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Intrusive Traumatic Re-Experiencing Domain: Functional Connectivity Feature Classification by the ENIGMA PTSD Consortium

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ABSTRACT

BACKGROUND: Intrusive traumatic re-experiencing domain (ITRED) was recently introduced as a novel perspective on posttraumatic psychopathology, proposing to focus research of posttraumatic stress disorder (PTSD) on the unique symptoms of intrusive and involuntary re-experiencing of the trauma, namely, intrusive memories, nightmares, and flashbacks. The aim of the present study was to explore ITRED from a neural network connectivity perspective.

METHODS: Data were collected from 9 sites taking part in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) PTSD Consortium (n = 584) and included itemized PTSD symptom scores and resting-state functional connectivity (rsFC) data. We assessed the utility of rsFC in classifying PTSD, ITRED-only (no PTSD diagnosis), and trauma-exposed (TE)–only (no PTSD or ITRED) groups using a machine learning approach, examining well-known networks implicated in PTSD. A random forest classification model was built on a training set using cross-validation, and the averaged cross-validation model performance for classification was evaluated using the area under the curve. The model was tested using a fully independent portion of the data (test dataset), and the test area under the curve was evaluated.

RESULTS: rsFC signatures differentiated TE-only participants from PTSD and ITRED-only participants at about 60% accuracy. Conversely, rsFC signatures did not differentiate PTSD from ITRED-only individuals (45% accuracy). Common features differentiating TE-only participants from PTSD and ITRED-only participants mainly involved default mode network–related pathways. Some unique features, such as connectivity within the frontoparietal network, differentiated TE-only participants from one group (PTSD or ITRED-only) but to a lesser extent from the other group.

CONCLUSIONS: Neural network connectivity supports ITRED as a novel neurobiologically based approach to classifying posttrauma psychopathology.

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Posttraumatic stress disorder (PTSD) involves maladaptive responses to traumatic events (1) as well as significant psychological dysfunction and health impairments (2,3). Despite extensive efforts, research on symptom-based PTSD diagnosis remains controversial (4–6). Specifically, when PTSD is defined only using current classifications, it may be unrealistic to expect a meaningful unraveling of biobehavioral mechanisms or development of an effective science-guided treatment (4,7). Arguably, treatment efficacy can only be achieved if the disorder in question is first accurately characterized and identified (8).

Despite extensive research, and nearly 4 decades since it was first introduced in the DSM-III, controversy concerning PTSD's diagnostic criteria still remains, with an ongoing debate concerning the role different symptoms play in defining PTSD and differentiating it from other psychopathologies (4–6,9,10). Indeed, the number and nature of individual symptoms and symptom clusters required for PTSD diagnosis have changed markedly over the years, with differences noted between different versions of specific diagnostic systems and between different diagnostic systems (i.e., DSM vs. ICD). Considering the DSM, the total number of potential symptoms

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has increased dramatically, from 12 across 3 symptom clusters in the DSM-III to 20 across 4 symptom clusters in the DSM-5 (4). While this increase was intended to better capture the wide array of maladaptive behaviors and symptoms that may ensue from a traumatic event (6), it has simultaneously increased the heterogeneity of the PTSD diagnosis (11), also affecting prevalence rates (4,12). Conversely, aiming to increase the specificity of the PTSD diagnosis, the ICD-11 (13) has reduced diagnostic symptoms from the 13 in the ICD-10 to only 6 symptoms assumed to reflect core PTSD symptoms (14,15), resulting in lower PTSD diagnosis rates compared with the DSM-5 (5,12,16). Yet, the ICD-11 definition of PTSD still includes mandatory diagnostic symptoms that are not specific to traumatic exposure (e.g., avoidance, hyperarousal) and that are also strongly associated with other disorders, such as depression and anxiety (7).

