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Deconstructing dissociation: a triple network model of trauma-related dissociation and its subtypes

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Trauma-related pathological dissociation is characterized by disruptions in one's sense of self, perceptual, and affective experience. Dissociation and its trauma-related antecedents disproportionately impact women. However, despite the gender-related prevalence and high individual and societal costs, dissociation remains widely underappreciated in clinical practice. Moreover, dissociation lacks a synthesized neurobiological model across its subtypes. Leveraging the Triple Network Model of psychopathology, we sought to parse heterogeneity in dissociative experience by examining functional connectivity of three core neurocognitive networks as related to: (1) the dimensional dissociation subtypes of depersonalization/derealization and partially-dissociated intrusions; and, (2) the diagnostic category of dissociative identity disorder (DID). Participants were 91 women with and without: a history of childhood trauma, current posttraumatic stress disorder (PTSD), and varied levels of dissociation. Participants provided clinical data about dissociation, PTSD symptoms, childhood maltreatment history, and completed a resting-state functional magnetic resonance imaging scan. We used a novel statistical approach to assess both overlapping and unique contributions of dissociation subtypes. Covarying for age, childhood maltreatment and PTSD severity, we found dissociation was linked to hyperconnectivity within central executive (CEN), default (DN), and salience networks (SN), and decreased connectivity of CEN and SN with other areas. Moreover, we isolated unique connectivity markers associated with depersonalization/derealization in CEN and DN, to partially-dissociated intrusions in CEN, and to DID in CEN. This suggests dissociation subtypes have robust functional connectivity signatures that may serve as targets for PTSD/DID treatment engagement. Our findings underscore dissociation assessment as crucial in clinical care, in particular, to reduce gender-related health disparities.

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INTRODUCTION

Pathological dissociation, the experience of detachment from or discontinuity in one's internal experience, sense of self, or surroundings [1], is a common experience in the aftermath of trauma [2, 3]. However, symptoms of trauma-related pathological dissociation and dissociative disorders remain at best underappreciated and, at worst, frequently go undiagnosed or misdiagnosed [4, 5]. Clinical misunderstanding about dissociation (For brevity, we use the term dissociation to refer to trauma-related pathological dissociation throughout the manuscript. It does not include non-pathological forms of dissociation.) is historically longstanding and rooted largely in an individual and societal reluctance to acknowledge the prevalence of childhood abuse and domestic violence and its impact, in particular, on women [4, 6]. The cost of this stigmatization and misunderstanding is high: it has prevented people from accessing appropriate and effective treatment, prolonged suffering, and stunted research on dissociation, the dissociative subtype of posttraumatic stress disorder (PTSD) and dissociative identity disorder (DID) [4, 6, 7]. More psychological and biological research in this area could serve as a lifebuoy—helping to destigmatize and understand these conditions, and how best to treat them.

Psychological research embracing trauma-related pathological dissociation has determined that it encompasses a range of experiences or "subtypes" [8]. Subtypes like depersonalization and derealization are frequent experiences in both the dissociative subtype of PTSD and DID [1]. Depersonalization and derealization involve feelings of detachment or disconnection from one's sense of self, body and environment [1]. Individuals report feeling like their body or surroundings are unreal or like they are in a movie. Dissociation also includes experiences of self-alteration common in DID in which people lose a sense of agency and ownership over their thoughts, emotions, actions and body [9]. With this loss of agency and ownership, people then experience some thoughts, emotions etc. as partially-dissociated intrusions [9]. Individuals report feeling like they are hearing voices or that their thoughts, emotions, and actions emerge without their control and 'intrude' on their conscious experience. Importantly, these intrusions are characterized as partially-dissociated rather than psychotic because the person retains fully intact reality-testing though

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subjectively feels "as if" the experiences do not belong to them [9]. Both depersonalization, derealization, and experiences of self-alteration can help people cope in the face of inescapable threat and trauma [10]. However, they can also impede one's ability to function and can interfere with new emotional learning [11]. This adds urgency to our need to better understand mechanisms of dissociation so we can enhance interventions that will ameliorate these symptoms.

Brain-based measures of dissociation can provide scientific evidence for the validity of these experiences and can link the clinical phenomenology with biological mechanisms. While foundational studies have begun to characterize the neurobiology of dissociation [12–14], the field lacks a synthesized model across the range of dissociative experiences that could place it in context with other common psychiatric conditions. This gap in our knowledge about experiences that disproportionately impact women [15–17] contributes to gender-related health disparities and must be addressed to help eliminate this inequity.

The Triple Network model of psychopathology may provide a synthesized neurobiological model for pathological dissociation. This model offers an integrative framework based in systems neuroscience for understanding cognitive and affective dysfunction across psychiatric conditions [18]. The basic model implicates altered intrinsic organization and interactions between three large-scale brain networks across disorders: the right-lateralized central executive network (rCEN), the medial temporal subnetwork of the default network (tDN), and the cingulo-opercular subnetwork of the SN (cSN; Fig. S1).

These three networks serve complementary functions. The rCEN, a lateral frontoparietal network, is strongly implicated in cognitive processes such as reasoning, attention, inhibition, and memory [19, 20]. The rCEN is distinct from left CEN, which is primarily involved in language processing [19, 20]. Conversely, tDN, a medial frontoparietal network [21], is involved in autobiographical memory, recollection of events in one's past (i.e., episodic memory retrieval) and simulating future events [22–25]. Lastly, cSN, a midcingulo-insular network [21], is involved in interoception, especially the experience of emotion derived from information about the internal milieu [26]. These subnetworks are easily identified using group independent component analysis and are highly reproducible [19, 20, 27].

Altered organization and interaction between CEN, DN, and SN are consistently reported across psychiatric disorders [18]. Central to these alterations is improper assignment of relevance or salience to either internal or external stimuli [18]. Inappropriate salience detection, failing to assign relevance to something important or assigning relevance to something unnecessarily, can create a cascade effect where the CEN and DN do not engage or disengage appropriately. Depending on the subtype of pathological dissociation (e.g., depersonalization/derealization, partially-dissociated intrusions etc.), these symptoms could involve inappropriate salience detection in either direction, and concomitant alterations in executive functioning and self-generated thought.

