</sup> Figure 3 summarizes the inclusion process of studies. To consider studies of comparable quality, the analysis included only studies that were published in scientific journals. PsychINFO, PubMed, ISI Web of Knowledge, and Scopus online databases were used to generate potentially relevant articles.

The online research was based on the following keywords: “dissociation,” “dissociat\* experiences,” “dissociat\* symptoms,” “depersonalization,” “derealization,” “absorption,” “somatoform dissociation,” “detachment,” “compartmentalization” AND “somatoform disorder,” “conversion disorder,” “nonepileptic seizures” “borderline personality disorder,” “post-traumatic stress disorder,” “ptsd,” “complex post-traumatic stress disorder,” “complex ptsd,”

“dissociative disorders” AND “fmri,” “functional magnetic resonance imaging,” “brain imaging,” “neuroimaging.” These key words were used in each online database. Keywords related to clinical conditions ascribed to the DS were chosen referring to the highest tail of the dissociative continuum showed by Lyssenko and colleagues.<sup>19</sup> Furthermore, we included specific keywords for complex PTSD according to a growing support for the validity and reliability of this diagnosis<sup>61</sup> and its differentiation from other disorders of the DS, such as PTSD and BPD.<sup>62,63</sup>

M.C. and A.S. conducted the online research. The screening process was double-checked in order to produce a reliable initial sample of articles to consider for the inclusion in the meta-analysis. From the initial online research, M.C. and A.S. considered for the screening process all articles that showed, within the abstract section, at least an assessment of dissociation or conditions included in the DS and experimental paradigms that administered emotional stimuli within fMRI tasks. Cohen  $k$ <sup>64</sup> was estimated for interrater reliability of studies selection.

In order to be included in the current meta-analytic review, the studies met the following inclusion criteria to support both the validity and the reliability of results:

- 1 All studies assessed clinical conditions with a high level of dissociation referring to valid and reliable diagnostic criteria (i.e., DSM and *International Classification of Diseases*);
- 2 According to empirical evidence regarding the large heterogeneity of dissociation among individuals with BPD,<sup>65,66</sup> studies evaluating the brain activity of individuals with BPD should include patients with high levels of dissociation or individuals with BPD who experienced comorbid conditions included in the DS (e.g., PTSD and DDs);
- 3 Studies that included participants recruited from the general population with high levels of dissociation should report clinically relevant scores using valid and reliable assessment tools;
- 4 All experimental paradigms administered emotional stimuli (e.g., pictures, trauma-related words, and script-driven imagery tasks) during the acquisition of brain activity through fMRI;
- 5 All experimental paradigms referred to the exposure to emotional stimuli without engaging in any cognitive tasks after their presentation. This approach should effectively support the comparability of results among studies and clinical conditions ascribed to the DS, controlling for possible confounding effects linked to the heterogeneity of intentional cognitive processes within and between studies included for meta-analytic procedures;
- 6 Studies included should have compared neural activity between a group characterized by phenomenological manifestations associated with underlying dissociative mechanisms (DG; clinical and non-clinical) and a healthy control (HC) group/group with low levels of dissociation (LDG);
- 7 Studies included should have compared brain activity of DG and LDG after the administration of stimuli with different emotional valences. Considering single-group design studies, the experimental condition administering neutral stimuli was considered as the control condition for the analysis.

Age and sex were not considered exclusion criteria of the meta-analysis. However, analysis explored their possible moderator effect on effect sizes. Table S1 included as supplementary material summarizes characteristics of studies and related references included in the current meta-analysis.

### Data analyses

The current work was based on two different meta-analytic methods. First, we conducted a ROI-based approach applying a network meta-analysis using a Bayesian hierarchical framework through the {gemtc} R package.<sup>57</sup> The most relevant advantage of the {gemtc} R package is that it automates most parts of the Bayesian inference

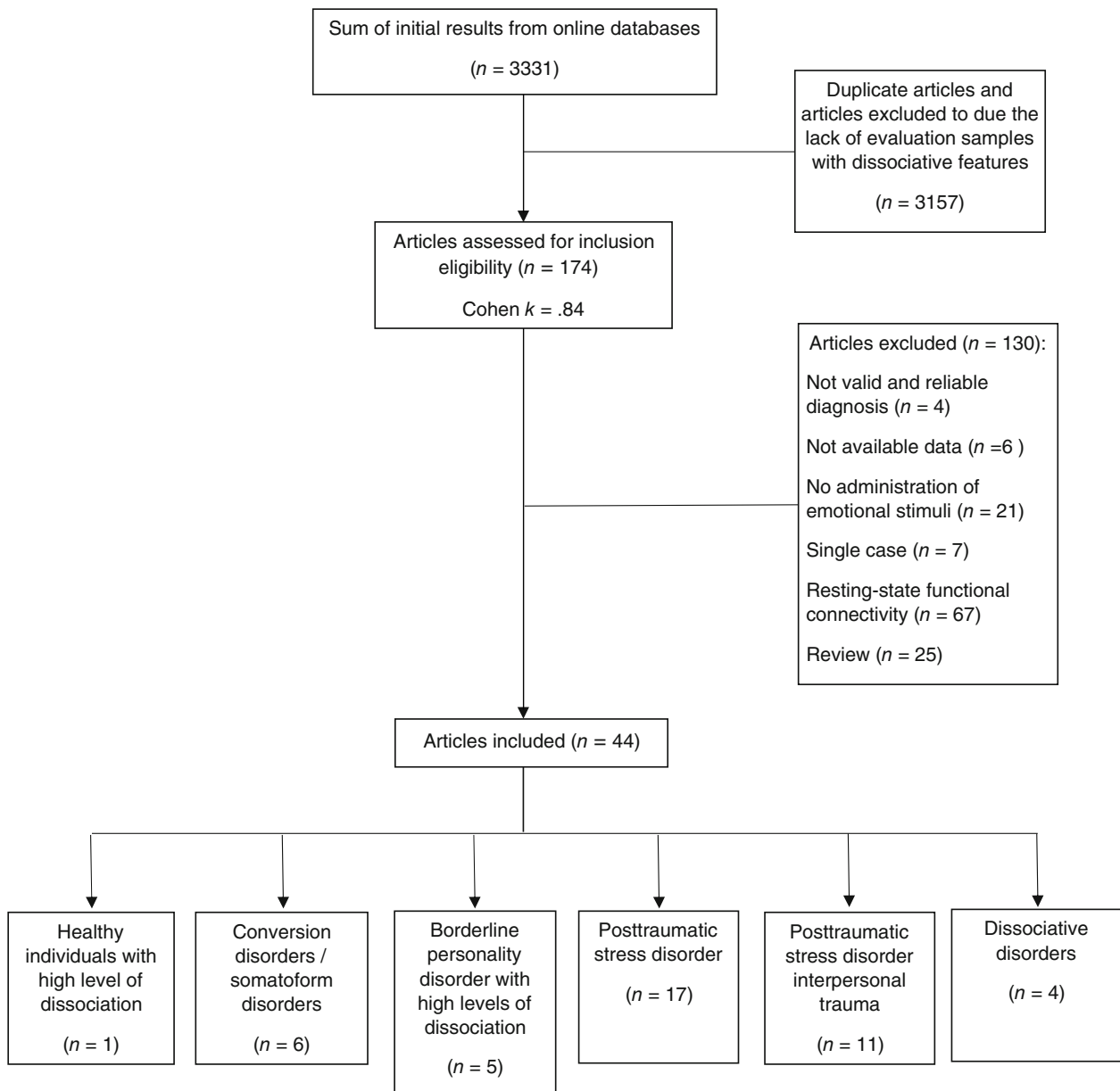


Fig. 3 CONSORT (Consolidated Standards of Reporting Trials) flow chart of studies inclusion process.

process, especially those related to the choice of adequate prior distributions for all parameters in the model (for a detailed description of rationale and statistical procedures see<sup>57</sup>). The Markov Chain Monte Carlo simulation was used to estimate the posterior distributions of model parameters, and thus to generate the results of network meta-analysis, namely a pooled effect size ( $d_{pooled}$ ) and its 95% credible interval (CrI). The analyses were conducted assuming a random-effect model using a normal likelihood distribution in line with continuous data reported by studies included. The Cohen  $d$ <sup>67</sup> was computed as a measure of effect size together with its standard error (SE) according to procedures needed to conduct network meta-analysis using the {gemtc} R package.<sup>57</sup> The Cohen  $d$  reflects the extent of difference of neural response between groups (i.e., DG vs HC/LDG) or between experimental conditions (i.e., emotional stimuli vs neutral stimuli) for single-group design studies. The index was primarily calculated using  $t$  and  $z$  values of peaks reported in the Results section of each study using appropriate procedures proposed by Borenstein and colleagues<sup>68</sup> and Wolf<sup>69</sup> to convert the previous indexes to  $d$ . The

nodesplit method<sup>70</sup> was adopted in order to assess the inconsistency of results within the network.

The Bayesian network meta-analysis also allows to conduct a meta-regression analysis evaluating the impact of relevant variables (age, percentage of women, years of publication, type of emotional stimuli [external stimuli vs script-driven], and severity of dissociative, depressive, and anxious symptoms) on effect sizes. According to the hypotheses of study, the Surface Under the Cumulative Ranking (SUCRA) score<sup>71</sup> was estimated in order to identify which brain activities could be the most representative for both the whole DS and each clinical condition ascribed to it. The SUCRA score reflects the cumulative probability of an ROI within the distribution of probabilities of analyzed ROIs to be the most representative considering the extent of brain activity differences between DG and HC/LDG. This index was computed considering both directions of effects sizes (i.e., negative = deactivation; positive = activation).