To address this state of affairs, Bar-Haim *et al.* (7) recently suggested to focus on intrusive and involuntary recollection and re-experiencing of the trauma, labeled intrusive traumatic re-experiencing domain (ITRED). ITRED criteria are met if a trauma-exposed individual fulfills one of the first 3 re-experiencing symptoms listed in DSM-5: symptoms B1 (recurrent, involuntary, and intrusive distressing memories of the traumatic event), B2 (recurrent distressing dreams in which the content and/or affect of the dreams are related to the traumatic event), or B3 (dissociative reactions [e.g., flashbacks] in which the individual feels or acts as if the traumatic event is recurring). ITRED severity is quantified by aggregating the individual scores of these 3 symptoms. ITRED could advance knowledge on mechanisms of PTSD. Importantly, ITRED can also assist in identifying trauma-exposed (TE) individuals who do not meet criteria for PTSD (e.g., failing to meet criteria C, D, or E of PTSD) but nonetheless experience markedly and chronically its core re-experiencing symptoms.

Following the introduction of ITRED, Bar-Haim *et al.* (7) examined key statistics of ITRED and PTSD prevalence rates across 5 different samples of TE individuals (i.e., treatment-seeking Israel Defense Force war veterans [n = 1826], active duty combat-exposed Israel Defense Force soldiers [n = 530], U.S. Army soldiers [n = 4227; both 3 months and 9 months following deployment], TE Australian [n = 987] and U.S. [n = 384] civilian patients), aiming to focus ITRED within the extant diagnostic space of symptomatic reactions to trauma exposure that currently define PTSD. Results showed that on average, 1) 94% (range, 86%–100%) of those who met diagnostic DSM criteria for PTSD also met ITRED criteria, 2) 10.5% (range, 7.3%–14.2%) of those who met ITRED criteria did not meet DSM criteria for PTSD, and 3) only 3% (range, 0%–13.9%) of TE individuals who met DSM criteria for PTSD did not meet ITRED criteria. From a clinical perspective, these results suggest that ITRED identifies the majority of PTSD patients using much more concise and succinct symptom criteria, while also identifying approximately 10% new TE individuals who fail to meet DSM criteria for PTSD but still experience its core re-experiencing symptoms (7).

The aim of the present study was to explore brain-related correlates of ITRED using neuroimaging data aggregated from 9 worldwide sites in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) PTSD Consortium. Item-level Clinician-Administered PTSD Scale for DSM-IV or DSM-5 (CAPS-4 or CAPS-5) scores of 584 TE individuals were examined: 239 individuals meeting PTSD diagnosis, irrelevant of their ITRED status (i.e., PTSD group); 106 individuals meeting ITRED diagnosis, with no PTSD criteria (i.e., ITRED-only group); and 239 TE individuals who did not meet the criteria for either (TE-only group). We assessed the utility of resting-state functional connectivity (rsFC) in classifying PTSD, ITRED-only, and TE-only groups using a machine learning (ML) approach. We included neural networks implicated in PTSD (17–20), including the default mode network (DMN), ventral attention network (VAN), frontoparietal network (FPN), salience network (SN), subcortical network (SC), dorsal attention network (DAN), and cingulo-opercular network (CO). We hypothesized that ML would distinguish the PTSD and ITRED-only groups from the TE-only group but would not distinguish the PTSD group from the ITRED-only group. We postulate that because re-experiencing symptoms is a core feature of PTSD, there should be no significant neurobiological differences between the DSM-ITRED diagnosis compared with a validated DSM-PTSD diagnosis. Such a result, if obtained, would support the ITRED domain as a valid, concise, and more inclusive diagnostic tool for posttrauma psychopathology from a neuroimaging perspective.