Neuroimaging work to date implicates altered connectivity of regions in all three networks [12, 14, 28]. These studies typically focus on dissociative symptoms of depersonalization and derealization—with both seed-based and group independent component analysis functional connectivity findings in the dissociative subtype of PTSD highlighting altered connectivity of regions located in the SN, DN, and CEN (e.g., amygdala, insula, prefrontal and parietal cortex [12, 29, 30]). One study from our team found that hyperconnectivity of regions in CEN and DN was associated with a measure of pathological dissociation that combined scores of depersonalization, derealization, and partially-dissociated intrusions in a PTSD, PTSD dissociative subtype, and DID sample [31]. Relatedly, there is also foundational work implicating altered activity in these networks in PTSD [12] and DID [13, 32–37]. Taken together, these findings cover a range of dissociation subtypes; however, they do not directly compare different subtypes. The unique contributions of different dissociation subtypes to altered connectivity in the three core networks of the Triple Network model are unknown. Parsing heterogeneity in dissociation could add significant impact to our understanding of differences in both illness and treatment trajectories across individuals – and represents the critical next step in advancing personalized medicine for dissociative symptoms.

To address this gap, we assessed the connectivity of rCEN, tDN, and cSN as related to different subtypes of pathological dissociation: the dimensional symptoms of depersonalization/derealization and partially-dissociated intrusions, and the diagnostic category of DID. Notably, we used a novel method for assessing both overlapping and unique contributions of different dissociation types [38]. Given prior work both in dissociation and the Triple Network model of psychopathology, we hypothesized all three networks would be implicated in dissociation and unique patterns of connectivity would emerge for each dissociative subtype.

MATERIALS AND METHODS

Participants

A total of 132 adult women with and without histories of childhood trauma, current PTSD, and varied levels of dissociative symptoms were enrolled in this cross-sectional study. A total of 23 were excluded based on our exclusion criteria, including standard contraindications to MRI, a history of neurological conditions, history of head injury resulting in a loss of consciousness for longer than 5 min, a current alcohol or substance use disorder within the past month, and a history of psychotic spectrum disorders. Of the remaining 109, a total of 18 datasets were excluded from analysis due to data quality issues, resulting in 91 datasets available for subsequent analysis. Table 1 lists demographic and clinical measures. Participants with PTSD ($N = 65$) had histories of childhood trauma and varied levels of pathological dissociation, including some with the PTSD dissociative subtype, and some with DID. These individuals were seeking treatment at a psychiatric hospital in the northeast region of the US. Participants without PTSD had no history of or current psychiatric disorders ($N = 26$).

All research procedures were approved by the Massachusetts General Brigham Human Research Affairs Institutional Review Board and performed in accordance with the Declaration of Helsinki human subject guidelines and regulations. All participants provided written informed consent and received $200 compensation. Data collection occurred between January 2015 and September 2019.

Diagnostic and symptom measures

Data collection followed the STROBE guidelines [39]. Psychiatric diagnoses were determined using the Structured Clinical Interview for the DSM-IV Axis I Disorders [40], the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; [41]) and the Structured Clinical Interview for DSM-IV Dissociative Disorders-revised [42].

For a measure of depersonalization and derealization symptoms, we used the average of the depersonalization and derealization subscales on the Multidimensional Inventory of Dissociation (MID; [43]). To measure partially-dissociated intrusions, we computed the average score of the following MID subscales: child voices, voices/internal struggle, persecutory voices, speech insertion, thought insertion, made/intrusive emotions, made/intrusive impulses, made/intrusive actions, temporary loss of well-rehearsed skills and knowledge, disconcerting experiences of self-alteration, and self-puzzlement. To control for PTSD symptom and childhood maltreatment severity in our analyses, we used the CAPS-5 total PTSD symptom severity score and the Childhood Trauma Questionnaire (CTQ) total score [44].

MRI procedures

See the supplementary for detailed information on MRI procedures, data quality assurance, preprocessing, and statistical analysis. We acquired resting-state fMRI data and conducted standardized preprocessing using *fMRIPrep* 20.0.1 [38, 45]. Resting-state networks were derived using group

Table 1. Demographics and clinical characteristics.

	Control	Conventional PTSD	PTSD Dissociative Subtype	DID[a]
	N	*N*	*N*	*N*
Sample size	28	19	18	26
Race				
American Indian	0	0	0	1
Asian	1	0	1	3
Black/African American	2	1	0	2
White	25	18	16	20
Other - unspecified	0	0	1	0
Ethnicity				
Hispanic/Latinx	3	1	0	1
Non-Hispanic/Latinx	25	18	17	25
Prefer not to answer	0	0	1	0
Education				
Grade 7–12 (without graduating high school)	0	0	0	1
High school or equivalent	1	0	1	0
Part of College	3	9	4	9
College (2 year)	0	0	2	1
College (4 year)	12	3	5	5
Part of Graduate/Professional School	4	3	4	3
Completed Graduate/Professional School	8	4	2	7
	M ± *SD*	*M* ± *SD*	*M* ± *SD*	*M* ± *SD*
Age	32.2 ± 11.2	33.4 ± 10.9	29.5 ± 9.6	37.4 ± 13.6
CTQ Total Severity	29.5 ± 6.6	63.6 ± 20.5	75.4 ± 22.6	88.1 ± 13.5
CAPS-5 Total Severity	0.64 ± 1.5	48.1 ± 10.6	48.5 ± 9.9	52.9 ± 13.6
PCL-5 Total	2.0 ± 4.4	53.9 ± 10.5	53.2 ± 12.3	50.5 ± 16.0
MID Severe Pathological Dissociation	2.2 ± 1.8	44.2 ± 22.6	76.3 ± 24.8	117.9 ± 29.2
MID Depersonalization/Derealization	0.51 ± 0.96	12.4 ± 9.2	30.1 ± 15.1	42.9 ± 19.6
MID Partially-Dissociated Intrusions	0.57 ± 0.66	13.9 ± 8.7	20.9 ± 12.9	45.2 ± 16.2

PTSD posttraumatic stress disorder, *CTQ* childhood trauma questionnaire, *CAPS-5* Clinician-Administered PTSD Scale for DSM 5, *PCL-5* PTSD Checklist for DSM 5, *MID* multidimensional inventory of dissociation.
[a]All participants with DID also met criteria for the dissociative subtype of PTSD. Total sample $N = 91$.