We also conducted a voxel-based meta-analysis of neuroimaging evidence using the Seed-based  $d$  Mapping Permutation of Subject

Images (SDM-PSI) (<https://www.sdmproject.com/>).<sup>72</sup> First, the SDM incorporates information about differences in effect size and the spatial correlations of different brain tissue types. Second, the SDM conducts permutation testing at the subject level that allows to estimate the statistical significance using voxel-wise tests. Third, the SDM uses voxel-wise significance combined with threshold-free cluster enhancement (i.e., a method that simulates cluster-wise effects by enhancing voxel-wise statistical values for voxels, which are close together) to adequately control for multiple comparisons while avoiding the use of arbitrary cluster size thresholds. Ultimately, voxel-based meta-analytic results were corrected using a family-wise error (i.e.,  $P < 0.005$ ) approach together with a threshold-free cluster enhancement.

## Results

### Descriptive statistics

Figure 3 summarizes the inclusion process of studies. The analysis showed good interrater reliability values (Cohen  $k = 0.84$ ) for the screening of articles. Forty-four independent studies were included for a total of 1384 individuals (DG = 741 patients) with a mean age of 34.95 years (standard deviation = 7.30 years). Seventeen studies (38.6%) assessed self-report levels of dissociative symptoms between groups showing that individuals ascribed to the DG had up to eight times (mean = 7.98; standard deviation = 9.77) greater severity of these phenomena than comparison conditions. Nineteen studies (43.1%) highlighted that the DG showed five times (mean = 5.47; standard deviation = 5.39) higher levels of depressive symptoms than control groups and, two times higher levels of anxiety ( $n = 7$  [15.9%]; mean = 2.14 [standard deviation = 1.18]). Table 1 summarizes descriptive statistics regarding characteristics of studies included for meta-analytic procedures together with the frequency of ROIs activity revealed among studies. Table S1 provides a detailed description of Cohen  $d$  and its 95% confidence interval of each ROI together with preprocessed data of the SDM algorithm and related effect sizes.

### Network meta-analysis

#### Overall dissociative spectrum

Table 2 summarizes effect sizes and related 95% CrIs of each ROI together with SUCRA values. Referring to a decreased neural activity in response to emotional stimuli, parahippocampal gyrus ( $d_{\text{pooled}} = -2.40$ , 95% CrI: [-3.20 to -1.70]; SUCRA = 0.94), insula ( $d_{\text{pooled}} = -2.40$ , 95% CrI: [-3.30 to -1.50]; SUCRA = 0.93), and amygdala ( $d_{\text{pooled}} = -1.90$ , 95% CrI: [-2.40 to -1.30] SUCRA = 0.80) were the most representative regions of the DS. Considering a heightened neural response, the hippocampus ( $d_{\text{pooled}} = 1.50$  [1.0–2.0]; SUCRA = 0.92), the cingulate cortex ( $d_{\text{pooled}} = 1.40$ , 95% CrI: [1.10–1.70]; SUCRA = 0.87), and the MFG ( $d_{\text{pooled}} = 1.30$ , 95% CrI: [1.10–1.60]; SUCRA = 0.83) represented key brain regions of the DS.

The network meta-regression (independent variables = sample size, age, percentage of women, years of publication, type of emotional stimuli, severity of dissociative, and depressive and anxious symptoms) found significant negative relationships between sample sizes and the extent of ROI effect sizes ( $\beta = -0.35$ , 95% confidence interval: [-58 to -0.14];  $P < 0.001$ ). The nodesplit analysis showed significant inconsistency within the network (i.e., six significant different estimations using direct and indirect values). According to this inconsistency and the hypotheses of study, we conducted a network meta-analysis for each specific condition ascribed to the DS.

#### BPD with high levels of dissociation

Table 3 summarizes effect sizes of each ROI and related SUCRA values. The nodesplit analysis confirmed the consistency of network. Despite the extent of large effect sizes for all ROIs, the Bayesian estimation showed that all 95% CrIs associated with pooled effect sizes of ROIs included the 0. The SUCRA analysis showed that the deactivation of amygdala ( $d_{\text{pooled}} = -2.00$ , 95% CrI: [-5.00–0.71];

**Table 1.** Descriptive statistics of studies ( $N = 44$ )

	Number	Percentage
Only women	18	31.8
Only men	1	2.3
Men and women	25	56.8
Individualized script-driven stimuli	29	65.9
Emotional stimuli (i.e., pictures, words, videoclips, and audio)	15	34.1
Borderline personality disorder	5	11.3
Somatiform disorder and conversion disorder	6	13.6
PTSD single nonrelational traumatic experiences	17	38.6
PTSD repeated interpersonal traumatic experiences	11	25.0
Dissociative disorders	4	9.1
↑ Cingulate cortex	14	31.8
↑ Middle frontal gyrus	12	27.2
↑ Superior frontal gyrus	10	22.7
↑ Insula	10	22.7
↑ Amygdala	10	22.7
↑ Inferior frontal gyrus	7	15.9
↑ Parahippocampal gyrus	6	13.6
↑ Hippocampus	4	9.0
↓ Middle frontal gyrus	5	27.2
↓ Amygdala	4	9.0
↓ Parahippocampal gyrus	3	6.8
↓ Hippocampus	3	6.8
↓ Insula	2	4.5
↓ Cingulate	2	4.5
↓ Inferior frontal gyrus	2	4.5
↓ Superior frontal gyrus	1	2.2

Abbreviation: PTSD, posttraumatic stress disorder.

SUCRA = 0.96) was the most representative neural response of individuals with BPD characterized by a high level of dissociation, compared with the other heightened brain activities.

#### CD and SDs

Table 4 highlights that patients with CD/SDs were characterized by a large deactivation of the MFG ( $d_{\text{pooled}} = -3.58$ , 95% CrI: [-7.20 to -0.51]), the insula ( $d_{\text{pooled}} = -2.20$ , 95% CrI: [-4.70 to -0.43]), and the parahippocampal gyrus ( $d_{\text{pooled}} = -1.90$ , 95% CrI: [-4.10 to -0.06]) together with a large hyperactivation of hippocampus ( $d_{\text{pooled}} = 3.70$ , 95% CrI: [0.68–6.50]). The nodesplit analysis supported the consistency of the network. SUCRA values showed that the most representative brain activity in response to emotional stimuli among individuals with CD/SDs were hyperreactivity of the hippocampus (SUCRA = 0.97) and reduced activity of the MFG (SUCRA = 0.93) and the insula (SUCRA = 0.77).

#### PTSD related to single nonrelational traumatic experiences

Table 5 summarizes results of network meta-analysis for patients with PTSD who were exposed to single nonrelational traumatic experiences. The Bayesian estimation of effect sizes showed large differences between patients with PTSD and control conditions considering all ROIs. The nodesplit analysis did not reveal inconsistency within the network. The SUCRA analysis suggested that the most representative brain responses to emotional stimuli of individuals with PTSD

**Table 2.** ROIs across the dissociative spectrum

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA deactivation	ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↓Parahippocampal gyrus ( $n = 3$ )	-2.40 (-3.20 to -1.70)	0.94	↑Hippocampus	1.50 (1.0-2.0)	0.92
↓Insula ( $n = 2$ )	-2.40 (-3.30 to -1.50)	0.93	↑Cingulate cortex	1.40 (1.10-1.70)	0.87
↓Amygdala ( $n = 4$ )	-1.90 (-2.40 to -1.30)	0.80	↑Middle frontal gyrus	1.30 (1.10-1.60)	0.83
↓Hippocampus ( $n = 3$ )	-1.80 (-2.50 to -1.20)	0.79	↑Inferior frontal gyrus	1.30 (0.88-1.70)	0.80
↓Inferior frontal gyrus ( $n = 2$ )	-1.60 (-2.40 to -0.85)	0.74	↑Superior frontal gyrus	1.30 (1.00-1.60)	0.79
↓Superior frontal gyrus ( $n = 1$ )	-1.60 (-2.60 to -0.61)	0.73	↑Parahippocampal gyrus	1.20 (0.75-1.60)	0.73
↓Cingulate cortex ( $n = 2$ )	-1.40 (-2.20 to -0.72)	0.68	↑Amygdala	1.10 (0.78-1.50)	0.68
↓Middle frontal gyrus ( $n = 5$ )	-1.20 (-1.70 to -0.75)	0.61	↑Insula	1.10 (0.77-1.40)	0.65
↑Insula ( $n = 10$ )	1.10 (0.77-1.40)	0.35	↓Middle frontal gyrus	-1.20 (-1.70 to -0.75)	0.39
↑Amygdala ( $n = 10$ )	1.10 (0.78-1.50)	0.32	↓Cingulate cortex	-1.40 (-2.20 to -0.72)	0.32
↑Parahippocampal gyrus ( $n = 6$ )	1.20 (0.75-1.60)	0.27	↓Superior frontal gyrus	-1.60 (-2.60 to -0.61)	0.27
↑Superior frontal gyrus ( $n = 10$ )	1.30 (1.00-1.60)	0.21	↓Inferior frontal gyrus	-1.60 (-2.40 to -0.85)	0.26
↑Inferior frontal gyrus ( $n = 7$ )	1.30 (0.88-1.70)	0.20	↓Hippocampus	-1.80 (-2.50 to -1.20)	0.21
↑Middle frontal gyrus ( $n = 12$ )	1.30 (1.10-1.60)	0.17	↓Amygdala	-1.90 (-2.40 to -1.30)	0.20
↑Cingulate cortex ( $n = 14$ )	1.40 (1.10-1.70)	0.13	↓Insula	-2.40 (-3.30 to -1.50)	0.07
↑Hippocampus ( $n = 4$ )	1.50 (1.0-2.0)	0.08	↓Parahippocampal gyrus	-2.40 (-3.20 to -1.70)	0.06