METHODS AND MATERIALS

Dataset: Imaging Data

We used a subset of ENIGMA resting-state functional magnetic resonance imaging data (n = 584) aggregated from 9 sites around the world that assessed PTSD symptoms of TE individuals using CAPS-4 or CAPS-5, while also providing item-level CAPS data. CAPS-4 and CAPS-5 scores were homogenized by calculating the percentage of the severity score relative to the maximum score possible for each instrument (21). The final sample included 239 PTSD participants (of whom 100% also met ITRED criteria), 106 ITRED-only participants, and 239 TE-only participants. Each individual was assigned to 1 of 3 groups: those meeting a PTSD diagnosis, irrespective of their ITRED status, were assigned to the PTSD group; those meeting the ITRED criteria, without meeting PTSD criteria, were assigned to the ITRED group; TE individuals not meeting either diagnosis criteria were considered TE-only participants. Descriptive information per group (PTSD, ITRED only, TE only) is summarized in Table 1 and presented per site in Tables 2 and 3.

Image Acquisition and Processing

All imaging data were acquired at contributing sites and processed with standardized protocols of the ENIGMA-PGC (Psychiatric Genomics Consortium) Consortium previously used in large-scale studies of other disorders (22).

Preprocessing was carried out with ENIGMA HALFpipe workflow (https://github.com/HALFpipe/HALFpipe), which is based on fMRIPrep (https://fmriprep.org/en/stable). Briefly, processing steps for T1 images included skull stripping, tissue segmentation, and spatial normalization to Montreal Neurological Institute space. Preprocessing steps for

Table 1. Descriptive Information per Group

	PTSD	ITRED	TE
Participants, *n* (%)	239 (40.9%)	106 (18.2%)	239 (40.9%)
Female, *n* (%)	94 (39.3%)	35 (33.0%)	67 (28.0%)
Age, Years, Mean ± SD	34.3 ± 9.1	32.3 ± 9.9	34.1 ± 10.2
Age Range, Years	18–59	18–85	18–60
Race/Ethnicity, *n*[a]			
Black	13	4	1
Caucasian	34	2	0
European	31	3	35
Hispanic	9	4	8
Mixed	10	2	1
Not Hispanic	19	13	47
Trauma Type, *n*			
Military combat	115	68	128
Sexual assault	8	5	7
Motor vehicle accident	2	5	18
Police work	32	3	36
Mixed[b]	82	25	50
Comorbidity, *n*[a]			
Yes	99	39	37
No	37	22	113
CAPS Scores, Mean ± SD[c]	49.6 ± 13.0	26.7 ± 11.9	7.7 ± 7.7

CAPS, Clinician-Administered PTSD Scale; ITRED, intrusive traumatic re-experiencing domain; PTSD, posttraumatic stress disorder; TE, trauma exposed.

[a]Data were not provided by all sites.

[b]Civilian-related mixed types of traumas.

[c]CAPS-4 and CAPS-5 score homogenization was accomplished by calculating the percentage of the severity score relative to the maximum score possible for each instrument (21).

functional images included motion correction using FSL MCFLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MCFLIRT), slice time correction using AFNI (Analysis of Functional Neuro-Images) 3dTshift (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dTshift.html), susceptibility distortion correction and coregistration to the reference T1-weighted image using FSL FLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT), and spatial normalization and warping to the template space using the MNI_2009 template. Each voxel was smoothed using signal from neighboring voxels with AFNI 3dBlurInMask (https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dBlurInMask.html) followed by weighting by an isotropic Gaussian kernel.

To ensure good quality of resting-state data, visual inspection was carried out on image registration, segmentation, and brain extraction. To control confounding effects of motion artifacts, several strategies were implemented: removing the top 5 aCompCor components (23), computing the framewise displacement for each run, and excluding subjects when more than 30% of frames had high levels of gross motion (framewise displacement >0.5 mm). Next, subjects with temporal signal-to-noise ratio below 1.5 times the IQR were excluded, and finally, subjects for whom more than 85% of independent component analysis components classified as noise were also excluded. The region of interest (ROI)-to-ROI functional connectivity was calculated by extracting the average time series of 264 ROIs defined by the Power atlas (24). A connectivity matrix between atlas regions was calculated using Pearson product-moment correlation with PANDAS (25). The final functional connectivity feature set contained 148 ROIs (n = 10,878 ROI-to-ROI connectivity measures), including within- and between-network connectivity and both the left and right hemispheres at both the training and validation stages. These regions are part of known networks including the DMN, VAN, FPN, SN, SC, DAN, and CO. To address between-site and between-subject variability, data were harmonized (i.e., regressing out site, age, and sex) using the ComBat method prior to analysis (26,27).