Independent Component Analysis (GICA; [46]). We then implemented a dual regression approach to obtain subject-specific network maps corresponding to each GICA component [47]. LDN and PK identified rCEN, cSN, and tDN by visual inspection of the spatial maps to find the components with the greatest spatial overlap with previously reported networks [19, 20, 48] (Fig. S1).

Statistical analysis

While all participants underwent a single study session (and thus blinding and randomization to treatments/conditions was not applicable), study staff who collected the imaging data from participants were blinded to participant diagnostic status.

DID diagnosis and the dimensional symptoms of depersonalization/derealization and partially-dissociated intrusions are highly collinear. Evaluating associations between each dissociation type and network connectivity in separate models could yield findings that are driven by shared variance due to their collinearity (Fig. 1). On the other hand, evaluating all three predictors within the same model will reduce sensitivity because shared variance between the predictors is ignored in the estimation.

To address these issues, we followed the novel two-step approach presented in [38] that relied on a series of multiple regressions with orthogonalization of predictors. First, full variance models were estimated with each network's set of connectivity maps as the dependent variable, and orthogonalized predictors of interest (i.e., DID, depersonalization/derealization, and partially-dissociated intrusions). This identified brain regions or "markers" associated with each predictor using the full variance associated with the predictor. We interpret these markers as being associated with "pathological dissociation," irrespective of subtype.

We then identified unique contributions of each dissociation subtype to the connectivity between markers and the network(s) by extracting the subject-level average regression weights for each marker. These weights were then used as dependent variables in a second set of multiple regressions with orthogonalizations to estimate regression coefficients that captured the unique effects of each subtype (see Fig. 1 and Supplementary for full details).

Each full variance model had one of the following independent variables as the predictor: diagnostic subgroup (PTSD, PTSD dissociative subtype, DID, and nonpsychiatric control) and two additional symptom severity scores (depersonalization/derealization, partially-dissociated intrusions). In addition, age, CTQ childhood maltreatment severity, and CAPS-5 PTSD total symptom severity were entered as covariates of no interest in all models. The CTQ score was missing for three participants (two with DID and one with the dissociative subtype of PTSD). Each score was replaced with average CTQ score for that diagnostic category. Every full variance model was evaluated using FSL Randomize for non-parametric permutation testing ($n = 5000$ permutations) with threshold-free cluster enhancement to control family-wise error ($p < 0.05$). As noted in [38], an additional correction for the multiple regression models is not necessary because all models explain the same total variance and, as such, are equivalent with respect to considerations of signal vs. noise. Further, as in [38], unique variance models were not corrected to retain sensitivity.

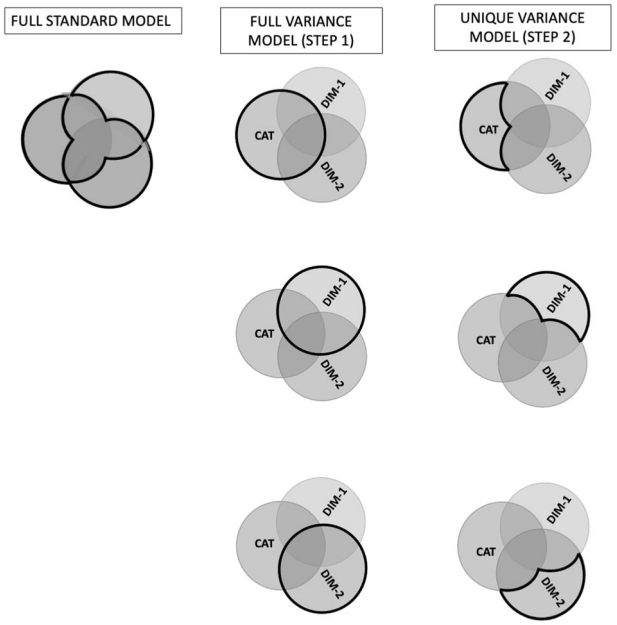

Fig. 1 Statistical Approach of the Full and Unique Variance models. Full standard model represents a multiple regression model that includes all diagnostic categorical (CAT) and dimensional (DIM) variables together. In this case, the shared variance between the variables (the areas of overlap in the center of the Venn diagram) are ignored when estimating the regression parameters. In contrast, full variance modeling (Step 1) involves running separate models that estimate the regression parameter of the variable using its full variance (heavy black circles) to yield a set of brain regions (or markers) whose connectivity with the network is associated with that variable. In Step 2, unique variance modeling identifies the unique association between the markers identified in Step 1 and each diagnostic categorical and dimensional variable. Adapted from [38].

RESULTS

Right central executive network (rCEN)

Full variance models showed the rCEN was most impacted by pathological dissociation; specifically, 39 clusters were linked to two types of alterations: (1) within-network hyperconnectivity; (2) Decreased connectivity with brain regions outside rCEN (Fig. 2, Table 2).

All three dissociation subtypes uniquely contributed to the altered connectivity of the rCEN (Fig. 3, Table 2). DID was associated with increased functional connectivity between rCEN and regions in tDN (cluster #40, 51, 53, 56), and with regions outside our three core networks (cluster #39, 43, 58). DID was also uniquely associated with decreased functional connectivity between rCEN and regions in tDN (cluster #27), cSN (cluster #24, 25), and regions outside our three networks (cluster #20, 22, 23, 28). Greater partially-dissociated intrusions were associated with rCEN within-network hyperconnectivity concentrated in lateral orbitofrontal cortex, middle and superior frontal gyrus (cluster #45), increased connectivity between rCEN and regions in tDN (cluster #27, 40, 53) and decreased connectivity between rCEN and posterior cingulate cortex/precuneus, also in tDN (#57). Greater depersonalization/derealization was associated with decreased connectivity between middle temporal gyrus and rCEN (cluster #40, 53), and increased connectivity between temporal-parietal-occipital junction and rCEN (cluster #51).

Medial temporal default network (tDN)

Ten clusters within tDN exhibited within-network hyperconnectivity related to pathological dissociation (Fig. 2). Only depersonalization/derealization showed unique associations with tDN connectivity, reflecting hyperconnectivity in parahippocampal gyrus (cluster #1, 3, 4; Fig. 3, Table 2).

Cingulo-opercular salience network (cSN)

Eight clusters within cSN were linked to greater pathological dissociation in two ways (Fig. 2, Table 2): (1) within-network hyperconnectivity; (2) decreased connectivity between regions in rCEN with cSN. There were no significant unique contributions of dissociation subtypes.