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.  
 ↓ = reduced activity; ↑ = increased activity

**Table 3.** Borderline personality disorder

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA deactivation	ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↓Amygdala ( $n = 2$ )	-2.00 (-5.00 to 0.71)	0.96	↑Insula	2.60 (-1.30 to 7.10)	0.75
↑Middle frontal gyrus ( $n = 1$ )	1.50 (-2.10 to 5.50)	0.45	↑Inferior frontal gyrus	2.20 (-1.60 to 6.7)	0.69
↑Cingulate cortex ( $n = 1$ )	1.80 (-1.90 to 6.2)	0.40	↑Superior frontal gyrus	1.90 (-0.82 to 5.50)	0.63
↑Superior frontal gyrus ( $n = 2$ )	1.90 (-0.82 to 5.50)	0.37	↑Cingulate cortex	1.80 (-1.90 to 6.2)	0.60
↑Inferior frontal gyrus ( $n = 1$ )	2.20 (-1.60 to 6.7)	0.31	↑Middle frontal gyrus	1.50 (-2.10 to 5.50)	0.55
↑Insula ( $n = 1$ )	2.60 (-1.30 to 7.10)	0.25	↓Amygdala	-2.00 (-5.00 to 0.71)	0.04

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.

**Table 4.** Conversion disorder and somatoforms disorders

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA deactivation	ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↓Middle frontal gyrus ( $n = 1$ )	-3.58 (-7.20 to -0.51)	0.93	↑Hippocampus	3.70 (0.68 to 6.50)	0.97
↓Insula ( $n = 2$ )	-2.20 (-4.70 to -0.43)	0.77	↑Parahippocampal gyrus	1.70 (-1.30 to 4.80)	0.81
↓Parahippocampal gyrus ( $n = 2$ )	-1.90 (-4.10 to -0.06)	0.71	↑Cingulate Cortex	1.60 (-1.40 to 4.60)	0.79
↓Hippocampus ( $n = 2$ )	-1.70 (-3.90 to 0.15)	0.65	↓Amygdala	-1.70 (-3.90 to 0.16)	0.36
↓Amygdala ( $n = 2$ )	-1.70 (-3.90 to 0.16)	0.64	↓Hippocampus	-1.70 (-3.90 to 0.15)	0.35
↑Cingulate cortex ( $n = 1$ )	1.60 (-1.40 to 4.60)	0.21	↓Parahippocampal gyrus	-1.90 (-4.10 to -0.06)	0.29
↑Parahippocampal gyrus ( $n = 1$ )	1.70 (-1.30 to 4.80)	0.19	↓Insula	-2.20 (-4.70 to -0.43)	0.23
↑Hippocampus ( $n = 1$ )	3.70 (0.68- 6.50)	0.03	↓Middle frontal gyrus	-3.58 (-7.20 to -0.51)	0.07

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.

were reduced activity of the hippocampus ( $d_{\text{pooled}} = -2.00$ , 95% CrI: [-2.90 to -1.00]; SUCRA = 0.92), the IFG ( $d_{\text{pooled}} = -1.80$ , 95% CrI: [-2.50 to -1.00]; SUCRA = 0.87), and the SFG

( $d_{\text{pooled}} = -1.60$ , 95% CrI: [-2.50 to -0.64]; SUCRA = 0.82) together with an enhanced reactivity of the amygdala ( $d_{\text{pooled}} = 1.50$ , 95% CrI: [0.65-2.30]; SUCRA = 0.87), the parahippocampal gyrus

**Table 5.** PTSD related to single nonrelational traumatic experiences

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA deactivation	ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↓Hippocampus ( $n = 1$ )	-2.00 (-2.90 to -1.00)	0.92	↑Amygdala	1.50 (0.65–2.30)	0.87
↓Inferior frontal gyrus ( $n = 2$ )	-1.80 (-2.50 to -1.00)	0.87	↑Parahippocampal gyrus	1.30 (0.36–2.20)	0.78
↓Superior frontal gyrus ( $n = 1$ )	-1.60 (-2.50 to -0.64)	0.82	↑Cingulate cortex	1.20 (0.86–1.50)	0.76
↓Middle frontal gyrus ( $n = 3$ )	-1.60 (-2.10 to -1.00)	0.80	↑Superior frontal gyrus	1.20 (0.83–1.50)	0.75
↓Cingulate cortex ( $n = 2$ )	-1.40 (-2.00 to -0.73)	0.75	↑Inferior frontal gyrus	1.20 (0.61–1.70)	0.74
↑Middle frontal gyrus ( $n = 4$ )	1.1 (0.58–1.60)	0.32	↑Insula	1.00 (0.16–1.90)	0.69
↑Insula ( $n = 1$ )	1.00 (0.16–1.90)	0.31	↑Middle frontal gyrus	1.1 (0.58–1.60)	0.68
↑Inferior frontal gyrus ( $n = 3$ )	1.20 (0.61–1.70)	0.26	↓Cingulate cortex	-1.40 (-2.00 to -0.73)	0.25
↑Superior frontal gyrus ( $n = 4$ )	1.20 (0.83–1.50)	0.25	↓Middle frontal gyrus	-1.60 (-2.10 to -1.00)	0.20
↑Cingulate cortex ( $n = 6$ )	1.20 (0.86–1.50)	0.24	↓Superior frontal gyrus	-1.60 (-2.50 to -0.64)	0.18
↑Parahippocampal gyrus ( $n = 1$ )	1.30 (0.36–2.20)	0.22	↓Inferior frontal gyrus	-1.80 (-2.50 to -1.00)	0.13
↑Amygdala ( $n = 1$ )	1.50 (0.65–2.30)	0.13	↓Hippocampus	-2.0 (-2.90 to -1.00)	0.08

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.

( $d_{\text{pooled}} = 1.50$ , 95% CrI: [0.65–2.30];  $P < 0.001$ ; SUCRA = 0.78), and the cingulate cortex ( $d_{\text{pooled}} = 1.20$ , 95% CrI: [0.86–1.50]; SUCRA = 0.76).

**PTSD related to repeated interpersonal traumatic experiences**

Table 6 provides results of network meta-analysis for patients with PTSD-IT. Results showed consistent heightened neural responses to emotional stimuli among individuals with PTSD-IT compared with control conditions. The effect sizes were large. The SUCRA values suggested that the most representative brain responses of individuals with PTSD-IT were an enhanced activity of the MFG ( $d_{\text{pooled}} = 1.20$ , 95% CrI: [0.77–1.80]; SUCRA = 0.79), the cingulate cortex ( $d_{\text{pooled}} = 1.20$ , 95% CrI: [0.79–1.60]; SUCRA = 0.74), and the IFG ( $d_{\text{pooled}} = 1.20$ , 95% CrI: [0.56–1.80]; SUCRA = 0.70).

**Dissociative disorders**

Table 7 reports results of network meta-analysis. Findings showed that patients with DDs were characterized by a consistent heightened brain activity in response to emotional stimuli compared with controls. All ROIs highlighted large effect sizes. The SUCRA values suggested that enhanced responses of the MFG ( $d_{\text{pooled}} = 2.30$ , 95%

CrI: [0.77–4.00]; SUCRA = 0.72), the cingulate cortex ( $d_{\text{pooled}} = 2.10$  [0.67–3.90]; SUCRA = 0.67), and the parahippocampal gyrus ( $d_{\text{pooled}} = 2.20$ , 95% CrI: [0.23–4.40]; SUCRA = 0.67) were the most representative for DDs.

**Summary of network meta-analysis**

A deactivation of limbic areas (i.e., amygdala and parahippocampal gyrus) and the insula together with heightened responses of the hippocampus, the cingulate cortex, and the MFG represented the most relevant ROIs characterizing the whole DS in response to emotional stimuli. Going within the DS, SUCRA analyses suggested that BPD and CD/SDs were mainly characterized by decreased responses within specific ROIs (i.e., amygdala, insula, and MFG). On the contrary, individuals with PTSD linked to single nonrelational traumatic experiences showed a mixed functioning, namely deactivation (i.e., hippocampus and frontal regions) and activation (i.e., limbic regions and cingulate cortex) of different ROIs within the ER network. Ultimately, PTSD-IT and DDs showed similar increased and consistent neural responses of the ER network to emotional stimuli, which were mainly represented by heightened activity of the MFG and the cingulate cortex (see Fig. 4 for a summary of network meta-analytic findings).

**Voxel-based meta-analysis**

Figure 4 and Table 8 show meta-analytic results using the SDM algorithm. The analysis found that the left anterior cingulate/paracingulate

**Table 6.** PTSD related to repeated interpersonal traumatic experiences

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↑Middle frontal gyrus ( $n = 4$ )	1.20 (0.77–1.80)	0.79
↑Cingulate cortex ( $n = 4$ )	1.20 (0.79–1.60)	0.74
↑Inferior frontal gyrus ( $n = 2$ )	1.20 (0.56–1.80)	0.70
↑Superior frontal gyrus ( $n = 3$ )	1.10 (0.66–1.60)	0.64
↑Parahippocampal gyrus ( $n = 3$ )	0.93 (0.46–1.50)	0.46
↑Insula ( $n = 6$ )	0.91 (0.61–1.30)	0.41
↑Amygdala ( $n = 6$ )	0.90 (0.57–1.30)	0.40
↑Hippocampus ( $n = 2$ )	0.82 (0.23–1.40)	0.36

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.