ML Analysis

We built classification models for distinguishing 3 groups: 1) PTSD; 2) ITRED-only; and 3) TE-only (no PTSD or ITRED). A random forest (RF) classifier was used for classification. An RF classifier has been widely used to classify individuals with psychiatric disorders from control individuals using neuroimaging data (28). RF uses a nonparametric method that does not depend on the distribution of the dataset. It also provides better generalization power and is able to handle multicollinearity, a problem that is common in the neuroimaging field (29).

ML algorithms and cross-validation (CV) pipelines were implemented in Python's *scikit-learn* library (30). First, we randomly split the data into two subsets: 70% of the data was used for training and validation, and the remaining 30% was used as a hold-out test dataset. Brain features with 30% of missing data were dropped from further analysis. RobustScaler from the *scikit-learn* library was used to scale the data, and missing values were imputed with the mean of the training dataset. The same scaler was applied to the test set. Based on previous research, we used 10-fold CV within the training sample, which generally provides better and more stable performance across different datasets, compared with leave-one-out CV (31). To achieve an equal number of samples for each group for each site, random undersampling was applied to the imbalanced groups, with the undersampling transform applied to the training dataset on each split of a repeated 10-fold CV. For each model, classification performance was measured using standard metrics including accuracy, sensitivity, specificity, and area under the receiver-operating characteristic curve (Table 4). For this study, 3 separate classifiers were trained and validated.

For sites that had imbalanced samples, a downsampling approach was used to have a distributed sample across the two groups. To maximize generalizability and avoid overfitting, we applied the support vector machine for each site using the default parameters (C=1), without grid search for optimal parameters, or feature reduction and selection. This method is stratified insofar as the proportion of cases and controls (in respective folds) is similar in both the training and validation sets. The support vector machine model was trained and evaluated using a 10-fold CV, and predictive performance was evaluated on the data from the held-out site.

Calculating Feature Importance. To find features that are the most predictive of PTSD, we used the Gini importance method calculated from an RF model. The Gini importance method was implemented using the *scikit-learn* library.

Table 2. Descriptive Information per Site

	Group	Amsterdam, the Netherlands	Cape Town, South Africa	Groningen, the Netherlands	Minneapolis, Minnesota	Toledo, Ohio	Tours, France	Utrecht, the Netherlands	Columbia, New York	Milwaukee, Wisconsin
Participants, *n*	–	71	31	37	231	25	20	80	27	62
PTSD Diagnosis, *n*	PTSD	32	23	35	75	2	8	40	9	15
	ITRED	3	6	2	56	5	5	12	2	15
	TE	36	2	0	100	18	7	28	16	32
PTSD Instrument	–	CAPS-4	CAPS-4	CAPS-4	CAPS-4	CAPS-4	CAPS-4	CAPS-4	CAPS-5	CAPS-5
CAPS Total Score, Homogenized, Mean (SD)[a]	PTSD	50.94 (10.23)	55.5 (15.7)	48.95 (9.81)	48.51 (14.41)	52.21 (5.2)	40.26 (9.48)	54.49 (9.04)	43.19 (15.69)	39.33 (13.85)
	ITRED	30.39 (20.09)	24.26 (12.31)	42.65 (1.04)	23.41 (9.13)	28.09 (9.44)	27.94 (9.59)	44.06 (6.93)	22.5 (1.77)	22.33 (12.42)
	TE	3.37 (3.43)	12.13 (2.6)	NA	11.48 (7.48)	9.83 (13.39)	14.18 (6.32)	4.13 (3.55)	5.23 (7.36)	6.52 (6.51)
Sex, *n*	Female	32	31	37	14	17	20	0	14	31
	Male	39	0	0	217	8	0	80	13	31
Age, Years, Mean (SD)	–	40.3 (9.63)	27.8 (7.23)	38.1 (9.6)	32.5 (7.81)	30.0 (10.06)	26.8 (9.34)	36.3 (9.58)	36.0 (12.38)	31.9 (10.61)
Population Sample	–	Civilian police	Civilian	Civilian	Military	Civilian	Civilian	Military	Civilian	Civilian
Sample Main Trauma	–	Police related	Mixed	Mixed	Combat	Motor vehicle accident	Sexual assault	Combat	Mixed	Mixed