DISCUSSION

To begin to build a large-scale functional network connectivity model of trauma-related pathological dissociation and its subtypes, we leveraged the Triple Network model of psychopathology. We tested the connectivity of three core neurocognitive networks as it related to DID and the dimensional subtypes of depersonalization/derealization and partially-dissociated intrusions. Consistent with our hypotheses, after controlling for age, childhood maltreatment and PTSD symptom severity, the rCEN, tDN, and cSN were all impacted by pathological dissociation.

First, we examined alterations in functional connectivity related to pathological dissociation broadly defined as an association with DID diagnosis, depersonalization/derealization, and/or partially-dissociated intrusions. While each brain region was identified using a specific full variance model for each subtype of dissociation, the different subtypes are highly collinear. Consequently, the findings could be driven by shared variance between the subtypes. Therefore, we discuss the results in the next paragraph as alterations due to "pathological dissociation," not a particular subtype.

Overall, the rCEN was the most impacted by pathological dissociation; however, we found that all core networks implicated in the Triple Network model of psychopathology were impacted. Specifically, pathological dissociation was associated with hyperconnectivity within rCEN, tDN, and cSN. Dissociation was also linked to decreased connectivity between rCEN and other brain regions, including areas within DN and cSN that may facilitate communication among networks. Furthermore, greater dissociation was related to decreased connectivity between cSN and rCEN regions. Taken together, these alterations may be an adaptive or compensatory response to childhood trauma and are a likely source of executive functioning differences, self-alteration experiences, and altered interoceptive/autonomic experiences reported by individuals with dissociative symptoms [9, 49, 50].

Next, we explored connectivity that was uniquely associated with each dissociation subtype. We found that depersonalization/derealization was uniquely associated with connectivity in two networks: the rCEN and tDN. First, depersonalization/derealization was related to decreased connectivity between rCEN and lateral middle temporal gyrus regions typically located in the DN and thought to facilitate retrieval of semantic/conceptual knowledge [23]. This finding may reflect decreased communication between these networks. In contrast, rCEN had increased connectivity with the temporal-parietal-occipital junction typically located in DN. This region is involved in mentalization, that is, reflecting on the mental states of others [23]. It is also implicated in out-of-body experiences [51]. Increased communication between this region and CEN may, in part, underlie feelings of detachment, strangeness, or unreality with one's body or environment.

Second, depersonalization/derealization was also associated with hyperconnectivity within tDN concentrated in parahippocampal gyrus. Parahippocampal gyrus is part of the medial temporal lobe memory system and has demonstrated connectivity with areas of the brain involved in vision [52]. Parahippocampal gyrus supports memory formation and retrieval, in particular, for episodic and autobiographical memory, and the context of an event [52]. Specifically, parahippocampal gyrus facilitates processing of spatial information essential for navigating one's environment [52]. Heightened communication within this region of DN