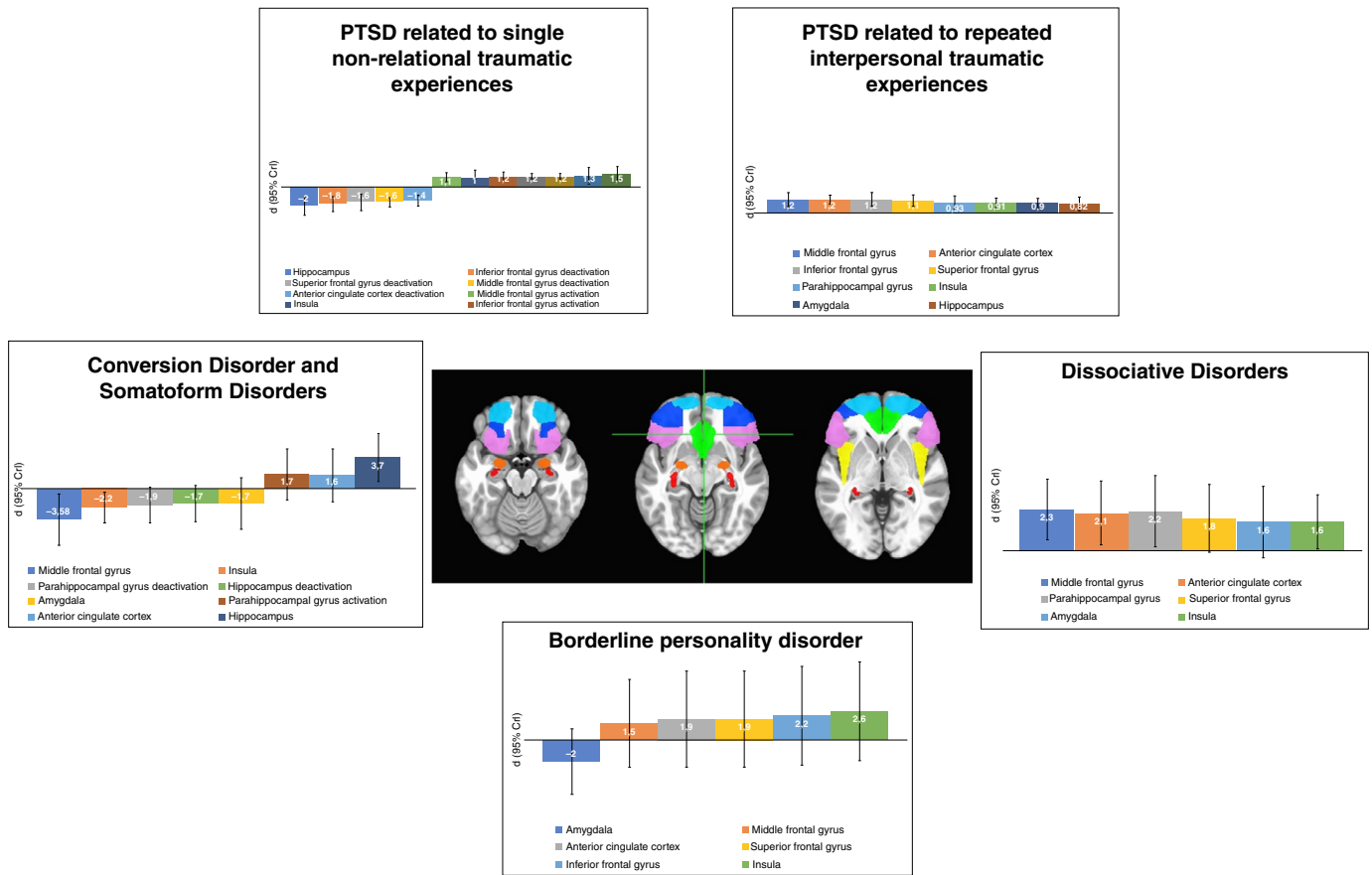
**Table 7.** Dissociative disorders

ROIs	$d_{\text{pooled}}$ (95% CrI)	SUCRA activation
↑Middle frontal gyrus ( $n = 2$ )	2.30 (0.77–4.00)	0.72
↑Cingulate cortex ( $n = 2$ )	2.10 (0.67–3.90)	0.67
↑Parahippocampal gyrus ( $n = 1$ )	2.20 (0.23–4.40)	0.67
↑Superior frontal gyrus ( $n = 1$ )	1.80 (-0.03–4.00)	0.54
↑Amygdala ( $n = 1$ )	1.60 (-0.42–3.60)	0.46
↑Insula ( $n = 2$ )	1.60 (0.08–3.20)	0.45

Abbreviations: CrI, credible interval; ROI, region of interest; SUCRA, Surface Under the Cumulative Ranking.



(a) Summary of network meta-analysis



(b) Voxel-based meta-analysis

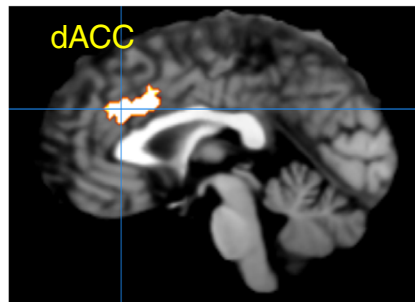


Fig. 4 Summary of (a) network- and (b) voxel-based meta-analysis. CrI, credible interval; dACC, dorsal anterior cingulate cortex; PTSD, posttraumatic stress disorder.

Table 8. SDM results for voxel-based meta-analysis

MNI coordinate x, y, z	SDM-Z	P value	Description	Brodmann area
0, 24, 28	4.53	0.004	Left anterior cingulate/paracingulate gyrus	24
0, 16, 30	4.39	0.004	Left anterior cingulate/paracingulate gyrus	24
4, 28, 28	4.37	0.004	Right anterior cingulate/paracingulate gyrus	24
0, 30, 28	4.36	0.004	Left anterior cingulate/paracingulate gyrus	24

Abbreviations: MNI, Montreal Neurological Institute; SDM, Seed-based *d* Mapping.

gyrus ( $x = 0$ ;  $y = 24$ ;  $z = 28$ ;  $Z = 4.53$ ;  $P = 0.004$ ; number of voxels = 70) was the key region characterizing the neural response to emotional stimuli of conditions ascribed to the DS. Specifically, the DG showed a significant and consistent heightened activity of this region (Hedges  $g_{\text{voxel}} = 0.14$ , 95% confidence interval: [0.08–0.20];  $P < 0.005$ ;  $Q^2 = 30.63$ ; not significant;  $I^2 = 1.69$ ). Egger regression did not detect publication bias ( $\alpha = 0.35$ ; not significant).

## Discussion

The current quantitative meta-analysis sought to clarify neural responses to emotional stimuli across the whole DS and within each condition ascribed to this psychopathological spectrum. The current study adopted a network meta-analytic approach focusing on ROIs relevant for ER processes together with a robust voxel-based meta-analysis. These methods were chosen in order to address limitations and to extend findings of prior neurobiological models of dissociation.<sup>28,29,56</sup>

The network meta-analysis confirmed that all ROIs comprising the ER network largely differentiated individuals ascribed to the DS from control conditions. Particularly, the analysis found differences between groups considering both heightened and reduced brain responses to the presentation of emotional stimuli. Particularly, the most representative neural response of individuals included in the DS were large deactivations of the amygdala, the parahippocampal gyrus, and the insula together with heightened activities of the hippocampus, the cingulate cortex, and the MFG.

Looking at evidence concerning the role of amygdala and parahippocampal gyrus in explaining automatic emotional processing,<sup>73,74</sup> the deactivation of these regions might be in line with clinical studies that reported common difficulties with a coherent encoding of emotional-eliciting events linked to maladaptive effects of dissociative reactions among conditions included in the DS.<sup>34,35</sup> The inhibition of limbic activity in response to emotional-eliciting stimuli is also in line with Chiba and colleagues' model<sup>28</sup> that views dissociative phenomena as a nonvoluntary attentional escape from threatening situations, which is mainly sustained by a deactivation of amygdala. This neurobiological evidence also fits with evidence-based psychological frameworks that have demonstrated a rigid avoidance function of dissociation in the context of ER.<sup>48</sup>

The large deactivation of insula might also suggest an additional maladaptive feature of neural response to emotional stimuli of individuals included in the DS, namely the lack of integration of different aspects of affective reactions (e.g., body sensations, impulse, arousal, cognitive features, and subjective experiences)<sup>36–38</sup> within the self.<sup>39,42,75</sup> This consideration is well-supported by a large number of empirical data that have demonstrated a key role of insula activation in sustaining adaptive interoception,<sup>76</sup> emotional awareness,<sup>77</sup> and the development of complex mental representations of emotional reactions.<sup>78,79</sup>

Meta-analytic findings also highlighted that the DS recurrently showed a heightened activity of regions (i.e., cingulate cortex and MFG) involved in top-down cognitive control of emotions, especially referring to response-focused ERs.<sup>49</sup> This evidence is in line with the Lanius and colleagues' model of PTSD dissociative subtype,<sup>28</sup> and it might be linked to previous meta-analytic results that showed a robust association between dissociative phenomena and psychological ERs with a cognitive overmodulatory function of affective states.<sup>48</sup> Interestingly, the analyses showed a key role of hyperactivity of the hippocampus in response to emotional stimuli among individuals included in the DS. The role of the hippocampus together with the previously mentioned responses of the ER brain network, especially the reduced amygdala activation, might suggest alterations of emotional learning (i.e., fragmented representations of emotional-eliciting events within memory systems and impairments of retrieval),<sup>33,80</sup> which are reported across conditions included in the DS.<sup>81–83</sup> However, the analyses also suggested the need to separately explore the neural functioning of each clinical condition of the DS.

