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SYSTEMATIC REVIEW

The nested hierarchical model of self and its non-relational vs relational posttraumatic manifestation: an fMRI meta-analysis of emotional processing

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Different kinds of traumatic experiences like natural catastrophes vs. relational traumatic experiences (e.g., sex/physical abuse, interpersonal partner violence) are involved in the development of the self and PTSD psychopathological manifestations. Looking at a neuroscience approach, it has been proposed a nested hierarchical model of self, which identifies three neural-mental networks: (i) interoceptive; (ii) exteroceptive; (iii) mental. However, it is still unclear how the self and its related brain networks might be affected by non-relational vs relational traumatic experiences. Departing from this background, the current study aims at conducting a meta-analytic review of task-dependent fMRI studies (i.e., emotional processing task) among patients with PTSD due to non-relational (PTSD-NR) and relational (PTSD-R) traumatic experiences using two approaches: (i) a Bayesian network meta-analysis for a region-of-interest–based approach; (ii) a coordinated-based meta-analysis. Our findings suggested that the PTSD-NR mainly recruited areas ascribed to the mental self to process emotional stimuli. Whereas, the PTSD-R mainly activated regions associated with the intero-exteroceptive self. Accordingly, the PTSD-R compared to the PTSD-NR might not reach a higher symbolic capacity to process stimuli with an emotional valence. These results are also clinically relevant in support of the development of differential treatment approaches for non-relational vs. relational PTSD.

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THE SELF AND ITS TRAUMA

The sense of self is usually considered the center of our inner mental activity. Concurrently, it has been shown how the relation between the individual and external animate environments plays a central role in the development of the self, referring to its adaptive and/or maladaptive manifestations including post-traumatic ones [1–3]. Recently, it has been proposed to view the self as "psychological baseline"—the baseline model of self-specificity (BMSS) [4–6] — suggesting how it serves as a fundamental reference for any input processing from the external environment, including emotional stimuli [7–9]. The role of the self as a baseline reference for any kind of input has been topographically supported by a nested hierarchical model [10]. This model has been developed on the base of a large-scale fMRI meta-analysis among healthy subjects, and it identifies three nested level of self-processing: (i) *interoceptive*, that refers to the processing of the body's inner organs relative to the incoming exteroceptive stimuli; (ii) *extero-proprioceptive* that focuses on external or proprioceptive bodily inputs; (iii) *mental* that considers the inner cognition in terms of self-related stimuli vs. non self.

According to meta-analytic findings, the interoceptive self has been related to the bilateral insula, dorsal anterior cingulate cortex (dACC), thalamus, and parahippocampus activities. The extero-proprioceptive self has been linked to the bilateral insula, inferior frontal gyrus (IFG), premotor cortex, temporo-parietal junction (TPJ) responses. Lastly, the mental self encompasses cortical midline regions of the default mode network (DMN), including the medial prefrontal cortex (MPFC) and posterior cingulate cortex. Interestingly, it includes regions from the extero-proprioceptive self (i.e., bilateral TPJ), and ones from the interoceptive self (i.e., bilateral insula, thalamus). Intriguingly, regions of the interoceptive self are also found within the other layers (extero-proprioceptive and mental self), where they are complemented by additional regions extending the topography of the self and its nestedness.

The organization of the self and its mechanisms involved in processing of different kinds of internal and external stimuli are closely related to and malleable by the events in the world. This supports adaptive and/or adverse/traumatic developmental trajectories [11] rooted in and mediated by the spatiotemporal features of the brain's neuronal activity [12–16]. Recently, it has been proposed how the nested hierarchy of self can be re-organized by traumatic experiences [3]. However, the neuronal and psychological correlates of self disturbances and their post-

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traumatic manifestations are still unclear, thus empirical clarification is needed. Addressing this gap is the goal of our paper.

Different gradients of traumatic experiences and their impacts on the self

Posttraumatic stress disorder (PTSD) was conceptualized as a diagnosis for the first time in the 3rd edition of the Diagnostic and Statistical Manual (DSM) [17]. Specifically, the first proposal identified three clusters of symptoms (i.e., re-experiencing, avoidance and numbing, and physiological arousal), and two additional criteria concerning the nature of the stressor (i.e., natural, accidental, or purposeful events). The DSM-5 [18] includes an additional cluster of symptoms (i.e., alterations in cognitions and mood) on the basis of factor analytic findings, and a dissociative subtype (i.e., experiencing of dissociative symptoms during and immediately after the trauma) [19, 20] has been recognized for the first time. The PTSD dissociative subtype also highlights a worse prognosis compared to the non-dissociative one [21]. Furthermore, the most recent ICD-11 [22] has proposed that exposure to trauma - an extremely threatening or horrific event or series of events - is needed to diagnose PTSD [23].

Despite a general consensus on the multifaceted PTSD clinical phenotype, several issues still remain open. First, clinical observations have suggested that relational traumatic events (e.g., assault, torture, sexual violence) are associated with more severe and long-lasting PTSD symptoms than non-relational or unexpected catastrophic events (e.g., natural disasters, accidents), which do not imply the purposeful inflicting of suffering on the victim of trauma. The DSM-5 has suggested that specific traumatic events (i.e., relational vs. natural events) could differently influence the PTSD prognosis. Accordingly, neuropsychodynamic and other clinical frameworks [11, 24–29] have widely recognized that traumatic natural catastrophes and relational traumatic experiences are associated to distinct PTSD psychopathological manifestations. For instance, has been demonstrated that direct experience of relational trauma (e.g., sex abuse) and childhood maltreatment [30, 31] fosters the development of the dissociative subtype of PTSD, which is estimated to occur in approximately 14% of patients with trauma-related disorders [32].

According to PTSD psychopathological heterogeneity, the ICD-11 and the 2nd edition of Psychodynamic Diagnostic Manual (PDM-2); [33] have included an additional diagnosis of Complex PTSD (CPTSD). The ICD-11 diagnosis of CPTSD [34] emphasizes disturbances in self-organization that result from multiple, chronic or repeated relational traumas from which escape is difficult or impossible. In this context, Herman [35] identified a class of relational traumatic situations linked to CPTSD characterized by captivity, which brings the victim into a prolonged contact with the perpetrator based on coercive control. Following the ICD-11, the CPTSD diagnosis is comprised of six clusters of symptoms: three are shared with PTSD (re-experiencing, avoidance, and sense of threat), and three additional clusters are related to disturbances in self-organization, namely: affect dysregulation, negative self-concept and interpersonal difficulties. These diagnostic features are in accordance with neuropsychodynamic models of trauma [11, 36–40], that suggest how the CPTSD is primarily associated with traumatic experiences due to human agency (i.e., human actions that intentionally affect physical and/or psychological integrity of another human being) rather than natural catastrophes or accidents. Furthermore, these models have emphasized how cumulative traumatic experiences since childhood affect the sense of self and its cohesive and nested organization.

These findings seem to suggest differences in pathogenesis and manifestations between non-relational vs. relational traumatic experiences. Moreover, several studies showed abnormalities in self and self-related processing among patients with PTSD [41–46]. Nevertheless, these findings mainly focused on the mental self in relation with subcortical limbic activity. Whereas the implications of more basic layers of the self (i.e., intero- and extero-ceptive) and relationships among the three self layers remain unclear considering different PTSD populations. Therefore, the main goal of the current work is to address this gap found in the PTSD literature.