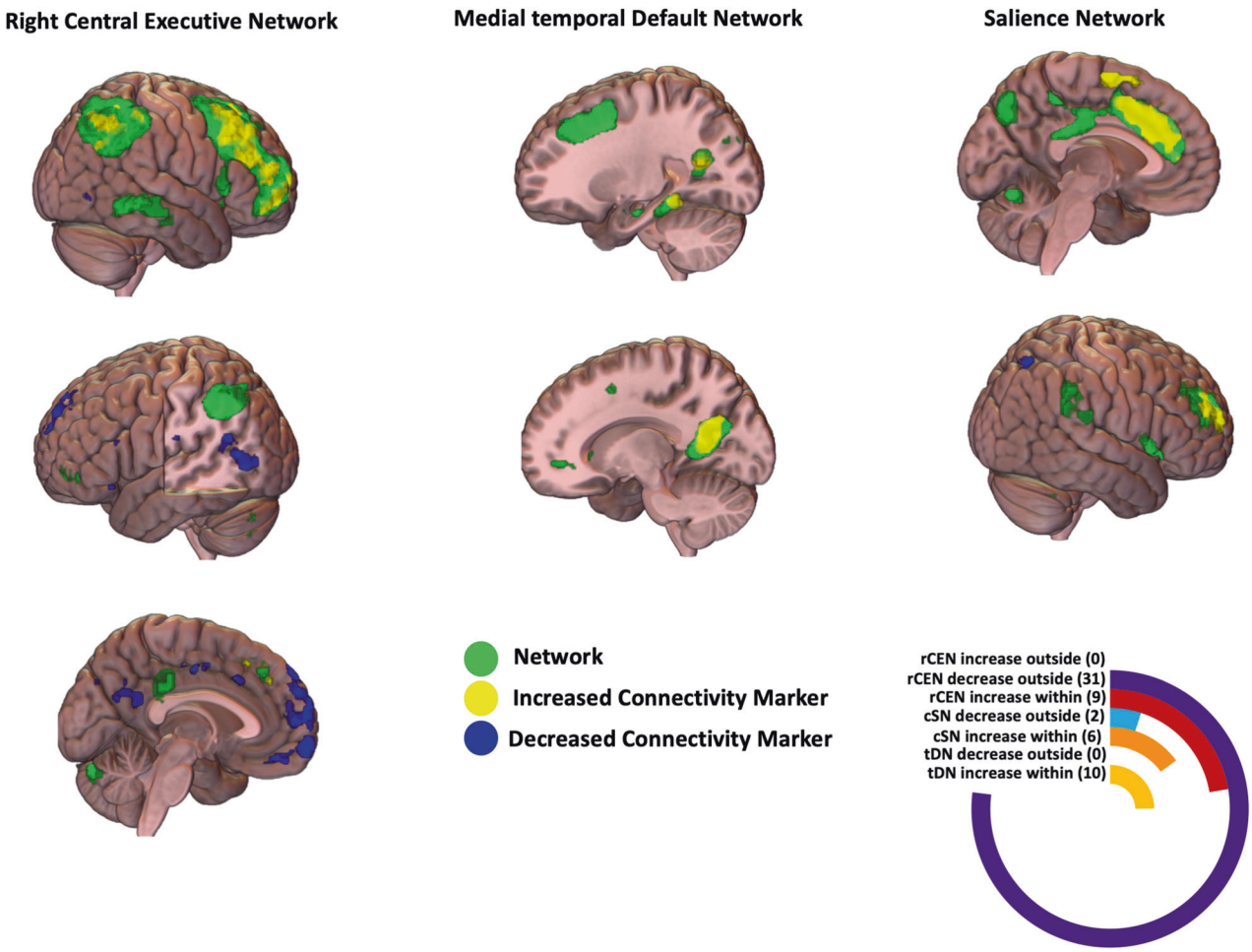

Fig. 2 Triple Network Model of Pathological Dissociation. The Triple Network Model of Pathological Dissociation depicts biomarkers (brain regions) with functional connectivity to our core networks (right central executive, medial temporal default network, and cingulo-opercular salience network) that is associated with the full variance of each pathological dissociation variable (dissociative identity disorder diagnosis, depersonalization/derealization, and partially-dissociated intrusions). Green regions indicate the network of interest (right central executive, medial temporal default network, or cingulo-opercular salience network). Yellow indicates areas with increased connectivity between that region and the network of interest that is associated with pathological dissociation. Blue indicates regions with decreased connectivity between that region and the network of interest that is associated with pathological dissociation. The radial bar graph depicts the number of markers linked with pathological dissociation in each network associated with increased or decreased connectivity either within or outside the network of interest. Images made with MRIcroGL (https://www.nitrc.org/plugins/mwiki/index.php/mricron:MainPage). rCEN right central executive network, cSN cingulo-opercular salience network, tDN medial temporal default network.

may facilitate altered spatial and perceptual experiences associated with depersonalization/derealization.

We found that partially-dissociated intrusions were linked to rCEN hyperconnectivity concentrated in lateral prefrontal cortex. This network is often active during cognitively challenging working memory, problem solving, and decision-making tasks [18]. This implies that greater partially-dissociated intrusions are related to heightened communication within CEN. This hyperconnectivity may also reduce the flexibility of the network to engage with other networks.

Second, partially-dissociated intrusions were associated with increased connectivity between DN regions (middle temporal gyrus) and rCEN. DN is often suppressed while CEN is engaged [18]. However, here we see some synchronization of these two networks. Intriguingly, this matches the subjective experience of partially-dissociated intrusions as "recurrent, jarring, involuntary intrusions into executive functioning and sense of self" [43].

In contrast, rCEN had decreased connectivity with tDN regions: the dorsal posterior cingulate cortex (dPCC) and precuneus, which may reflect decreased communication between these networks. These regions are involved in self-generated thought [23]. In particular, the dPCC may serve to regulate global brain dynamics—helping to balance internally vs. externally focused attention and the breadth of attentional focus (i.e., narrow vs. broad; [53]). Furthermore, recent theories speculate dPCC may facilitate fast shifts between different mental states [53].

The unique contributions of a DID diagnosis to altered connectivity were concentrated in the rCEN. Specifically, DID diagnosis was associated with a complex pattern of both increased and decreased connectivity between rCEN and regions distributed across tDN, cSN, and other networks. The dominant finding was one of rCEN hyperconnectivity with regions in tDN. DN is often suppressed while CEN is engaged [18], but in DID we instead saw some synchronization of these networks.

A pattern of decreased CEN connectivity with regions in cSN also emerged in DID. SN may facilitate shifts between CEN and DN [26]. Decreased communication between rCEN and cSN could impact the appropriate engagement or disengagement of CEN and DN [18].

Overall, these findings support a plausible mechanism underlying executive functioning difficulties and differences in DID. For example, individuals with DID report experiences of amnesia,

Table 2. Connectivity in default, salience and central executive network related to pathological dissociation.