## Borderline personality disorder

The network meta-analysis found that individuals with BPD characterized by high levels of dissociation showed reduced activity of the amygdala together with heightened activity of the MFG, cingulate cortex, SFG, IFG, and insula. This neural profile might suggest an implicit overcontrol of emotional responses associated with a shoutdown of limbic activity, which has been associated with depersonalization and derealization symptoms<sup>28</sup> representing diagnostic features of this disorder.<sup>4</sup> On the one hand, meta-analytic results showed large effect sizes for all ROIs. On the other hand, these effect sizes showed 95% CrIs that included the 0. This evidence is not fully surprising considering the large heterogeneity of severity of dissociation among individuals with BPD.<sup>65,66</sup> According to the current neurobiological results and clinical perspectives, we could suggest that dissociative mechanisms with a function of ER represent a relevant, albeit not core, feature of BPD.<sup>20</sup>

## CD and SDs

Patients with CD/SDs highlighted a large deactivation of MFG, insula, and parahippocampal gyrus in response to emotional stimuli compared with control conditions. Accordingly, these neural responses to emotional stimuli might suggest that CD/SDs are characterized by alterations of integrative mechanisms considering different domains of functioning, namely: (i) encoding processes of emotional-eliciting situations; (ii) mind–body representations of emotional reactions; and (iii) episodic memory consolidation and retrieval.<sup>74,79,84–86</sup> Therefore, these results might support the clinical perspective that includes CD and SDs within the DS.<sup>27</sup> For these conditions, the key dissociative mechanisms might refer to alternations of integrative processes during the stages of emotion generation and regulation.

## PTSD related to single nonrelational traumatic experiences

The network meta-analysis highlighted that: (i) all ROIs included in the ER network largely differentiated individuals with PTSD from control conditions; (ii) prefrontal areas (i.e., IFS, MFG, and SFG) and the cingulate cortex showed both heightened and reduced responses to the presentation of emotional stimuli; and (iii) the most representative differences in brain responses between patients with PTSD and control groups were a deactivation of hippocampus together with a hyperreactivity of the amygdala and the parahippocampal gyrus.

The coexistence of both heightened and reduced prefrontal responses to emotional stimuli partially confirms Chiba and colleagues' model<sup>29</sup> of PTSD based on a reciprocal inhibition between the amygdala and prefrontal areas. Particularly, the heightened reactivity of the amygdala and the parahippocampus together with the deactivation of prefrontal areas (i.e., IFS, MFG, and SFG) overlap with the undermodulation state proposed by previous neurobiological models of PTSD,<sup>28,29</sup> which is characterized by a predominance of positive dissociative phenomena (e.g., reexperiencing). This conclusion could be further supported by the key role of hippocampus deactivation, especially referring to clinical perspectives that view dissociative reexperiencing as brief and intense trauma-related misperceptions of environmental sensory stimuli.<sup>87</sup> Indeed, the hippocampus activity is crucial for recognition memory, which includes the ability to judge the prior occurrence of a stimuli constellation<sup>88</sup> or to evaluate environmental stimuli as familiar.<sup>89</sup>

However, meta-analytic results also highlight significant and large activations of the cingulate cortex and prefrontal regions (i.e., IFG and SFG) among patients with PTSD. These results might partially support the hypothesis regarding the PTSD overmodulation state proposed by Chiba and colleagues,<sup>29</sup> who explain the PTSD dissociative subtype through a hypermodulation of affective states associated with dissociative prefrontal-based avoidance reactions (e.g., depersonalization and derealization).

Current meta-analytic data show a heightened response of the amygdala to emotion stimuli contrary to prior neurobiological models

of PTSD dissociative subtype.<sup>28,29</sup> This evidence was not fully surprising in light of robust associations between depersonalization/derealization reactions and PTSD hyperarousal cluster of symptoms.<sup>90,91</sup> Furthermore, psychophysiological studies on depersonalization consistently showed an association between this phenomenon and a heightened tonic arousal (for a meta-analysis see<sup>92</sup>). The same finding was replicated across several studies evaluating psychophysiological responses of patients with PTSD (for a meta-analysis see<sup>93</sup>). Therefore, this neurobiological evidence might support that patients with PTSD may be characterized by an extensive and dynamic constellation of dissociative mechanisms (i.e., positive dissociative symptoms, overmodulatory, or avoidance dissociative processes) in response to emotional stimuli compared with controls.

### PTSD related to repeated interpersonal traumatic experiences

Meta-analytic results highlighted three main findings: (i) the most representative neural responses refer to a heightened activity of prefrontal regions (i.e., MFG, IFG, and SFG) and the cingulate cortex; (ii) the most recurrent results reported across studies were hyperactivity of amygdala and insula; and (iii) the patterns of neural activity in response to emotional stimuli was qualitatively different from individuals with PTSD who were exposed to single non-relational traumatic experiences.

According to considerations discussed in the previous sections, the heightened prefrontal and cingulate cortex responses to emotional stimuli might be associated with overmodulatory mechanisms that alter emotional reactions and related somatosensory experiences. This neurobiological evidence is in line with clinical studies that highlight a role of maladaptive ERSs with a function of overcontrol of affective states (i.e., expressive suppression and nonacceptance) as core ER mechanisms adopted by individuals with complex PTSD.<sup>94,95</sup>

Interestingly, one of the most recurrent findings was the hyperactivity of the amygdala in response to emotional stimuli. Furthermore, the current meta-analysis showed relevant implications of a heightened insula activity. There are consistent findings suggesting that the hyperactivity of the amygdala is involved in implicit threats processing, especially among patients with PTSD.<sup>96</sup> Several neurobiological studies also show that the insula is associated with two different neuromental activities, including processing of emotional valence, long-term retention of appetitive-aversive-novelty-driven learning, and decision-making processes based on the anticipation of negative and positive outcomes.<sup>97</sup> Accordingly, these neural responses might also suggest key alterations of threat appraisal of a wide range of emotional-eliciting situations, which have been associated with maladaptive effects of dissociative processes.<sup>98</sup> Ultimately, the current meta-analysis provides a provisional neurobiological support for growing evidence related to the distinction between complex PTSD and PTSD.<sup>99</sup>

### Dissociative disorders

Meta-analytic results showed that individuals with DDs highlighted an increased neural response to emotional stimuli compared with control conditions, which was similar to individuals with PTSD-IT. Indeed, a consistent enhanced response to emotional stimuli of prefrontal areas (i.e., MFG, and SFG), the cingulate cortex, the parahippocampal gyrus, and the amygdala together with the insula was found. Furthermore, there was a substantial overlap of the extent of effect sizes found among individuals with DDs and PTSD-IT (Tables 6 and 7). This evidence might provide empirical support for clinical theories that identify a trauma-related spectrum that includes PTSD, complex PTSD, and more complex dissociative conditions such as dissociative disorder not otherwise specified and DID.<sup>10,31</sup>

### ACC as a dissociative signature across the spectrum

The robust voxel-based meta-analysis showed that clinical conditions constituting the DS showed a heightened activity of dACC in

response to emotional stimuli compared with control groups. Referring to the emotional functioning, empirical evidence has demonstrated that the dACC is a key region involved in threat and noxious stimuli appraisal<sup>100</sup> and it supports the expressions of negative affective states (e.g., fear),<sup>101</sup> especially experiences of pain<sup>102</sup> and related emotional components.<sup>103</sup> Moreover, a recent fMRI meta-analysis<sup>104</sup> showed a key role of dACC in connection with right anterior insula (as part of the salience network) on the functional relationship between interoception and ER. Taken these findings together, the key role of dACC in the whole DS suggests an abnormal detected internal-external salience in response to emotional stimuli. Moreover, imaging studies have found a robust association between dACC and several processes relevant for ER, namely conflict monitoring and emotional awareness,<sup>105–109</sup> that are affected by dissociative mechanisms during emotional tasks among individuals included in the DS.<sup>110,111</sup>

Therefore, the involvement of dACC among conditions included in the DS could support the hypothesis that: (i) they are characterized by implicit and rigid evaluations of external and internal emotionally relevant situations as threatening and/or noxious for own mental and physical integrity; (ii) they experience emotions associated with painful sensations, which could reflect a correspondence between physical and psychological pain<sup>112</sup>; and (iii) difficulties with the management of real or perceived threatening situations reported by individuals included in the DS might be linked to altered emotional awareness and conflict monitoring processes.<sup>113,114</sup>

### Limitations

Despite the evidence provided in the previous sections, some limitations must be discussed. First, the brain network of patients with BPD who had high levels of dissociation were based on a limited number of independent studies ( $n = 5$ ). This might provide a possible explanation for the 95% CIs that included the 0. Accordingly, further neuroimaging research should be conducted on this well-recognized subgroup of patients with BPD,<sup>64,65</sup> especially comparing them with individuals with BPD who do not report dissociative symptoms. This should further clarify the neurobiological underpinnings of dissociative mechanisms in the context of maladaptive ER among patients with BPD. Similar considerations could be extended to CD and SDs. Particularly, it could be useful to enrich neurobiological evidence concerning the emotional functioning of CD and other SDs in order to better sustain the inclusion of these conditions within the DS. Additional empirical research should be performed among patients with different DDs, including DID, dissociative amnesia, and depersonalization/derealization disorder. On the one hand, the current meta-analysis computed pooled effect sizes for DDs combining results for all previous conditions. On the other hand, it might be beneficial to conduct further neuroscience research in order to support whether brain responses to emotional stimuli could be the same among these disorders or, a continuum of an increasing activation of ROIs in line with results of self-report measures might exist.<sup>19</sup> An additional limitation refers to the inclusion of healthy individuals as controls for detecting underlying mechanisms of the DS. Accordingly, future neuroimaging studies should compare disorders included in the DS with clinical conditions characterized by low levels of dissociation (e.g., mood disorders, anxiety disorders, and obsessive-compulsive disorder)<sup>19</sup> during the presentation of emotional stimuli in order to effectively detect neural underpinnings of latent dissociative dimensions in the context of emotion functioning.