Neurobiological models of post traumatic manifestations

The first proposal for a neurobiological model of PTSD without and with dissociation often associated with relational traumatic experiences [40] has been provided by Lanius and colleagues [47]. The PTSD without dissociation is characterized by a predominant state of "*emotional under modulation*" (e.g., re-experiencing and hyper-arousal symptoms), which has been associated to a low activation in the ventromedial prefrontal cortex (VMPFC) and rostral ACC, together with an increased activation of amygdala, especially in response to trauma-related stimuli. Conversely, the PTSD dissociative subtype is characterized by a predominant state of "*emotional over modulation*" (e.g., depersonalization, derealization) linked to an abnormal increased activation of dACC and the MPFC, together with a concurrent shutdown of subcortical limbic regions (e.g., amygdala). Recently, Chiba and colleagues [48] have provided a partial revision suggesting a reciprocal inhibition between the amygdala and VMPFC that generates dynamic alternations between states of emotional under- and over-modulation. Extending these results [49], it has been proposed a neurobiological model of dissociative-related conditions including the PTSD and its subtypes. This model suggested a hyperactivity of prefrontal regions (e,g., prefrontal and cingulate cortices) and parahippocampal gyri. Furthermore, a quantitative fMRI meta-analysis showed an abnormal dACC activation as a signature across dissociative-related disorders, such as different subtypes of PTSD [50]. Another recent fMRI meta-analysis [51] showed a key role of the dACC in connection with right the anterior insula on the functional relationship between interoception and emotional regulation.

Unfortunately, these neurobiological models did not make a distinction between relational (CPTSD, PTSD due to sex and physical abuse across the life-span, PTSD due to intimate partner violence; PTSD-IPV) and non-relational (PTSD due to natural disasters or accidents) traumatic experiences. Hence, the goal of our study is an attempt to integrate clinical and neurobiological models of post-traumatic manifestations taking into account changes in brain activity of the different layers of self, and how they are affected by different traumatic experiences (i.e., non-relational vs. relational).

The present study

Departing from the three-layer nested model of self [10] and its implications for understanding the effects of different traumatic experiences [3], the current study aims at conducting a meta-analytic review of neuroimaging research on different forms of PTSD due to non-relational (PTSD-NR) and relational traumatic experiences (PTSD-R). According to available scientific literature, the PTSD-R group includes different populations of individuals who met criteria for CPTSD, PTSD due to sex and physical abuse across the life-span and PTSD-IPV.

The current work was focused on task-dependent fMRI studies that administered emotional-eliciting stimuli. This was chosen according to well-supported emotional "under-regulation" and "over-modulation" states linked to PTSD manifestations, which are triggered by several emotional and trauma-related stimuli and considered as core features of these conditions [47, 48].

According to a suggested continuum of severity from non-relational to relational traumatic experiences, we hypothesize that:

i. Patients with PTSD-NR vs. controls should be mainly characterized by an altered subcortical limbic activity in response to emotional stimuli. This was assumed in accordance with existing PTSD neurobiological models [47, 48] that have supported dynamic alternations of emotional under- and over-modulations states at the base of PTSD clinical manifestations. This organization of brain responses might also reflect the demonstrated impacts of adverse non-relational events on the development of subcortical limbic networks and its connection with self areas [52].

ii. Patients with PTSD-R vs. controls should highlight an increased and predominant recruitment of intero- and extero-ceptive self [3], rather than subcortical limbic and mental self responses to process emotion-eliciting stimuli. This should further corroborate the notion that repeated relational traumatic experiences could specifically affect the self organization and its nested neural networks.

iii. According to the heterogeneity of relational traumatic experiences (e.g., sex abuse, victims of physical violence, tortures, prisoners and hostages), and their cumulative effects on the development of PTSD and CPTSD [34, 35], the PTSD-R group might be composed of different subgroups characterized by specific brain responses toward emotional stimuli reflecting different degrees of traumatic organization [53, 54].

iv. Comparing neural responses between PTSD groups, individuals with PTSD-NR should show a main recruitment of mental-self areas. Whereas, the PTSD-R group should highlight a core activation of intero- and extero-ceptive self. This scenario should be in line with clinical frameworks and empirical findings that have supported how relational traumatic experiences significantly disrupt the development of reflective abilities on affective states [55]. Furthermore, these differences might support the notion that relational traumatic experiences affect the development of an integrated organization of self [3, 39, 40, 56, 57].

To test our hypotheses, the first step was the identification of regions of interest (ROIs) related to the hierarchical topography of self (i.e., interoceptive, exteroceptive and mental) and subcortical limbic areas. Referring to these ROIs, a meta-analysis using a Bayesian hierarchical framework [58] was conducted. This method allows to compute effect sizes of between-group differences comprehensively considering the complex ROIs responses [59]. 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 among individuals with PTSD-NR and PTSD-R. Ultimately, a whole brain voxel-based approach was used as proof of principle to further corroborate a distinction of these conditions referring to the hypothesized differential patterns of neural activity.

METHODS

Study selection

The current meta-analytic review was conducted in line with Meta-Analysis Reporting Standards (MARS) of *American Psychological Association* [60] and PRISMA guidelines [61]. Figure 1 summarizes the inclusion process of studies. To consider studies of comparable quality, the analysis included only studies that were published on scientific journals. PsychINFo, Pubmed, ISI Web of Knowledge and Scopus online databases were used to generate potentially relevant articles (for more details about the keywords used for the online research, the screening and the inclusion/exclusion criteria of the articles see Supplementary Materials).

Network meta-analysis and ALE meta-analysis

We conducted two meta-analytic procedures: (a) a ROI-based approach applying a network meta-analysis using a Bayesian hierarchical framework through the *gemtc R* package [58] and (ii) a voxel wise approach through the Ginger ALE 3.0.2 software (http://www.brainmap.org/), which was used to perform coordinate-based meta-analyses of neuroimaging results [62–64] (see supplementary materials for a detailed description of methodological approaches).

RESULTS

Figure 1 summaries inclusion process of studies used for meta-analytic procedures. Table 1 provides descriptive characteristics of studies included. Forty studies were included for a total of 1363 subjects (PTSD: 719). Twenty-five studies (62.5%) evaluated brain responses to emotional stimuli of patients with PTSD-NR. Fifteen studies (37.5%) included subjects with PTSD-R. This group included subjects with PTSD-IPV ($N_{studies} = 7$; 17.5%), PTSD due to sex and physical abuse across life-span ($N_{studies} = 3$; 7.5%) and CPTSD according to ICD criteria ($N_{studies} = 5$; 12.5%). The mean age of subjects was 35.03 (SD = 7.92). Thirteen studies (32.5%) recruited samples composed of only females. Three studies (7.5%) evaluated samples composed of only males. The remaining 22 studies (55.0%) included both males and females. Looking at control groups, 6 studies (15.0%) included subjects exposed to traumatic experiences without PTSD (TECs), 28 studies (70.0%) healthy controls (HCs) and 2 studies (5.0%) compared PTSD individuals with both TECs and HCs. Four studies (10.0%) were based on a single group design, which evaluated the brain reactivity of PTSD individuals comparing responses to emotional stimuli with neutral ones. Twenty-one studies (52.5%) administered pictures characterized by different emotional valence—12 (30.0%) studies used human faces, 4 (10%) studies showed pictures of traumatic events (e.g., accidents, fires, assaults), 5 (12.5%) studies were based on the presentation of pictures from the International Affective Picture System (IAPS) [65]. Fourteen (35.0%) studies administered words characterized by emotional valences, especially associated to traumatic events ($N_{studies} = 12$; 30.0%). Two (5.0%) studies used distressing auditory stimuli and, 2 (5.0%) studies administered videoclips showing human interactions. One (2.5%) study administered noxious electric stimuli.