Cluster index	Brain region	Network of brain region	Direction of full variance relationship	Full variance model	Cluster size	MNI coordinates (x, y, z)	Unique variance contributions		
							DID Diagnosis t (p) $N = 54$	Depersonalization/ Derealization t (p) $N = 91$	Partially-dissociated Intrusions t (p) $N = 91$
Medial Temporal Default Network									
1	L Parahippocampal gyrus	tDN	DID	DID-HC	36	−28, −44, −12	−1.88 (0.064)	2.13 (0.036)[a]	−0.45 (0.652)
2	R Retrosplenial	tDN	DID	DID-HC	195	6, −50, 8	−0.04 (0.970)	0.45 (0.656)	−0.20 (0.841)
3	R Parahippocampal gyrus	tDN	+	Dep/Der	37	28, −40. −14	−1.57 (0.121)	2.97 (0.004)[a]	−1.42 (0.163)
4	L Parahippocampal gyrus	tDN	+	Dep/Der	90	−26, −46, −12	−1.84 (0.070)	2.10 (0.039)[a]	−0.60 (0.549)
5	L Retrosplenial, vPCC, Precuneus	tDN	+	Dep/Der	395	−14, −62, 16	0.67 (0.505)	−0.89 (0.374)	1.37 (0.175)
6	R Retrosplenial, vPCC, Precuneus	tDN	+	Dep/Der	774	6,−50, 8	0.41 (0.680)	0.16 (0.875)	0.32 (0.753)
7	R middle Occipital gyrus, middle temporal gyrus, Angular Gyrus	tDN	+	PDI	54	48, −64, 245	−1.30 (0.197)	−0.33 (0.742)	0.41 (0.680)
8	L Parahippocampal gyrus, Fusiform gyrus	tDN	+	PDI	113	−28, −44, −12	−1.84 (0.070)	1.62 (0.109)	−0.33 (0.739)
9	R Parahippocampal gyrus, Fusiform gyrus	tDN	+	PDI	172	28, −40, −14	−1.31 (0.192)	1.94 (0.056)	−0.81 (0.421)
10	R Retrosplenial, vPCC, Precuneus	tDN	+	PDI	1802	6, −50, 8	0.61 (0.543)	−0.69 (0.495)	1.12 (0.264)
Salience Network									
11	L Frontal operculum, insula	cSN	+	Dep/Der	453	−32, 12, 4	0.46 (0.649)	0.68 (0.497)	0.95 (0.345)
12	R Frontal pole, vlPFC	cSN	+	Dep/Der	997	32, 60, 12	0.09 (0.931)	−0.01 (0.995)	1.34 (0.183)
13	L Frontal pole, vlPFC, dlPFC, supplementary motor area, dACC R dlPFC, supplementary motor area, dACC	cSN	+	Dep/Der	5454	−34, 44, 10	0.66 (0.511)	0.44 (0.658)	1.64 (0.105)
14	R Superior Parietal Lobule	rCEN	-	Dep/Der	44	32, −70, 58	1.93 (0.057)	0.11 (0.914)	−1.03 (0.307)
15	L Frontal operculum, insula	cSN	+	PDI	367	−36, 16, −2	0.51 (0.615)	0.33 (0.744)	1.29 (0.201)
16	R Frontal pole, vlPFC	cSN	+	PDI	1280	32, 58, 12	0.23 (0.816)	−0.18 (0.859)	1.47 (0.146)
17	L Frontal pole, vlPFC, dlPFC, supplementary motor area, dACC R supplementary motor area, dACC	cSN	+	PDI	5852	−20, 52, 14	0.77 (0.444)	0.03 (0.974)	1.95 (0.054)
18	R Superior Parietal Lobule	rCEN	-	PDI	54	30, −72, 58	1.91 (0.059)	0.18 (0.857)	−1.12 (0.266)
Right Central Executive Network									
19	L ACC	cSN	HC	HC–DID	14	−8, 20, 40	1.96 (0.054)	−0.33 (0.743)	0.07 (0.941)
20	L Inferior frontal gyrus	---	HC	HC-DID	18	−52, 20, 22	2.04 (0.045)[a]	−0.79 (0.432)	0.87 (0.389)
21	L Mid cingulate cortex	cSN	HC	HC– DID	19	0, −4, 46	1.74 (0.086)	0.38 (0.705)	0.12 (0.908)
22	L Frontal pole	---	HC	HC– DID	55	−4, 68, −14	2.68 (0.009)[a]	−0.45 (0.657)	0.72 (0.475)
23	R Inferior Occipital gyrus	---	HC	HC-DID	65	46, −74, −2	3.39 (0.001)[a]	1.02 (0.311)	0.16 (0.875)
24	L/R Mid cingulate	cSN	HC	HC– DID	75	2,−12, 42	2.97 (0.004)[a]	−0.49 (0.629)	1.14 (0.259)
25	L Precuneus, superior occipital gyrus	cSN	HC	HC– DID	77	−16, −64, 34	2.05 (0.043)[a]	1.30 (0.196)	−1.55 (0.125)
26	L Frontal Opercular	cSN	HC	HC– DID	91	−36, 32, −2	0.93 (0.357)	−0.91 (0.364)	−0.17 (0.865)
27	L Middle Temporal Gyrus	tDN	HC	HC– DID	457	−48, −66, 8	6.38 (0.000)[a]	−1.35 (0.182)	3.39 (0.001)[a]
28	L dmPFC	---	HC	HC– DID	485	−8, 54, 10	2.97 (0.004)[a]	−0.13 (0.894)	0.10 (0.924)
29	R Angular gyrus	rCEN	DID	DID– HC	16	32, −66, 48	−0.90 (0.372)	0.85 (0.399)	0.09 (0.933)
30	R vlPFC, Frontal pole	rCEN	DID	DID– HC	16	28, 52, 0	−1.61 (0.112)	−0.76 (0.449)	0.95 (0.347)
31	R dlPFC, Middle frontal gyrus	rCEN	DID	DID– HC	686	30, 34,42	−1.35 (0.182)	0.66 (0.510)	0.47 (0.642)
32	R dmPFC	rCEN	+	Dep/Der	388	6, 42,34	0.62 (0.537)	−0.55 (0.585)	1.97 (0.053)
33	R lOFC, Frontal pole	rCEN	+	Dep/Der	459	30, 52, 0	−0.50 (0.616)	−1.01 (0.317)	1.83 (0.071)
34	R Angular gyrus, Inferior Parietal Lobule	rCEN	+	Dep/Der	700	32, −66, 48	0.13 (0.894)	0.48 (0.630)	1.27 (0.208)

Table 2. continued

Cluster index	Brain region	Network of brain region	Direction of full variance relationship	Full variance model	Cluster size	MNI coordinates (x, y, z)	Unique variance contributions		
							DID Diagnosis t (p) $N = 54$	Depersonalization/ Derealization t (p) $N = 91$	Partially-dissociated Intrusions t (p) $N = 91$
35	R dlPFC, Inferior, Middle, Superior frontal gyrus	rCEN	+	Dep/Der	1837	32, 32, 40	−0.21 (0.835)	0.51 (0.611)	1.30 (0.197)
36	L dPCC	---	-	Dep/Der	13	−6, −50, 24	−1.20 (0.232)	−0.96 (0.341)	−1.32 (0.192)
37	L Cuneus	---	-	Dep/Der	22	−6,−80, 34	0.90 (0.372)	−1.95 (0.055)	0.44 (0.659)
38	L dlPFC, Superior Frontal gyrus	---	-	Dep/Der	25	−14, 46, 42	1.49 (0.140)	−1.70 (0.093)	0.70 (0.484)
39	L Frontal pole/amPFC	---	-	Dep/Der	35	−4, 68, −14	2.58 (0.012)[a]	−0.69 (0.491)	0.87 (0.385)
40	L Middle Temporal Gyrus	tDN	-	Dep/Der	43	−48, −64, 10	3.99 (0.000)[a]	−2.76 (0.007)[a]	3.23 (0.002)[a]
41	L Precuneus, Superior Occipital Gyrus	cSN, tDN	-	Dep/Der	49	−16, −70, 28	1.40 (0.165)	0.74 (0.464)	−1.38 (0.173)
42	L Frontal Opercular	cSN	-	Dep/Der	60	−40, 28, −2	0.72 (0.474)	−1.35 (0.181)	0.002 (0.999)
43	L dmPFC	---	-	Dep/Der	348	−6, 58, 8	2.40 (0.019)[a]	−0.45 (0.652)	−0.10 (0.923)
44	R Angular Gyrus, Inferior Parietal Lobule	rCEN	+	PDI	1125	32, −66, 48	0.40 (0.692)	0.06 (0.950)	1.60 (0.113)
45	R lOFC, Middle frontal gyrus, Superior Frontal gyrus	rCEN	+	PDI	4074	50,38, 24	0.26 (0.795)	−0.42 (0.673)	2.21 (0.030)[a]
46	L lOFC	---	-	PDI	9	−42, 36,−12	0.07 (0.943)	−0.89 (0.374)	0.27 (0.791)
47	L Postcentral gyrus	---	-	PDI	11	−50, −20, 24	1.27 (0.207)	0.00 (1.000)	−0.90 (0.369)
48	L lOFC	cSN	-	PDI	13	−50, 24,−10	−0.09 (0.926)	−0.24 (0.808)	−0.49 (0.624)
49	L Cuneus	---	-	PDI	26	−6, −80, 34	0.94 (0.352)	−1.86 (0.066)	0.45 (0.658)
50	L Superior Temporal Gyrus	---	-	PDI	32	−60, −52, 22	1.48 (0.142)	0.26 (0.793)	−1.24 (0.220)
51	L Temporal-parietal-occipital junction	tDN	-	PDI	36	−36, −66, 24	3.39 (0.001)[a]	2.23 (0.028)[a]	−0.84 (0.406)
52	L Inferior frontal gyrus	---	-	PDI	36	−50, 20, 22	1.73 (0.088)	−0.62 (0.539)	0.44 (0.659)
53	L Middle Temporal	tDN	-	PDI	46	−48, −64, 10	3.82 (0.000)[a]	−2.38 (0.021)[a]	2.87 (0.005)[a]
54	L dACC	cSN	-	PDI	61	−8, 20, 38	1.06 (0.293)	0.11 (0.915)	−0.86 (0.392)
55	L Frontal operculum	cSN	-	PDI	157	−36, 32, −2	0.69 (0.489)	−0.70 (0.489)	−0.39 (0.695)
56	L mOFC, vmPFC	tDN	-	PDI	256	−2, 66, 12	2.13 (0.036)[a]	0.46 (0.645)	−0.32 (0.753)
57	L dPCC, Precuneus	tDN	-	PDI	306	−16, −70, 26	0.54 (0.591)	0.49 (0.626)	−2.20 (0.030)[a]
58	L dmPFC	---	-	PDI	665	−6, 54, 8	2.01 (0.047)[a]	−0.26 (0.798)	−0.45 (0.653)