Moreover, the sample size represented a confounding factor on the extent of effect size. Particularly, studies with smaller sample sizes reported larger differences between the DG and control conditions. Ultimately, the meta-regression did not detect a significant association between the severity of self-report dissociative symptoms and ROIs activity in response to emotional stimuli. This could reflect that patients might have moderate difficulties with an accurate evaluation of implicit mental phenomena, such as dissociation.<sup>115</sup> Accordingly,

future neuroimaging studies on this topic should systematically assess the severity of dissociative symptoms through the administration of well-validated semistructured interviews (e.g., Dissociative Disorders Interview Schedule for DSM-5<sup>116</sup>; Structured Clinical Interview for DSM-IV Dissociative Disorders<sup>117</sup>). An additional explanation for the lack of significant associations between self-report measures of dissociation and neural responses to emotional stimuli could be attributed to the trait-based quality of measures that are not able to capture transient dissociative phenomena during the experimental paradigms. Therefore, future studies might benefit from the administration of self-report measures that evaluate states of dissociation (e.g., Dissociation-Tension-Scale [DSS-4]<sup>118</sup>).

## Conclusions

Despite these limitations, this is, to the best of our knowledge, the first quantitative meta-analytic review of neuroimaging studies that applied robust methods to clarify neural responses to emotional stimuli across the DS. According to the current findings, we could hypothesize that:

- 1 the core neural signature shared by clinical conditions ascribed to the DS capture alterations of encoding mechanisms that are characterized by implicit appraisals of emotion-eliciting stimuli as threatening and/or noxious for mental and physical integrity of the individual together with painful subjective experiences associated with physiological emotional reactions;
- 2 across the DS, the most representative brain responses suggested different maladaptive processes in response to emotional stimuli, namely avoidance and overcontrol of affective states together with a disruption of integrative processes of emotional mind–body features; and
- 3 clinical conditions ascribed to the DS with different phenomenological manifestations could be differentiated on the base of specific patterns of neural responses within the extended brain network involved in ER, which could be linked to different latent dissociative mechanisms characterizing each disorder.

Moreover, these findings could inform clinical practice related to the DS. First, the efficacy of well-recognized psychotherapeutic interventions for the treatment of dissociation (e.g., dialectical behavior therapy, dialectical dynamic therapy, psychodynamic-oriented therapies, affect regulation therapy; right brain psychotherapy; mindfulness-based interventions, sensory-based programs; eye movement desensitization and reprocessing; and conversational model) (e.g., references 24, 119–128) should be further demonstrated. Specifically, future research on psychotherapy will need to take into account therapeutic changes considering a phenomenological level (e.g., severity of dissociative symptoms) and latent neural mechanisms (i.e., threat appraisal, quality of emotional experiences, implicit avoidance and overcontrol of emotional reactions, and integration of emotional mind–body features). Departing from specific theoretical frameworks, additional therapeutic strategies should be developed to address effectively altered mechanisms linked to dissociation in the context of emotional functioning.

Looking at meta-analytic findings concerning specific neural profiles associated with each condition ascribed to the DS, future clinical studies should demonstrate with robust research designs (e.g., controlled and randomized controlled trials) which intervention could be more effective compared with others for the treatment of specific dissociative-related disorders.

## Author contributions

A.S. and M.C. designed the theoretical framework and the logic of the study. M.C. analyzed the data and together with AS wrote a first draft of the manuscript that was critically revised by G.N. All authors approved the final version of the manuscript.

## Disclosure statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no relevant financial conflicts.

## References

1. Janet P. *L'Automatisme Psychologique: Essai de Psychologie Expérimentale sur les Formes Inférieures de l'Activité Humaine 1889* [Psychological Automatism: Essay on the Experimental Psychology of the Inferior Forms of Human Activity]. Paris, France: Felix Alcan. Société Pierre Janet/Payot, Paris, 1973.
2. Janet P. *L'Etat Mental des Hystériques*, 2nd edn. Felix Alcan, Paris, France, 1911.
3. van der Hart O, Dorahy MJ. History of the concept of dissociation. **In:** Dell PF, O'Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond*. Routledge, New York, 2009; 3–26.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Publisher, Washington, DC, 2013.
5. World Health Organization. *International classification of diseases for mortality and morbidity statistics* (11th Revision). 2018.
6. Nijenhuis ER. Somatoform dissociation: Major symptoms of dissociative disorders. *J Trauma Dissociation* 2001; **1**: 7–32.
7. Nijenhuis ER. *Somatoform Dissociation: Phenomena, Measurement and Theoretical Issues*. Norton & Company, Norton New York, 2004.
8. van Dijke A, van der Hart O, Ford JD, van Son M, van der Heijden P, Bühring M. Affect dysregulation and dissociation in borderline personality disorder and somatoform disorder: Differentiating inhibitory and excitatory experiencing states. *J Trauma Dissociation* 2010; **11**: 424–443.
9. Nijenhuis ER, Den Boer JA. Psychobiology of traumatization and trauma related structural dissociation of the personality. **In:** Dell PF, O'Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond*, Vol. 2009. Routledge, New York, 2009; 337–367.
10. Van der Hart O, Nijenhuis E, Steele K. *The Haunted Self: Structural Dissociation and the Treatment of Chronic Traumatization*. Norton & Company, Norton New York, 2006.
11. Allen JG. *Traumatic Relationships and Serious Mental Disorders*. John Wiley and Sons, New York, 2001.
12. Holmes EA, Brown RJ, Mansell W *et al.* Are there two qualitatively distinct forms of dissociation? A review and some clinical implications. *Clin. Psychol. Rev.* 2005; **25**: 1–23.
13. Van der Kolk B. *The Body Keeps the Score: Mind, Brain and Body in the Transformation of Trauma*. Penguin, UK, 2014.
14. Putnam FW, Helmers K, Trickett PK. Development, reliability, and validity of a child dissociation scale. *Child Abuse Negl.* 1993; **17**: 731–741.
15. Ross CA. History, phenomenology, and epidemiology of dissociative disorders. **In:** Michelson LK, Raym WJ (eds). *Handbook of Dissociation*. Plenum, New York, 1996; 3–24.
16. Dalenberg CJ, Paulson K. The case for the study of “normal” dissociation processes. **In:** Dell PF, O'Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond*. Taylor & Francis, New York, 2009; 145–154.
17. Eisen ML, Carlson EB. Individual differences in suggestibility: Examining the influence of dissociation, absorption, and a history of childhood abuse. *Appl. Cogn. Psychol.* 1998; **12**: S47–S61.
18. Van der Hart O, Nijenhuis E, Steele K, Brown D. Trauma-related dissociation: Conceptual clarity lost and found. *Aust. N. Z. J. Psychiatry* 2004; **38**: 906–914.
19. Lyssenko L, Schmahl C, Bockhacker L, Vonderlin R, Bohus M, Kleindienst N. Dissociation in psychiatric disorders: A meta-analysis of studies using the dissociative experiences scale. *Am. J. Psychiatry* 2018; **175**: 37–46.
20. Scalabrini A, Cavicchioli M, Fossati A, Maffei C. The extent of dissociation in borderline personality disorder: A meta-analytic review. *J Trauma Dissociation* 2017; **18**: 522–543.
21. Kotov R, Krueger RF, Watson D *et al.* The hierarchical taxonomy of psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J. Abnorm. Psychol.* 2017; **126**: 454–477.
22. Korzekwa MI, Dell PF, Links PS, Thabane L, Fougere P. Dissociation in borderline personality disorder: A detailed look. *J Trauma Dissociation* 2009; **10**: 346–367.