Descriptive statistics of neural responses within the three-layer self and subcortical limbic brain networks

Table 1S (see Supplementary Materials) provides a detailed description of neural responses found across studies included in the current work. The PTSD-R group showed a significant higher frequency of overall heightened brain responses toward emotional stimuli compared to the PTSD-NR one ($\chi^2_{(1)} = 5.43$ $p < 0.05$). Regarding the interoceptive self, the most recurrent finding among individuals with PTSD-R was an increased activity of insula. The PTSD-NR group showed a recurrent heightened response of superior temporal gyrus. The exteroceptive self among subjects with PTSD-R was mainly represented by an increased activity of IFG, premotor cortex and fusiform gyrus. Conversely, the PTSD-NR group showed more recurrent activations of precuneus, occipital gyrus and decreased responses of premotor cortex. Referring to the mental self, the PTSD-R group highlighted frequent increased activity of dorsolateral PFC, middle frontal gyrus and VMPFC. The PTSD-NR group showed heightened responses of MPFC, ACC and a decreased activity of middle frontal gyrus. The increased reactivity of amygdala was the most representative region for both PTSD groups. While a difference between PTSD groups was observed in hippocampus activity. Indeed, the PTSD-NR group was characterized by a decreased response of this region; whereas, the PTSD-R group showed a consistent heightened activity.

Network meta-analysis

Table 2S (see Supplementary Materials) provides a detailed description of effect sizes computed for each region detected within studies included in the current meta-analysis.

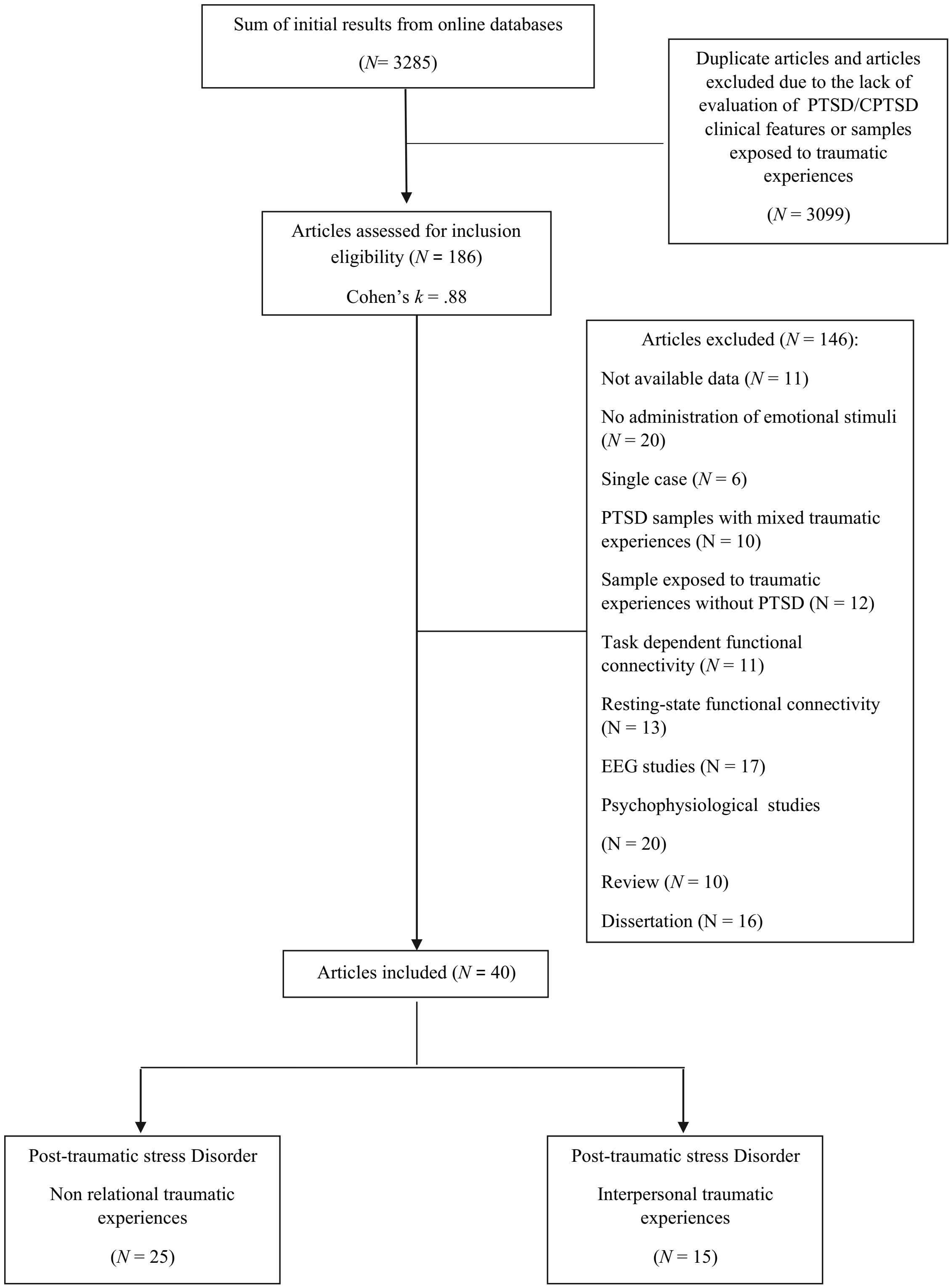

Fig. 1 CONSORT flow chart of studies inclusion process.

PTSD due to non-relational traumatic experiences (PTSD-NR). Table 2 summarizes results of network meta-analytic procedures used for the estimation of pooled effect sizes linked to each self and subcortical limbic network. Table 2 also provides SUCRA values of each brain network characterizing the PTSD-NR group. The analyses found large differences between the PTSD-NR group and controls considering self and subcortical limbic brain networks. The nodesplit analysis demonstrated consistent results. This evidence excluded sources of heterogeneity (e.g., sex, age) of findings. Accordingly, the meta-regression analysis was not conducted. The SUCRA values highlighted that subcortical limbic and exteroceptive self networks were the most representative ROIs of the PTSD-NR group. Specifically, subjects with PTSD-NR were characterized by both large heightened and decreased responses of these ROIs to the presentation of emotion-eliciting stimuli (see Table 2S for detailed information concerning each ROI).

Table 1. Characteristics of studies included.