Brain region indicates markers with altered connectivity with either Default, Salience or Central Executive Network related to pathological dissociation as identified from full variance models ($p < 0.05$, corrected for number of voxels and networks). Network of Brain Region indicates the network membership of the brain region marker identified in the full variance model. A "---" indicates the region was not located in tDN, cSN, or rCEN. Direction of Full Variance Relationship indicates the direction of the relationship between the brain region marker connectivity and "pathological dissociation:" "+" indicates increased connectivity between marker and network of interest; "-" indicates decreased connectivity between marker and network of interest; DID indicates increased connectivity between marker and network of interest related to pathological dissociation; HC indicates decreased connectivity between marker and network of interested related to pathological dissociation. Full Variance Model indicates which full variance model the marker was found in. Unique variance contributions indicate whether DID diagnosis, depersonalization/derealization and/or partially-dissociated intrusions had a unique association with the connectivity between the brain region marker and the network of interest.

tDN medial temporal default network, *cSN* cingulo-opercular salience network, *rCEN* right central executive network, *HC* healthy control, *Dep/Der* depersonalization/derealization, *PDI* partially-dissociated intrusions, *DID* dissociative identity disorder, *R* right, *L* left, *vPCC* ventral posterior cingulate cortex, *vlPFC* ventrolaterial prefrontal cortex, *dlPFC* dorsolateral prefrontal cortex, *dACC* dorsal anterior cingulate cortex, *dmPFC* dorsomedial prefrontal cortex, *lOFC* lateral orbitofrontal cortex, *amPFC* anterior medial prefrontal cortex, *mOFC* medial orbitofrontal cortex, *vmPFC* ventromedial prefrontal cortex.

[a]Indicates a significant unique variance contribution.