23. Stiglmayr CE, Ebner-Priemer UW, Bretz J *et al.* Dissociative symptoms are positively related to stress in borderline personality disorder. *Acta Psych. Scand.* 2008; **117**: 139–147.
24. Stiglmayr CE, Shapiro DA, Stieglitz RD, Limberger MF, Bohus M. Experience of aversive tension and dissociation in female patients with borderline personality disorder—A controlled study. *J. Psychiatr. Res.* 2001; **35**: 111–118.
25. Bohus M, Schmahl C, Fydrich T *et al.* A research programme to evaluate DBT-PTSD, a modular treatment approach for complex PTSD after childhood abuse. *Borderline Personal. Disord. Emot. Dysregulation* 2019; **6**: 1–16.
26. Chapman AL, Specht MW, Cellucci T. Borderline personality disorder and deliberate self-harm: Does experiential avoidance play a role? *Suicide Life Threat. Behav.* 2005; **35**: 388–399.
27. Brown RJ, Cardeña E, Nijenhuis E, Sar V, Van Der Hart O. Should conversion disorder be reclassified as a dissociative disorder in DSM-V? *Psychosomatics* 2007; **48**: 369–378.
28. Lanius RA, Vermetten E, Loewenstein RJ *et al.* Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. *Am. J. Psychiatry* 2010; **167**: 640–647.
29. Chiba T, Ide K, Taylor JE *et al.* A reciprocal inhibition model of alternations between under-/overemotional modulatory states in patients with PTSD. *Mol. Psychiatry* 2021; **26**: 5023–5039.
30. Van Der Hart O, Nijenhuis ER, Steele K. Dissociation: An insufficiently recognized major feature of complex posttraumatic stress disorder. *J. Trauma. Stress* 2005; **18**: 413–423.
31. Nijenhuis ERS. *The Trinity of Trauma: Ignorance, Fragility, and Control. Enactive Trauma Therapy.* Vandenhoeck & Ruprecht, Göttingen, 2017.
32. Hyland P, Shevlin M, Fyvie C, Cloitre M, Karatzias T. The relationship between ICD-11 PTSD, complex PTSD and dissociative experiences. *J. Trauma Dissociation* 2020; **21**: 62–72.
33. Carlson EA, Yates TM, Sroufe LA. Dissociation and development of the self. In: Dell PF, O'Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond*, Vol. 2009. Routledge/Taylor & Francis Group, New York, 2009; 39–52.
34. Conway MA, Pleydell-Pearce CW. The construction of autobiographical memories in the self-memory system. *Psychol. Rev.* 2000; **107**: 261–288.
35. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. *Annu. Rev. Neurosci.* 2012; **35**: 73–89.
36. Bremner JD, Vermetten E, Southwick SM, Krystal JH, Charney DS. *Trauma, memory, and dissociation: An integrative formulation.* American Psychiatric Association Press, New York, 1998; 365–402.
37. Foa EB, Riggs DS. Posttraumatic stress disorder following assault: Theoretical considerations and empirical findings. *Curr. Dir. Psychol. Sci.* 1995; **4**: 61–65.
38. Van der Kolk BA, McFarlane AC. *Traumatic Stress: The Effects of Overwhelming Experience on Mind, Body, and Society.* Guilford Press, New York, 1996.
39. Bromberg PM. One need not be a house to be haunted: On enactment, dissociation, and the dread of “not-me”—A case study. *Psychoanal. Dialogues* 2003; **13**: 689–709.
40. Liotti G. Attachment and dissociation. In: Dell PF, O'Neil JA (eds). *Dissociation and Dissociative Disorders: DSM-V and beyond.* Routledge, New York, 2009; 53–65.
41. Meares R. *A Dissociation Model of Borderline Personality Disorder.* WW Norton & Company, New York, 2012.
42. Scalabrini A, Mucci C, Esposito R, Damiani S, Northoff G. Dissociation as a disorder of integration—on the footsteps of Pierre Janet. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2020; **101**: 109928.
43. Northoff G, Scalabrini A. “Project for a spatiotemporal neuroscience”—brain and psyche share their topography and dynamic. *Front. Psychol.* 2021; **21**: 4500.
44. Mucci C, Scalabrini A. Traumatic effects beyond diagnosis: The impact of dissociation on the mind–body–brain system. *Psychoanal. Psychol.* 2021; **38**: 279–289.
45. Schore AN. Relational trauma and the developing right brain. *Ann. N. Y. Acad. Sci.* 2009; **1159**: 189–203.
46. Naragon-Gainey K, McMahon TP, Chacko TP. The structure of common emotion regulation strategies: A meta-analytic examination. *Psychol. Bull.* 2017; **143**: 384–427.
47. Bromberg PM. Multiple self-states, the relational mind, and dissociation: A psychoanalytic perspective. In: Dell PF, O'Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond.* Routledge/Taylor & Francis Group, New York, 2009; 637–652.
48. Cavicchioli M, Scalabrini A, Northoff G, Mucci C, Ogliaeri A, Maffei C. Dissociation and emotion regulation strategies: A meta-analytic review. *J. Psychiatr. Res.* 2021; **143**: 370–387.
49. Morawetz C, Bode S, Derntl B, Heekeren HR. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev.* 2017; **72**: 111–128.
50. Doll A, Hölzel BK, Bratec SM *et al.* Mindful attention to breath regulates emotions via increased amygdala–prefrontal cortex connectivity. *Neuroimage* 2016; **134**: 305–313.
51. Lutz J, Herwig U, Opialla S *et al.* Mindfulness and emotion regulation—An fMRI study. *Soc. Cogn. Affect. Neurosci.* 2014; **9**: 776–785.
52. van Kleef RS, Marsman JBC, van Valen E, Bockting CL, Aleman A, van Tol MJ. Neural basis of positive and negative emotion regulation in remitted depression. *NeuroImage Clin.* 2022; **34**: 102988.
53. Weber-Goericke F, Muehlhan M. A quantitative meta-analysis of fMRI studies investigating emotional processing in excessive worriers: Application of activation likelihood estimation analysis. *J. Affect. Disord.* 2019; **243**: 348–359.
54. Schlund MW, Magee S, Hudgins CD. Human avoidance and approach learning: Evidence for overlapping neural systems and experiential avoidance modulation of avoidance neurocircuitry. *Behav. Brain Res.* 2011; **225**: 437–448.
55. Lanius RA, Brand B, Vermetten E, Frewen PA, Spiegel D. The dissociative subtype of posttraumatic stress disorder: Rationale, clinical and neurobiological evidence, and implications. *Depress. Anxiety* 2012; **29**: 701–708.
56. Roydeva MI, Reinders AA. Biomarkers of pathological dissociation: A systematic review. *Neurosci. Biobehav. Rev.* 2021; **123**: 120–202.
57. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods* 2012; **3**: 285–299.
58. Efthimiou O, Debray TP, van Valkenhoef G *et al.* GetReal in network meta-analysis: A review of the methodology. *Res. Synth. Methods* 2016; **7**: 236–263.
59. American Psychological Association. Reporting standards for research in psychology: Why do we need them? What might they be? *Am. Psychol.* 2008; **63**: 839–851.
60. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann. Intern. Med.* 2009; **151**: 264–269.
61. Brewin CR, Cloitre M, Hyland P *et al.* A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. *Clin. Psychol. Rev.* 2017; **58**: 1–15.
62. Cloitre M, Garvert DW, Weiss B, Carlson EB, Bryant RA. Distinguishing PTSD, complex PTSD, and borderline personality disorder: A latent class analysis. *Eur. J. Psychotraumatol.* 2014; **1**: 25097.
63. Hyland P, Shevlin M, Fyvie C, Karatzias T. Posttraumatic stress disorder and complex posttraumatic stress disorder in DSM-5 and ICD-11: Clinical and behavioral correlates. *J. Trauma. Stress* 2018; **31**: 174–180.
64. Cohen J. A coefficient of agreement for nominal scales. *Educ. Psychol. Meas.* 1960; **20**: 37–46.
65. Korzekwa MI, Dell PF, Pain C. Dissociation and borderline personality disorder: An update for clinicians. *Curr. Psychiatry Rep.* 2009; **11**: 82–88.
66. Zanarini MC, Frankenburg FR, Jager-Hyman S, Reich DB, Fitzmaurice G. The course of dissociation for patients with borderline personality disorder and axis II comparison subjects: A 10-year follow-up study. *Acta Psychiatr. Scand.* 2008; **118**: 291–296.
67. Cohen J. *Statistical Power Analysis for the Behavior Science.* Lawrence Erlbaum Association, New York, 1988.
68. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Introduction to Meta-analysis.* Wiley, Chichester, 2011.
69. Wolf FM. *Meta-Analysis: Quantitative Methods for Research Synthesis* Sage, Vol. 59. Sage, Thousand Oaks, 1986.
70. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat. Med.* 2010; **29**: 932–944.
71. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014; **9**: e99682.
72. Albajes-Eizaguirre A, Solanes A, Vieta E, Radua J. Voxel-based meta-analysis via permutation of subject images (PSI): Theory and implementation for SDM. *Neuroimage* 2019; **186**: 174–184.