Study	*N*	Gender	Age	PTSD group	Control	Experimental paradigm
Aupperle et al., 2012	71 PTSD: 37 CG: 34	PTSD: 100% F CG: 100% F	38.01 PTSD: 38.32 CG: 37.76	PTSD-R IPV	HC	Negative and positive emotional pictures IAPS
Bomyea et al., 2017	36 PTSD: 19 CG: 17	PTSD: 100% M CG: 100% M	29.50 PTSD: 30.0 CG: 29.1	PTSD-NR	TEC	Emotional stimuli vs neutral Human faces
Bremner et al., 2005	17 PTSD-G: 8 CG: 11	PTSD-G: 25% M; 75% F CG: 21% M; 79% F	37.00 PTSD: 34.90 CG: 36.30	PTSD-R Childhood sex abuse	HC	Fear conditioning task Noxious electric stimuli
Brinkmann et al., 2017	32 PTSD-G: 16 CG: 16	PTSD-G: 100% F CG: 100% F	26.02 PTSD: 26.60 CG: 25.44	PTSD-R Sex abuse	HC	Aversive human voices
Brunetti et al., 2015	20 PTSD: 10 CG: 10	PTSD: 40%M; 60% F CG: 40%M; 60% F	38.25 PTSD: 39.7 CG: 36.8	PTSD-NR	HC	Negative picture vs neutral picture IAPS
Bryant et al., 2021	67 PTSD: 28 CG: 39	PTSD: 14.3% M; 85.7% F CG: 28.2% M; 71.8% F	38.90 PTSD: 39.60 CG: 38.30	PTSD-R CPTSD	TEC	Negative and positive emotional pictures Human faces
Bryant et al., 2010	24 PTSD: 12 CG: 12	Not reported	34.21 PTSD: 35.00 CG: 33.42	PTSD-NR	TEC	Negative and positive emotional pictures Human faces
Dahlgren et al., 2018	52 PTSD: 12 CG: 40	PTSD: 100% M CG: 100% M	61.91 PTSD-G: 60.75 CG: 63.07	PTSD-NR	HC + TEC	Individualized trauma-script
Dickie et al., 2008	27 PTSD: 27 CG: -	PTSD: 29.7% M; 70.3% F CG: -	36.0 PTSD: 36.0 CG: -	PTSD-NR	-	Fearful faces pictures vs neutral faces pictures
Felmingham et al., 2008	23 PTSD: 23 CG: -	PTSD: nr CG: nr	38.5 PTSD: nr CG: nr	PTSD-NR	-	Fearful faces pictures vs neutral faces pictures
Fonzo et al., 2013	33 PTSD-G: 33 CG: -	PTSD-G: 100% F CG: -	39.27 PTSD-G: 39.27 CG: -	PTSD-R IPV	-	Angry and fearful faces vs geometric figures
Fonzo et al., 2010	24 PTSD: 12 CG: 12	PTSD: 100%F CG: 100%F	Not reported	PTSD-R IPV	HC	Angry and happy faces
Garrett et al., 2019	40 PTSD-G: 20 CG: 20	PTSD-G: 10.0% M; 90.0% F CG: 10.0% M; 90.0% F	14.9 PTSD-G: 15.3 CG: 14.5	PTSD-NR	HC	Angry faces
Harnett et al., 2018	40 PTSD: 21 CG: 19	PTSD: 71.4% M 28.6%F CG: 73.7% M 26.3%F	25.45 PTSD: 29.65 CG: 24.26	PTSD-NR	HC	Fear conditioning task Distressing sounds
Herzog et al., 2019	84 PTSD: 28 CG: 56	PTSD: 100% F CG: 100% F	30.44 PTSD: 30.61 CG: 30.35	PTSD-R CPTSD	HC + TEC	Interpersonal trauma-related words
Hopper et al., 2007	27 PTSD-G: 27 CG: -	PTSD: 26% M; 74% F CG: -	35.9 PTSD-G: 35.9 CG: -	PTSD-NR	-	Individualized trauma-script vs neutral words
Jacques et al., 2011	29 PTSD: 15 CG: 14	PTSD: 26.6% M; 73.3% F CG: 50.0% M; 50.0% F	23.32 PTSD: 22.21 CG: 24.43	PTSD-NR	HC	Individualized trauma-script
Lanius et al., 2002	17 PTSD-G: 7 CG: 10	PTSD: 100% F CG: 100% F	35.5 PTSD: 36.00 CG: 35.00	PTSD-NR	HC	Individualized trauma-script

Table 1. continued

Study	*N*	Gender	Age	PTSD group	Control	Experimental paradigm
Lanius et al., 2007	31 PTSD: 15 CG: 16	PTSD-G: 26.6% M; 73.3% F CG: 18.7% M; 81.3% F	34.2 PTSD: 34.6 CG: 33.8	PTSD-NR	HC	Individualized trauma-script
Lloyd et al., 2021	46 PTSD: 28 CG: 18	PTSD: 89.2% M; 10.8% F CG: 41.1% M; 58.9% F	40.8 PTSD: 48.5 CG: 33.1	PTSD-NR	HC	Morally injurious script
Lee et al., 2022	26 PTSD: 12 CG: 14	PTSD: 91.7% M; 8.3% F CG: 92.9% M; 7.1% F	48.40 PTSD-G: 52.2 CG: 44.6	PTSD-NR	HC	Trauma-related picture
Mazza et al., 2012	20 PTSD-G: 10 CG: 10	PTSD: 20%M; 80% F CG: 30% M; 70% F	30.50 PTSD: 33.90 CG: 27.10	PTSD-NR	HC	Emotional pictures Human faces
Mickleborough et al., 2011	43 PTSD: 17 CG: 26	PTSD: 46.4% M; 53.6% F CG: 57.7% M; 42.3% F	36.75 PTSD: 36.7 CG: 36.8	PTSD-NR	HC	Individualized trauma-script
Moser et al., 2015	35 PTSD-G: 16 CG: 19	PTSD: 100% F CG: 100%F	33.40 PTSD: 32.3 CG: 34.5	PTSD-R IPV	HC	Video clips on interpersonal interactions
Mueller-Pfeiffer et al., 2013	39 PTSD: 18 CG: 21	PTSD: 5.6% M; 94.4% F CG: 14.3% M; 85.7% F	37.00 PTSD: 37.3 CG: 36.7	PTSD-NR	TEC	Negative and positive emotional faces
Neumeister et al., 2018	38 PTSD: 19 CG: 19	PTSD: 100% F CG: 100% F	26.84 PTSD: 26.79 CG: 26.89	PTSD-R IPV	HC	Trauma-related and neutral pictures
Patel et al., 2016	22 PTSD: 11 CG: 11	PTSD: 45.4% M; 54.6% F CG: 27.2% M; 72.8% F	37.00 PTSD: 37.3 CG: 36.7	PTSD-NR	TEC	Negative and positive emotional pictures IAPS
Protopopescu et al., 2005	25 PTSD: 9 CG: 14	PTSD: 22.2% M; 77.8% F CG: 50% M; 50% F	31.00 PTSD: 35.00 CG: 27.00	PTSD-R Sex and physical abuse	HC	Trauma-related words vs positive valence words vs neutral words
Rabellino et al., 2017	36 PTSD: 18 CG: 18	PTSD: 38.9% M; 61.1% F CG: 50.0% M; 50.0% F	35.65 PTSD: 38.4 CG: 32.9	PTSD-NR	HC	Individualized trauma-script
Sakamoto et al., 2005	32 PTSD: 16 CG: 16	PTSD: 50.0% M; 50.0% F CG: 50.0% M; 50.0% F	41.75 PTSD: 41.2 CG: 42.3	PTSD-NR	HC	Traumatic-related and neutral pictures
Schechter et al., 2012	20 PTSD: 11 CG: 9	PTSD: 100% F CG: 100% F	29.95 PTSD: 29.5 CG: 30.4	PTSD-R IPV	HC	Interpersonal separation videoclips
Shin et al., 2005	26 PTSD: 13 CG: 13	Not reported	51.25 PTSD: 52.8 CG: 49.7	PTSD-NR	TEC	Fearful vs happy faces
Terpou et al. [46]	46 PTSD: 26 CG: 20	PTSD: 42.3% M; 57.7% F CG: 50.0% M; 50.0% F	35.65 PTSD: 38.8 CG: 32.5	PTSD-NR	HC	Trauma-related and neutral pictures
Thomaes et al., 2009	14 PTSD: 9 CG: 5	PTSD: 100% F CG: 100% F	31.75 PTSD: 30.6 CG: 32.9	PTSD-R CPTSD	HC	Negative and neutral emotional words
Thomaes et al., 2012	51 PTSD: 29 CG: 22	PTSD-G: 100% F CG: 100% F	34.25 PTSD-G: 33.5 CG: 35.2	PTSD-R CPTSD Childhood sex abuse	HC	Trauma-related and neutral words