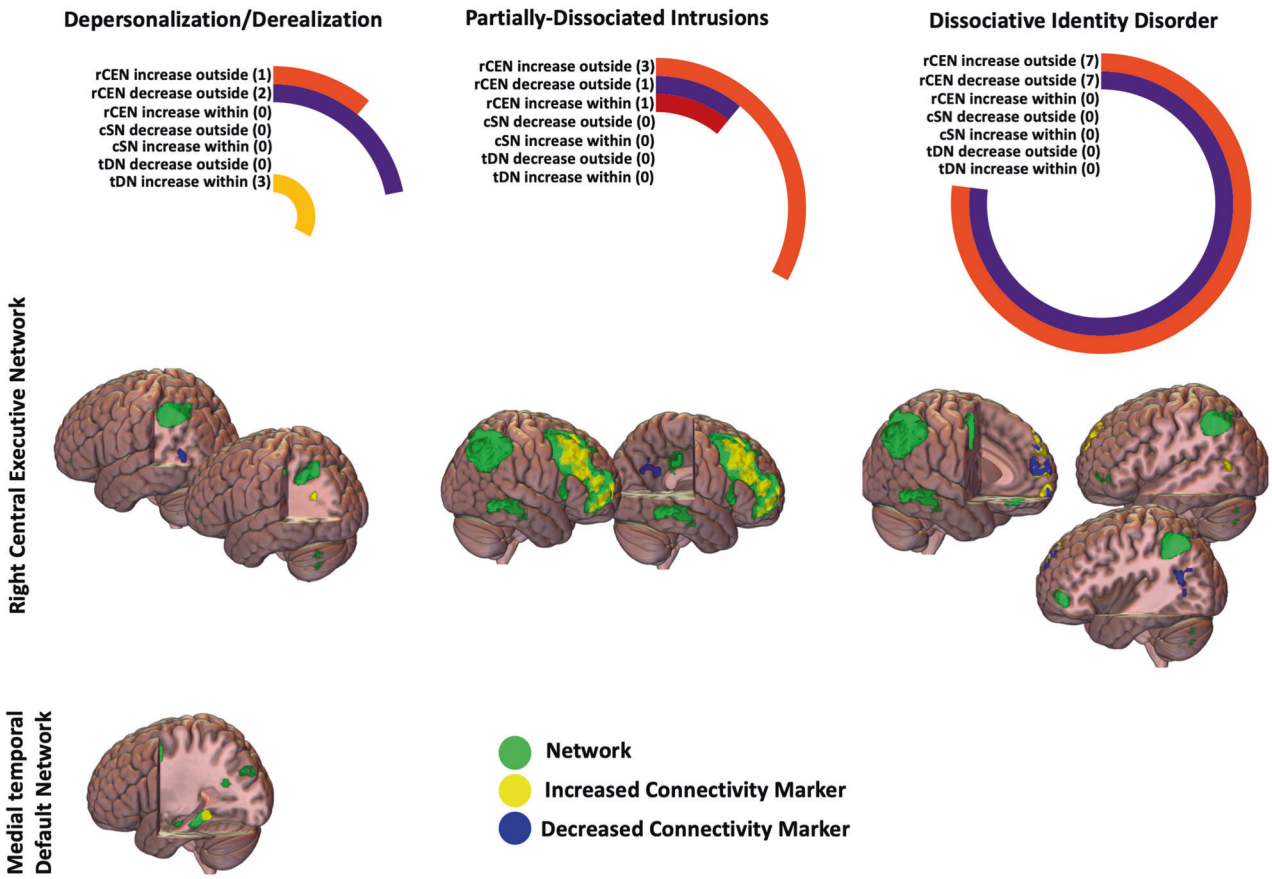

Fig. 3 Unique Associations between Connectivity Biomarkers and Depersonalization/Derealization, Partially-Dissociated Intrusions and Dissociative Identity Disorder Diagnosis. Here we depict biomarkers (brain regions) with functional connectivity to our core networks (right central executive, medial temporal default network, and cingulo-opercular salience network) that is uniquely associated with each of the pathological dissociation variables (dissociative identity disorder diagnosis, depersonalization/derealization, and partially-dissociated intrusions). Green regions indicate the network of interest (right central executive, medial temporal default network). Only two of the three networks are shown because no markers with functional connectivity to salience network were uniquely associated with one of the dissociation variables. Yellow indicates regions with increased connectivity between that region and the network of interest uniquely associated with the dissociation variable. Blue indicates regions with decreased connectivity between that region and the network of interest with the dissociation variable. The radial bar graphs depict the number of markers linked with each type of dissociation in each network. The markers reflect either increased or decreased connectivity of regions within or outside the network of interest. Images made with MRIcroGL (https://www.nitrc.org/plugins/mwiki/index.php/mricron:MainPage). rCEN right central executive network, cSN salience network, tDN medial temporal default network.

partially-dissociated intrusions, or working memory difficulties [9, 54]. Interestingly, there have also been some reports of preserved or even enhanced executive functioning for individuals with dissociative disorders or high levels of dissociation in which they out-perform control participants on executive functioning, working memory and spatial memory tasks that are not emotionally-provocative [49, 55, 56]. It may be that some of the altered rCEN connectivity we identified could facilitate this enhanced executive functioning in certain contexts. Future work involving tasks that elicit CEN activity are needed to sort out when and how these alterations may facilitate enhanced vs. diminished executive functioning.

Several models of pathological dissociation have been previously proposed, and taken together our work builds logically on this foundational research. For example, the corticolimbic model of dissociation focuses on trauma-related depersonalization and derealization in the context of PTSD [12], and other work has extended this model to the experience of DID [13]. This model proposes trauma-related pathological depersonalization and derealization involve hyperactivation of brain regions involved in emotion and arousal regulation such that people experience emotion/arousal over-regulation. A recent systematic review provided transdiagnostic support for this model across trauma and non-trauma-related disorders with experiences of dissociation, as well as elucidated a distributed pattern of brain regions, in particular in prefrontal cortex, implicated in pathological dissociation [14]. Our work focused on trauma-related pathological dissociation and implicates many of the brain regions identified in prior models, however, we now place them in the context of communication within three core neurocognitive networks. Moreover, we have shown how altered connectivity and perhaps communication in these networks provides possible mechanisms specific to a range of dissociation experiences (e.g., executive functioning differences, self-alteration experiences, and altered interoceptive/autonomic experiences).

While we provide robust evidence for alterations in resting-state networks associated with pathological dissociation, future task-based analyses that directly measure self-generated thought, memory, and salience detection are needed to aid the interpretation of these findings. We also limited our analyses to rCEN, tDN, and cSN. Our findings suggest alterations between these three networks and other networks play a role in pathological dissociation, but we did not test this network-to-network connectivity directly. Furthermore, we focused our analysis on

depersonalization/derealization, partially-dissociated intrusions and DID, and our results may not be generalizable to other forms of pathological dissociation, which would be fruitful directions for future work (e.g., dissociative amnesia). However, our PTSD/DID samples were recruited from hospital level-of-care and therefore are highly generalizable to individuals with more severe symptoms of PTSD/DID. Our PTSD/DID sample was also taking various forms of psychiatric medication, which we were not powered to address. Finally, our sample was limited to individuals who were assigned female sex at birth, and it is unknown whether results generalize to other sexes.

While gaps remain, this study contributes new data supporting the neurobiological basis of dissociative symptoms as a disruption of brain networks. Moreover, we have begun to develop a network-based brain connectivity "fingerprint" [31] specific to different types of dissociation. In the future, these neuromarkers could be used to stratify samples for randomized control trials, to monitor recovery, or to target directly with neuromodulatory techniques as a treatment intervention itself.

Given the complex and highly subjective nature of these conditions, neurobiological evidence is critical to ensuring that individuals who experience dissociation receive timely assessment and appropriate treatment, as with any serious neuropsychiatric condition. Ultimately, we believe this work will increase awareness about dissociation, destigmatize these experiences, and contribute to reducing gender-related health disparities.

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AUTHOR CONTRIBUTIONS

LAML: Conceptualization, Methodology, Investigation, Resources, Data Curation, Writing—Original Draft, Visualization, Supervision, Project administration, Funding acquisition; PK: Conceptualization, Methodology, Software, Formal analysis, Data Curation, Writing—Original Draft; CAP: Investigation, Data Curation, Writing—Review & Editing, Project administration; AML: Investigation, Writing—Review & Editing; LO: Investigation, Writing—Review & Editing; JDW: Investigation, Writing—Review & Editing, Project administration; JTB: Conceptualization, Writing—Review & Editing; SAG: Conceptualization, Supervision, Writing—Review & Editing; NLS: Investigation, Writing—Review & Editing; KJR: Conceptualization, Writing—Review & Editing; MAR: Writing—Review & Editing; SW: Conceptualization, Investigation, Writing—Review & Editing; LDN: Conceptualization, Methodology, Software, Formal analysis, Writing—Review & Editing, Supervision; MLK: Conceptualization, Investigation, Resources, Writing—Review & Editing, Supervision, Project administration, Funding acquisition.

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COMPETING INTERESTS

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