73. Dolan RJ, Vuilleumier P. Amygdala automaticity in emotional processing. *Ann. N. Y. Acad. Sci.* 2003; **985**: 348–355.
74. Fusar-Poli P, Placentino A, Carletti F *et al.* Laterality effect on emotional faces processing: ALE meta-analysis of evidence. *Neurosci. Lett.* 2009; **452**: 262–267.
75. Scalabrini A, Mucci C, Northoff G. The nested hierarchy of self and its trauma: In search for a synchronic dynamic and topographical re-organization. *Front. Hum. Neurosci.* 2022; **16**: 98035.
76. Schulz SM. Neural correlates of heart-focused interoception: A functional magnetic resonance imaging meta-analysis. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 2016; **371**: 20160018.
77. Craig AD. How do you feel–now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 2009; **10**: 59–70.
78. Craig AD. The sentient self. *Brain Struct Funct* 2010; **214**: 563–577.
79. Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. *Ann. N. Y. Acad. Sci.* 2011; **1225**: 72–82.
80. Van der Kolk BA, Fisler R. Dissociation and the fragmentary nature of traumatic memories: Overview and exploratory study. *J. Trauma. Stress* 1995; **8**: 505–525.
81. Diez I, Larson AG, Nakhate V *et al.* Early-life trauma endophenotypes and brain circuit–gene expression relationships in functional neurological (conversion) disorder. *Mol. Psychiatry* 2021; **26**: 3817–3828.
82. Ebner-Priemer UW, Mauchnik J, Kleindienst N *et al.* Emotional learning during dissociative states in borderline personality disorder. *J. Psychiatry Neurosci.* 2009; **34**: 214–222.
83. Harnett NG, Goodman AM, Knight DC. PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Exp. Neurol.* 2020; **330**: 113331.
84. Carter RM, O’Doherty JP, Seymour B, Koch C, Dolan RJ. Contingency awareness in human aversive conditioning involves the middle frontal gyrus. *Neuroimage* 2006; **29**: 1007–1012.
85. Leung HC, Gore JC, Goldman-Rakic PS. Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. *J. Cogn. Neurosci.* 2002; **14**: 659–671.
86. Rajah MN, Languar R, Grady CL. Age-related changes in right middle frontal gyrus volume correlate with altered episodic retrieval activity. *J. Neurosci.* 2011; **31**: 17941–17954.
87. Carlson EB, Dalenberg C, McDade-Montez E. Dissociation in post-traumatic stress disorder part 1: Definitions and review of research. *Psychol. Trauma* 2012; **2**: 479–489.
88. Brown MW, Aggleton JP. Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2001; **2**: 51–61.
89. Manns JR, Hopkins RO, Reed JM, Kitchener EG, Squire LR. Recognition memory and the human hippocampus. *Neuron* 2003; **37**: 171–180.
90. Armour C, Contractor AA, Palmieri PA, Elhai J. Assessing latent level associations between PTSD and dissociative factors: Is depersonalization and derealization related to PTSD factors more so than alternative dissociative factors? *Psychol. Injury Law* 2014; **7**: 131–142.
91. Choi KR, Seng JS, Briggs EC *et al.* The dissociative subtype of post-traumatic stress disorder (PTSD) among adolescents: Co-occurring PTSD, depersonalization/derealization, and other dissociation symptoms. *J. Am. Acad. Child Adolesc. Psychiatry* 2017; **56**: 1062–1072.
92. Horn M, Fovet T, Vaiva G, Thomas P, Amad A, d’Hondt F. Emotional response in depersonalization: A systematic review of electrodermal activity studies. *J. Affect. Disord.* 2020; **276**: 877–882.
93. Pole N. The psychophysiology of posttraumatic stress disorder: A meta-analysis. *Psychol. Bull.* 2007; **133**: 725–746.
94. Karatzias T, Shevlin M, Hyland P *et al.* The role of negative cognitions, emotion regulation strategies, and attachment style in complex post-traumatic stress disorder: Implications for new and existing therapies. *Br. J. Clin. Psychol.* 2018; **57**: 177–185.
95. Frewen PA, Dozois DJA, Neufeld RWJ, Lanius RA. Disturbances of emotional awareness and expression in posttraumatic stress disorder: Meta-mood, emotion regulation, mindfulness, and interference of emotional expressiveness. *Psychol. Trauma* 2012; **4**: 152–161.
96. Kredlow AM, Fenster RJ, Laurent ES, Ressler KJ, Phelps EA. Prefrontal cortex, amygdala, and threat processing: Implications for PTSD. *Neuropsychopharmacology* 2022; **47**: 247–259.
97. Gogolla N. The insular cortex. *Curr. Biol.* 2017; **27**: R580–R586.
98. Morgan CA III, Hazlett G, Wang S, Richardson EG Jr, Schnurr P, Southwick SM. Symptoms of dissociation in humans experiencing acute, uncontrollable stress: A prospective investigation. *Am. J. Psychiatry* 2001; **158**: 1239–1247.
99. Cloitre M. Complex PTSD: Assessment and treatment. *Eur. J. Psychotraumatol.* 2021; **12**: 1866423.
100. Xiao X, Ding M, Zhang YQ. Role of the anterior cingulate cortex in translational pain research. *Neurosci. Bull.* 2021; **37**: 405–422.
101. Etkin A, Egner T, Kalisch R. Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn. Sci.* 2011; **15**: 85–93.
102. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat. Rev. Neurosci.* 2005; **6**: 533–544.
103. Xiao X, Zhang YQ. A new perspective on the anterior cingulate cortex and affective pain. *Neurosci. Biobehav. Rev.* 2018; **90**: 200–211.
104. Tan Y, Yan R, Gao Y, Zhang M, Northoff G. Spatial-topographic nestedness of interoceptive regions within the networks of decision making and emotion regulation: Combining ALE meta-analysis and MACM analysis. *Neuroimage* 2022; **260**: 119500.
105. Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 1999; **402**: 179–181.
106. Bush G, Vogt BA, Holmes J *et al.* Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proc. Natl Acad. Sci. USA* 2002; **99**: 523–528.
107. McRae K, Reiman EM, Fort CL, Chen K, Lane RD. Association between trait emotional awareness and dorsal anterior cingulate activity during emotion is arousal-dependent. *Neuroimage* 2008; **41**: 648–655.
108. Van Veen V, Krug MK, Schooler JW, Carter CS. Neural activity predicts attitude change in cognitive dissonance. *Nat. Neurosci.* 2009; **12**: 1469–1474.
109. Weissman DH, Giesbrecht B, Song AW, Mangun GR, Woldorff MG. Conflict monitoring in the human anterior cingulate cortex during selective attention to global and local object features. *Neuroimage* 2003; **19**: 1361–1368.
110. Jungilligens J, Wellmer J, Schlegel U, Kessler H, Axmacher N, Popkirov S. Impaired emotional and behavioural awareness and control in patients with dissociative seizures. *Psychol. Med.* 2020; **50**: 2731–2739.
111. Candel I, Merckelbach HLGJ, Kuijpers M. Dissociative experiences are related to commissions in emotional memory. *Behav. Res. Ther.* 2003; **2003**: 719–725.
112. Vastag B. Scientists find connections in the brain between physical and emotional pain. *JAMA* 2003; **290**: 2389–2390.
113. Legault L, Al-Khindi T, Inzlicht M. Preserving integrity in the face of performance threat: Self-affirmation enhances neurophysiological responsiveness to errors. *Psychol. Sci.* 2012; **23**: 1455–1460.
114. Baer MM, LaCroix JM, Browne JC *et al.* Lack of emotional awareness is associated with thwarted belongingness and acquired capability for suicide in a military psychiatric inpatient sample. *Suicide Life Threat. Behav.* 2019; **49**: 1395–1411.
115. Frankel AS. Dissociation and dissociative disorders: Clinical and forensic assessment with adults. In: Dell PF, O’Neil JA (eds). *Dissociation and the Dissociative Disorders: DSM-V and beyond*. Routledge, New York, 2009; 571–583.
116. Ross CA. *The Dissociative Disorders Interview Schedule–DSM-5 Version*. Colin A. Ross Institute. Retrieved July 26, Dallas, TX, 2008.
117. Steinberg M. *Structured Clinical Interview for DSM–IV Dissociative Disorders–Revised (SCID-D)*, 2nd edn. American Psychiatric Press, Washington, 1994.
118. Stiglmayr C, Schmahl C, Bremner JD, Bohus M, Ebner-Priemer U. Development and psychometric characteristics of the DSS-4 as a short instrument to assess dissociative experience during neuropsychological experiments. *Psychopathology* 2009; **42**: 370–374.
119. Harned MS, Korslund KE, Linehan MM. A pilot randomized controlled trial of dialectical behavior therapy with and without the dialectical behavior therapy prolonged exposure protocol for suicidal and self-injuring women with borderline personality disorder and PTSD. *Behav. Res. Ther.* 2014; **55**: 7–17.
120. Foote B, Van Orden K. Adapting dialectical behavior therapy for the treatment of dissociative identity disorder. *Am. J. Psychother.* 2016; **70**: 343–364.
121. Şar V. The dialectical dynamic therapy of trauma. *J. Trauma Dissociation* 2022; **23**: 339–355.
122. Zerubavel N, Messman-Moore TL. Staying present: Incorporating mindfulness into therapy for dissociation. *Mind* 2015; **6**: 303–314.
123. Fraser K, MacKenzie D, Versnel J. Complex trauma in children and youth: A scoping review of sensory-based interventions. *Occup. Ther. Ment. Health* 2017; **33**: 199–216.
124. van der Hart O, Nijenhuis ER, Solomon R. Dissociation of the personality in complex trauma-related disorders and EMDR: Theoretical considerations. *J. EMDR Pract. Res.* 2010; **4**: 76–92.

125. Spermon D, Darlington Y, Gibney P. Psychodynamic psychotherapy for complex trauma: Targets, focus, applications, and outcomes. *Psychol. Res. Behav. Manage* 2010; 3: 119–127.
126. Mucci C. *Borderline Bodies: Affect Regulation Therapy for Personality Disorders (Norton Series on Interpersonal Neurobiology)*. WW Norton & Company, New York, 2018.
127. Meares R. *Borderline Personality Disorder and the Conversational Model: A Clinician's Manual (Norton Series on Interpersonal Neurobiology)*. WW Norton & Company, New York, 2012.
128. Schore AN. *Right Brain Psychotherapy (Norton Series on Interpersonal Neurobiology)*. WW Norton & Company, New York, 2019.

### Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.