Table 1. continued

Study	N	Gender	Age	PTSD group	Control	Experimental paradigm
Thomaes et al., 2013	49 PTSD: 28 CG: 21	PTSD: 100% F CG: 100% F	nr	PTSD-R CPTSD	HC	Negative emotional words vs no stimuli
Van Rooij et al., 2015	54 PTSD: 29 CG: 25	PTSD: 100% M CG: 100% M	36.4 PTSD: 35.97 CG: 35.38	PTSD-NR	HC	Negative and neutral emotional pictures IAPS
Wang et al., 2016	38 PTSD: 16 CG: 22	PTSD: 37.5%M; 62.5%F CG: 27.3% M; 82.7%F	33.15 PTSD: 31.6 CG: 34.7	PTSD-NR	HC	Human faces showing emotional reactions
Weaver et al., 2020	19 PTSD: 10 CG: 9	PTSD: 100% F CG: 100% F	32.8 PTSD: 33.8 CG: 31.8	PTSD-R IPV	HC	Trauma-related words
Whalley et al., 2009	48 PTSD: 16 CG: 32	PTSD: 37.5% M; 62.5% F CG: 31.2% M; 68.8% F	34.3 PTSD: 36.8 CG: 3305	PTSD-NR	HC	Negative and neutral emotional pictures IAPS

CG Control Group, *CPTSD* Complex Post Traumatic Stress Disorder, *HC* Healthy Controls, *IAPS* International Affective Picture System, *PTSD-IPV* Post Traumatic Stress Disorder due to intimate partner violence, *PTSD-NR* Post Traumatic Stress Disorder due to non-relation traumatic experiences, *PTSD-R* Post Traumatic Stress Disorder due to interpersonal traumatic experiences, *TEC* Traumatic Experiences Controls.

Table 2. Results of network meta-analysis for PTSD-NR group.

Brain Network	d_{pooled} (95% CrI)	SUCRA	Brain Network	d_{pooled} (95% CrI)	SUCRA
↑Subcortical Limbic	1.40 (0.89–1.90)	0.86	↓ Exteroceptive Self	−1.90 (−2.90 to −0.92)	0.86
↑ Exteroceptive Self	1.40 (0.96–1.80)	0.85	↓ Limbic	−1.90 (−2.90 to −0.90)	
↑ Interoceptive Self	1.30 (0.99–1.60)	0.79	↓ Mental Self	−1.80 (−2.10 to −1.40)	0.84
↑ Mental Self	1.20 (1.00–1.40)	0.74	↓ Interoceptive Self	−1.40 (−1.80 to −1.10)	0.69
↓ Interoceptive Self	−1.40 (−1.80 to −1.10)	0.31	↑ Mental Self	1.20 (1.00–1.40)	0.26
↓ Mental Self	−1.80 (−2.10 to −1.40)	0.16	↑ Interoceptive Self	1.30 (0.99–1.60)	0.20
↓ Subcortical Limbic	−1.90 (−2.90 to −0.90)	0.14	↑ Exteroceptive Self	1.40 (0.96–1.80)	0.15
↓ Exteroceptive Self	−1.90 (−2.90 to −0.92)		↑ Subcortical Limbic	1.40 (0.89–1.90)	0.14

PTSD due to interpersonal traumatic experiences (PTSD-R). The results of nodesplit analysis found a significant inconsistency of results among PTSD-R studies. Accordingly, a post-hoc exploration of effect sizes identified two sub-networks characterized by distinct brain responses toward emotion-eliciting stimuli.

The first group was composed of studies ($N = 5$) that reported a combination of heightened and decreased brain responses among individuals who met criteria for PTSD-IPV ($N = 4$; 80%) and PTSD due to childhood sex abuse ($N = 1$). On the contrary, the second group included studies ($N = 10$) that highlighted consistent increased brain activities in response to the presentation of emotional stimuli among individuals who met criteria for CPTSD ($N = 5$), PTSD associated to childhood sex and physical abuse ($N = 2$) and PTSD-IPV ($N = 3$). Comparing clinical characteristics of the previous groups, the analysis suggested a higher frequency of PTSD-IPV in the first group ($\chi^2_{(1)} = 3.49$; $p = 0.06$); whereas a higher frequency of ICD-11 CPTSD diagnosis was found in the second group ($\chi^2_{(1)} = 3.75$; $p = 0.05$).

The network meta-analysis applied to findings of the first group of studies mainly composed of individuals with PTSD-IPV showed consistent findings based on the nodesplit analysis. Therefore, meta-regression was not conducted in order to evaluate the presence of possible sources of heterogeneity. The most representative heightened brain response of this group was a hyper-reactivity of the subcortical limbic network together with the exteroceptive one. Concurrently, a decreased activity of the exteroceptive self network should be considered as key brain responses toward emotional-eliciting stimuli of subjects with PTSD-IPV compared to controls.

Conversely, the second group of studies mainly composed of individuals with CPTSD showed consistent increased responses toward emotional stimuli, as suggested by the nodesplit analysis. Accordingly, sources of heterogeneity were excluded and, in turn, meta-regression analysis was not estimated. Specifically, increased activities of self networks, especially the exteroceptive one, were the most representative brain responses toward emotional stimuli of this group compared to controls. (See Table 3 for a summary of effect sizes of these subgroups of studies).

Summary of network meta-analysis results. Network meta-analysis procedures supported a distinction between PTSD-NR and PTSD-R, together with an additional differentiation between two subgroups of individuals with PTSD-R. First, individuals with PTSD-NR might show opposite functioning (i.e., under- and over-modulation states) [47, 48] in response to the presentation of emotional stimuli. Specifically, they were characterized by significant both heightened and reduced activities of subcortical limbic and self networks, especially considering the exteroceptive one.

Regarding PTSD-R, post-hoc network meta-analyses results identified two subgroups suggesting a different traumatic organization of neural activity across relational post-traumatic manifestations. The first PTSD-R subgroup was mainly represented by subjects who met criteria for PTSD-IPV. Neural activity of this group is characterized by heightened subcortical limbic responses as core features. Differently from PTSD-NR, this group did not highlight significant decreases of subcortical limbic activity in

Table 3. Network meta-analysis results for PTSD linked to interpersonal traumatic experiences groups (PTSD-R): PTSD-IPV and CPTSD.

Brain Network	d_{pooled} (95% CrI)	SUCRA	Brain Network	d_{pooled} (95% CrI)	SUCRA
PTSD-IPV					
↑ Subcortical Limbic	1.80 (0.16–3.40)	0.82	↓ Exteroceptive Self	−2.10 (−3.90 to −0.43)	0.94
↑ Exteroceptive Self	1.80 (0.13–3.50)		↓ Interoceptive Self	−1.70 (−3.32 to −0.25)	0.88
↑ Mental Self	1.60 (0.17–3.32)	0.78	↓ Mental Self	−0.75 (−2.30 to 0.82)	0.71
↑ Interoceptive Self	1.30 (−0.55–3.20)	0.70	↑ Interoceptive Self	1.30 (−0.55 to 3.20)	0.30
↓ Mental Self	−0.75 (−2.30 to 0.82)	0.28	↑ Mental Self	1.60 (0.17–3.32)	0.22
↓ Interoceptive Self	−1.70 (−3.32 to −0.25)	0.11	↑ Exteroceptive Self	1.80 (0.13–3.50)	0.18
↓ Exteroceptive Self	−2.10 (−3.90 to −0.43)	0.06	↑ Subcortical Limbic	1.80 (0.16–3.40)	
CPTSD					
↑ Exteroceptive Self	1.20 (0.76–1.70)	0.83			
↑ Interoceptive Self	1.10 (0.77–1.40)	0.67			
↑ Mental Self	1.10 (0.79–1.40)				
↑ Subcortical Limbic	0.87 (0.60–1.20)	0.34			

responses to emotional stimuli. Similarly to PTSD-NR, this group was characterized by a core decrease of exteroceptive self activity. The second PTSD-R subgroup mainly composed of individuals with CPTSD showed a neural response toward emotional responses strongly organized around an increased activity of self networks.

Therefore, these results suggest similarities and differences between PTSD-R subgroups (i.e., PTSD-IPV and CPTSD), which might be related to different degrees of severity of brain and self traumatic re-organization (see Fig. 2 for a graphical summary of network meta-analysis findings).

ALE meta-analysis

PTSD due to non-relational traumatic experiences. Table 3S (see Supplementary Materials) reported results of the most representative clusters of activation reflecting heightened responses of individuals with PTSD-NR compared to control conditions. The analysis used an uncorrected $p < 0.005$ threshold with a minimum cluster size of 300 mm^3. The ALE meta-analytic findings suggested a brain network characterized a heightened activity of medial and superior prefrontal cortices (i.e., mental self), temporal and parietal areas (i.e., exteroceptive self) together with an increased activation of subcortical limbic areas (i.e., bilateral parahippocampal gyrus) and bilateral insula (i.e., interoceptive self).

PTSD due to relational traumatic experiences. Table 4S (see Supplementary Materials) reported results of the most representative clusters of activation (i.e., uncorrected $p < 0.005$ threshold with a minimum cluster size of 300mm^3) reflecting increased responses of individuals with PTSD-R compared to control conditions. The ALE meta-analytic results highlighted that the clinical group showed increased responses toward emotional stimuli, especially considering bilateral parahippocampal gyrus and insula (i.e., subcortical limbic areas and interoceptive self). Results also found a recruitment dACC (i.e., interoceptive self) and medio-lateral prefrontal cortices (i.e., exteroceptive and mental self).

According to results of network meta-analysis, we further conducted two subgroup ALE meta-analyses separately considering a group composed of individuals with PTSD-IPV, and another group including individuals with CPTSD and PTSD due to sex and physical abuse across life-span. This was chosen in line with results of post-hoc PTSD-R subgroup network meta-analyses. Table 5S (see Supplementary Materials) reports results for the comparison between PTSD-IPV patients with controls. The analysis mainly detected a heightened responsiveness of parahippocampal gyrus and right insula (i.e., subcortical limbic and interoceptive self areas) within the clinical group.

Table 5S also shows ALE meta-analysis findings concerning the comparisons between individuals with CPTSD/PTSD due to sex/physical abuse vs. control conditions. These results highlighted increased activities of prefrontal cortices linked to exteroceptive and mental self networks.

ALE contrast analysis

Figure 3 shows results of ALE contrast analysis (i.e., uncorrected threshold $p < 0.05$ applying 10,000 permutations) that compared brain responses toward emotional stimuli between PTSD-NR and PSTSD-R. Table 6S (see Supplementary Materials) shows that PTSD-NR is characterized by a significant higher activity than PTSD-R within a single cluster composed of bilateral anterior cingulate and medial frontal gyrus (i.e., mental self). Whereas, individuals with PTSD-R highlighted greater responses than PTSD-NR within different clusters, comprising intero-exteroceptive self regions such as insula, supplementary motor area, IFG, together with subcortical limbic regions (e.g., parahippocampal gyrus, amygdala).

According to post-hoc results of network meta-analysis, supplementary materials include tables (Tables 7S, 8S) reporting ALE contrast analyses between the PTSD-NR group with PTSD-R subgroups. Briefly, the PTSD-IPV group highlighted increased responses of left precentral gyrus, amygdala and parahippocampal gyrus together with right insula and middle frontal gyrus (i.e., subcortical limbic, interoceptive-mental self networks) compared to PTSD-NR. Individuals with CPTSD and PTSD due to sex/physical abuse showed higher activity than PTSD-NR within a network composed of left IFG and dACC (i.e., intero-exteroceptive self networks). Ultimately, the PTSD-IPV group showed a heightened activity of left amygdala and right insula (i.e., subcortical limbic and interoceptive self networks) compared to individuals with CPTSD/PTSD due to sex and physical abuse. Lastly, supplementary materials also report results for conjunction analysis between PTSD-R and PTSD-NR (Table 9S). Briefly, results show a common pattern of increased responses of subcortical limbic areas (parahippocampal gyrus and amygdala), bilateral insula and superior frontal gyrus (i.e., intero-mental self networks) in both PTSD-R and PTSD-NR compared to controls.

DISCUSSION

According to the nested hierarchy model of self and its traumatic re-organization [3], the current study sought to summarize empirical findings from fMRI data in order to provide a neurobiological support for a differentiation between PTSD-NR and PTSD-R. Hypothesizing a continuum of severity from non-

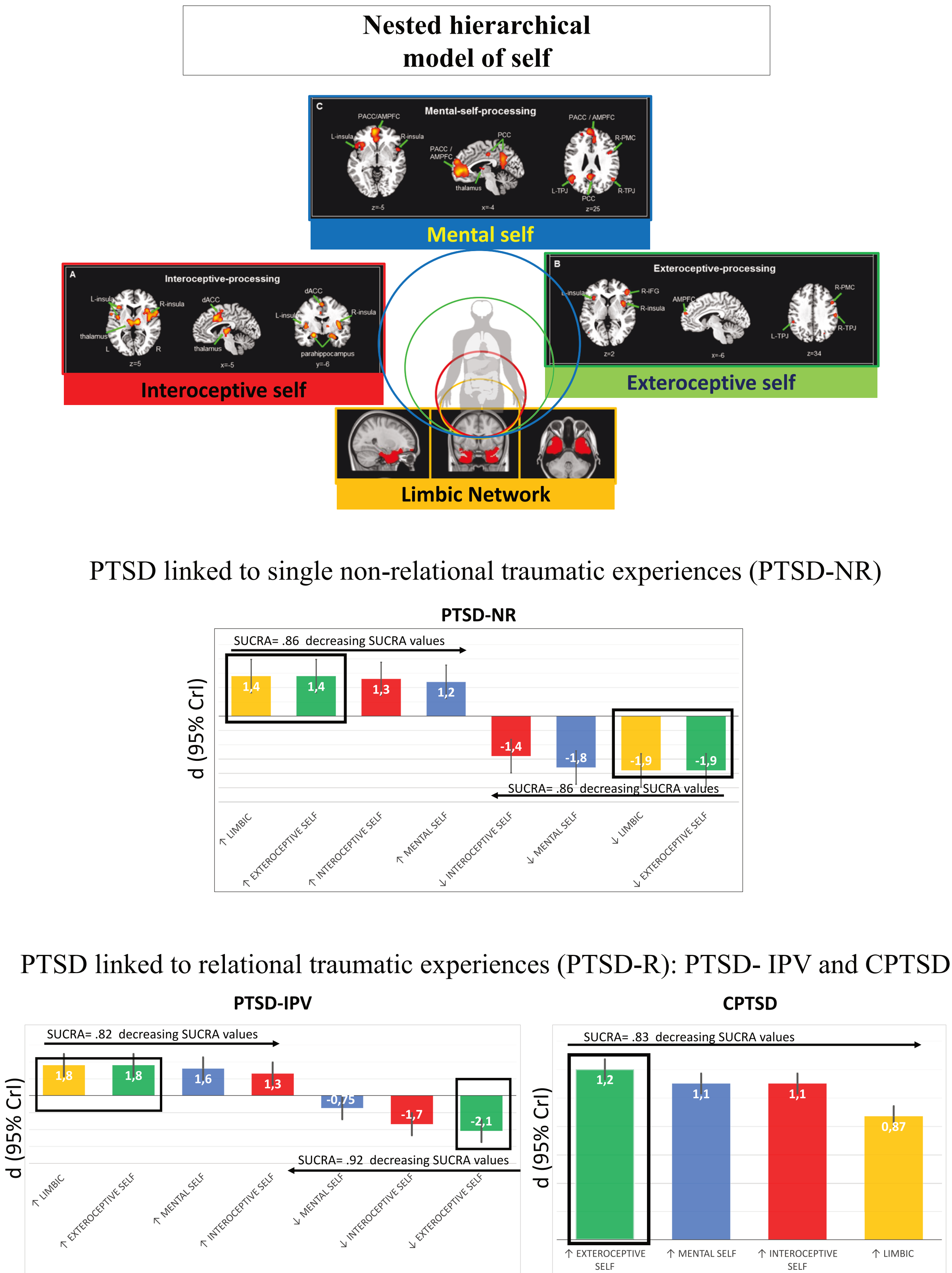

Fig. 2 Visual representation of network meta-analysis results. Upper part is a graphical representation of the nested hierarchical model of self and limbic network. Lower part shows the network meta-analysis findings for PTSD-NR and for the two subgroups related to PTSD-R. d= pooled effect size; CrI= Credible Interval.

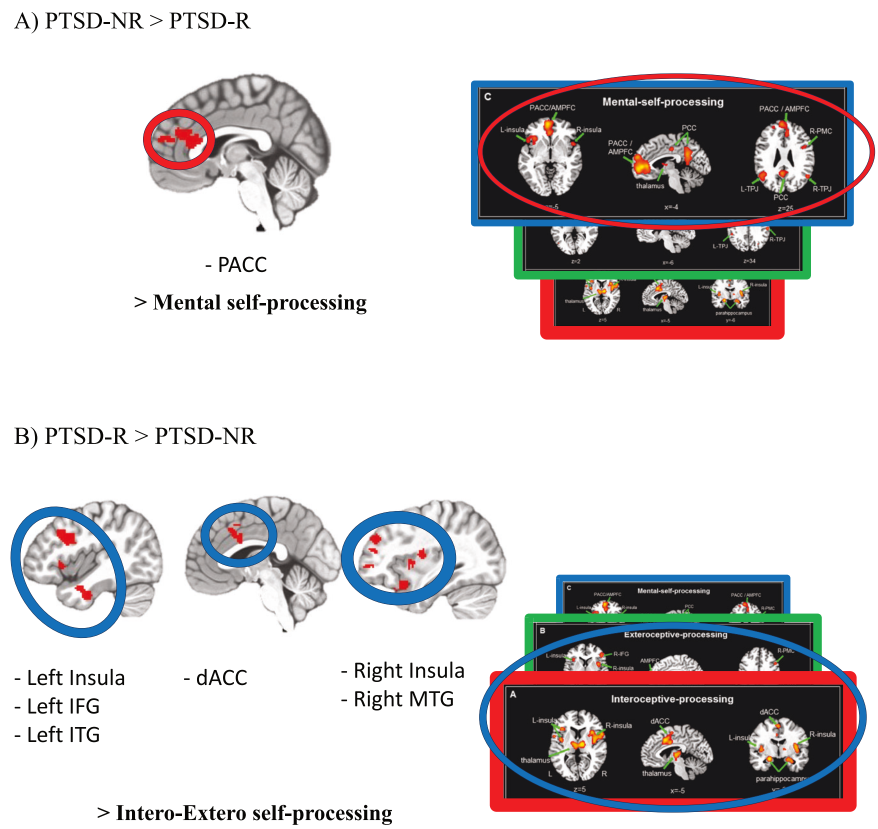

Fig. 3 Visual representation of ALE contrast analysis. A Contrasto analysis PTSD-NR > PTSD-R. **B** Contrasto analysis PTSD-R > PTSD-NR.

relational to most severe forms of relational trauma and their PTSD manifestations, we explored the differential impact of these experiences.

Network meta-analytic findings showed that individuals with PTSD-NR were characterized by patterns of heightened and decreased responses of subcortical limbic and self networks, although subcortical limbic ones resulted as the most representative of this group. Regarding the PTSD-R group, our findings highlighted two subgroups of individuals suggesting different degrees of traumatic re-organization. The first group was mainly represented by subjects who met criteria for PTSD-IPV. This subgroup showed heighted subcortical limbic responses as the most representative of this condition. Moreover, the PTSD-IPV group was also characterized by reduced activities of the three-layer self-processing brain networks. Whereas, the group mainly composed of individuals with CPTSD and PTSD linked to childhood sex/physical abuse showed a neural response toward emotional stimuli organized around an increased activity of networks related to the self, especially the exteroceptive one (i.e., highest SUCRA value).

Moreover, the ALE meta-analytic results further confirm the previous findings: (i) patients with PTSD-NR, compared to controls, showed increased responses toward emotional stimuli within a network that included the frontal gyrus (i.e., superior and medial), temporo-parietal regions and subcortical limbic areas; (ii) individuals with PTSD-R were characterized by an increased recruitment of intero-exteroceptive regions comprising supplementary motor areas and hyper-reactivity of subcortical limbic regions in response to the administration of emotional stimuli.

We also performed a conjunction and contrast analyses between these two forms of PTSD to further expand and sustain our hypotheses. The conjunction analysis showed common abnormal responses of subcortical limbic and interoceptive self areas among both forms of PTSD. Concurrently, our comparison suggested that the PTSD-NR is characterized by a significant higher activation of anterior cingulate and medial frontal gyrus than PTSD-R. While, the PTSD-R shows heightened responses within distinct frontal regions (i.e., supplementary motor area, IFG), subcortical limbic areas and insula compared to PTSD-NR. This is one of the main findings of our work, and it emphasizes how non-relational vs relational traumatic experiences might differently affect the self-organization of brain topography in response to emotional stimuli. This finding supports our theoretical model [3, 11] suggesting how the PTSD-NR group recruits high level mental self brain regions to process emotional stimuli. Whereas, the PTSD-R group mainly recruits regions belonging to lower-layers of self, such as the intero- and extero-ceptive ones. This might suggest that the sense of self of individuals with PTSD-R doesn't reach a higher symbolic capacity, but it is embedded at an intero-exteroceptive bodily level including its internal and external relation. This alteration of "embodiment" can be interpreted as a more primitive form of affective regulation [8, 39, 66].

The current findings related to PTSD-NR are partially in line with existing neurobiological models of PTSD [42, 47, 48] that assume two distinct states of functioning. The increased activity of superior and medial frontal gyrus compared to control conditions might capture the PTSD "emotional over-modulation state" characterized by dissociative reactions, which have been associated to maladaptive cognitive emotion regulation strategies [67]. Accordingly, there are consistent fMRI results that have demonstrated a key role of superior frontal/medial gyrus and temporal areas in sustaining the engagement in maladaptive cognitive emotion regulation strategies [68] to decrease emotional reactions. Furthermore, the increased activity of subcortical limbic regions found among individuals with PTSD-NR compared to controls seemed to be consistent with the "under-modulation state" [47, 48], which is mainly characterized by positive dissociative symptoms (e.g., re-experience of traumatic memories), hyper-arousal and vigilance. These meta-analytic results might suggest a co-existence of these mental states among individuals with PTSD-NR. This was supported by SUCRA values that confirmed as the most representative responses of this clinical group both heightened and decreased activations of subcortical limbic and exteroceptive self regions.

Looking at voxel-based meta-analytic results of the PTSD-R group, findings showed a hyper-reactivity of bilateral parahippocampal gyrus and left supplementary motor areas than control conditions. Furthermore, individuals with PTSD-R were characterized by a significant higher reactivity of subcortical limbic areas, IFG and right insula compared to patients with PTSD-NR. These results supported the distinction between PTSD-NR and PTSD-R. Specifically, the greater reactivity of parahippocampal gyrus might suggest that individuals with PTSD-R are characterized by a heightened proneness to abnormally process emotional stimuli, especially human [69]. Moreover, recent evidence has suggested that contextual processing deficits are associated with hippocampal function among individuals with PTSD [70]. Referring to our data, the hippocampus, which is associated to the encoding of emotional memories [71], seems to be more involved in the PTSD-R. However, findings from task-dependent fMRI studies are mixed, and future research is needed to better understand the role of hippocampus in different forms of PTSD (for reviews see: [72]) (See Supplementary material for a more detailed discussion on the role of hippocampus).

Regarding the increased activity of interoceptive self regions the most relevant area was the anterior insula, a key hub for emotional awareness [73–76], that has been associated with the processing of emotional valence and long-term retention of appetitive-aversive-novelty-driven learning and decision-making processes [77]. Intriguingly, the insula also serves as a linkage between the three layers of self departing from the interoceptive one [10, 78]. Thus, the current finding concerning an altered activation of anterior insula in the PTSD-R seems to suggest how this condition might be characterized by an abnormal nestedness among the three layers of self. This might support the view of PTSD-R as a disorder of self-organization.

Moreover, the increased activity of exteroceptive self areas (i.e., supplementary motor, IFG) found among individuals with PTSD-R, compared to PTSD-NR and controls, suggested an engagement in non-mentalized and rudimental emotional regulation processes [50, 79], especially considering interpersonal contexts [80, 81]. This evidence supports the notion that individuals with PTSD-R might be characterized by a more pronounced interpersonal sensitivity compared to patients who were exposed to non-relational traumatic experiences [82, 83].

Another relevant finding is the difference between PTSD-IPV and CPTSD within the group of PTSD-R. These might be provisionally interpreted as a possible continuum of the severity of relational traumatic events and their impacts on the brain and self organization. Precisely, this continuum could capture how individuals with PTSD-R move towards a more primitive processing related to: (i) a heightened activity of lower hierarchical layers of self-processing networks (i.e., intero- and exteroceptive self); (ii) a reduced capacity to modulate subcortical limbic and self-processing regions across the spectrum.

These findings and interpretations again confirm our hypothesis related to the close connection with the topography of intero-exteroceptive processing at the expense of the mental-self processing in individuals with a history of cumulative relational traumatic experiences [3, 11, 57, 66].

Overall, our findings seem to suggest that the PTSD-R should be mainly considered as a disorder of the most basic layers of self-processing and self-organization. This evidence supports the notion that these individuals are not only characterized by emotional dysregulation, but their core feature is a disrupted nestedness of self layers and their organization. Our proposal to view the PTSD-R as disorder of intero-exteroceptive self seems also to be coherent with other theories of self (e.g., [84, 85]). Specifically, Damasio [84] has theorized the "proto self", which represents a foundational layer generating basic feelings at a subconscious level. This foundational self serves as a baseline for the higher layers, such as the "core self" (i.e., the transient experiences due to the relationship between an individual and the surrounding environment) and the "autobiographical self". These formulations reinforce the idea of a self that is functionally organized across various layers, encompassing an unconscious, pre-reflective, and minimal self to a reflective, phenotypic "idiographic", narrative self shaped by interpersonal and socio-cultural experiences. Coherently with other theories of self, we can consider PTSD-R as disorder of self and its fundamental layer or its psychological baseline [1, 2, 4].

Some limitations must be discussed. First of all, there are few studies that directly compared neural functioning of PSTD-NR with PTSD-R. Accordingly, future neuroscience research should be carried out on this topic in order to effectively evaluate distinct brain activity patterns of these conditions. Second, future longitudinal studies should evaluate how different traumatic experiences might affect the development of neural networks involved in processing and regulation of emotion-eliciting situations. Third, there is a lack of empirical data that confirm a link between alternations of neural functioning with shared PTSD clusters of symptoms (i.e., re-experiencing, avoidance, sense of threat) and specific CPTSD clusters of symptoms (i.e., affect dysregulation, negative self-concept, interpersonal problems). Ultimately, the limited number of studies included for each clinical group did not allow to conduct robust voxel-based meta-analytic procedures that control results for multiple comparisons. The limited number of studies that reported increased brain responses among control conditions compared to PTSD groups did not allow to estimate a robust voxel-based meta-analysis in order to corroborate results of network meta-analysis, especially referring to the PTSD-NR group. Similarly, the small number of studies for each subgroup of PTSD-R did not allow to support results of ROI-based network meta-analysis with a robust voxel-based approach. Therefore, future research on PTSD should move toward systematic evaluations of different forms of these conditions departing from a distinction of the quality of traumatic experiences. Ultimately, the implications of self-processing brain networks for different forms of PTSD should be further supported by specific experimental paradigms that allow to differentiate self-related mechanisms from other neuro-mental processes relevant for post-traumatic manifestations, especially source monitoring [86, 87] that shares with self-processing layers common brain networks (e.g., MPFC, anterior cingulate) [88].

Future research might also shed a light on the differences in resting state fMRI. Investigating trauma-related pathological dissociation (i.e., disruptions of sense of self, perceptual, and affective experience), [89] observed that dissociation was linked to hyperconnectivity within central executive (CEN), default (DMN), and salience networks (SN), and decreased connectivity of CEN and SN with other areas. These findings proposing functional connectivity signatures of dissociative dimensions within the CEN seem also to be coherent with the current results related to emotional processing in PTSD-R vs. PTSD-NR. Thus, future research is needed to integrate findings on emotional task-evoked activity alongside resting state brain activity.

CONCLUSION

In conclusion, this is the first study based on meta-analytic fMRI findings that supported a distinction between PTSD-NR and PTSD-R showing how different conditions linked to specific traumatic events might involve different layers of self-processing. These results are also clinically relevant and informative in support of the development of differential treatment approaches for different forms of PTSD referring to psychological and brain-based models of nested hierarchy of self and its implications for specific traumatic experiences. Specifically, well-validated therapy based on specific cognitive-behavioral procedures (e.g., prolonged exposure therapy; EMDR) [90] might be considered effective for the PTSD-NR according to the preserved reflective abilities on emotional states characterizing this group. Whereas, relational-oriented therapies, especially psychodynamic ones (e.g., [27, 91]), could be more effective for the PTSD-R due to their focus on re-establishing a well-integrated sense of self from interoceptive to the more mental features, thus re-establishing a sense of self-continuity that was impaired by the cumulation of relational traumatic experiences [3]. In conclusion, our findings underscore the importance of looking for the "common currency" of psyche and brain [92], as also suggested by Spatiotemporal Psychopathology framework [93]. This approach aims at integrating psychological and neuronal dynamics that could serve for a more precise differential diagnosis and treatment indication of different forms of trauma.

DATA AVAILABILITY

All data supporting the findings of this study are available within the paper and its Supplementary Information.

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AUTHOR CONTRIBUTIONS

AS and MC designed the theoretical framework and the logic of the study, analyzed the data and wrote a first draft of the manuscript that was critically revised by GN. All authors approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted following the Meta-Analysis Reporting Standards (MARS) of *American Psychological Association* and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

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