CAPS, Clinician-Administered PTSD Scale; ITRED, intrusive traumatic re-experiencing domain; PTSD, posttraumatic stress disorder; TE, trauma exposed.

[a]CAPS-4 and CAPS-5 score homogenization was accomplished by calculating the percentage of the severity score relative to the maximum score possible for each instrument (21).

RESULTS

Demographics and Clinical Characteristics

A one-way analysis of variance revealed a significant group difference in CAPS scores ($F_{2,536} = 767.13$, $p < .001$). Follow-up analyses showed that compared with TE-only participants, both PTSD and ITRED-only participants had significantly higher CAPS scores ($t_{396} = -41.63$ and $t_{150} = -14.77$, respectively; all $p < .001$). Comparing PTSD and ITRED-only participants showed higher CAPS scores among the PTSD group ($t_{214} = -15.91$, $p < .001$).

A χ^2 test revealed a significant group difference in sex ($\chi^2_{536} = 6.86$, $p < .05$), ethnicity ($\chi^2_{536} = 71.56$, $p < .001$), and comorbidity ($\chi^2_{536} = 71.49$, $p < .001$). A one-way analysis of variance revealed no significant group difference in age ($F_{2,536} = 1.9$, $p > .05$).

CV Sample

We used 70% of the data, randomly selected, for training and CV of the classification model. We used an RF classifier among 3 main contrasts (PTSD vs. ITRED-only; PTSD vs. TE-only; ITRED-only vs. TE-only) to assess whether the classifier could distinguish between the groups (see Table 4). We found that PTSD versus TE-only and ITRED-only versus TE-only classification showed similar area under the curve (AUC) results of medium effect sizes (CV AUC = 63%, Cohen's $d = 0.467$; 95% CI, 0.68–0.85; and CV AUC = 61%; Cohen's $d = 0.396$; 95% CI, 0.53–0.74, respectively). Conversely, classifying PTSD from ITRED only showed lower AUC results, lower than at chance level (CV AUC = 42%; Cohen's $d = 0$; 95% CI, 0.53–0.72).

Test Sample

We used the remaining 30% of the data as the independent test dataset. Again, we used an RF classifier among 3 main contrasts (PTSD vs. ITRED-only; PTSD vs. TE-only; ITRED-only vs. TE-only) to test the classification performance to distinguish between the groups in an independent dataset (see Table 4). We found that PTSD versus TE-only and ITRED-only versus TE-only classifications showed similar AUC results of medium effect sizes (test AUC = 60%, Cohen's $d = 0.354$; and test AUC = 61%, Cohen's $d = 0.396$, respectively) (Figure 1A, B). Conversely, classifying PTSD from ITRED-only showed AUC results at chance level (test AUC = 45%, Cohen's $d = 0$) (Figure 1C).

Feature Importance

We used the Gini importance method to identify features of importance when distinguishing TE-only from PTSD and from ITRED-only classifications. Results showed several common features differentiating the TE-only group from both the PTSD (Figure 2A) and the ITRED-only groups (Figure 2B), which included the CO-FPN, DMN-DMN, DMN-FPN, DMN-VAN, DMN-SC, DMN-SN, FPN-FPN, FPN-SN, and SC-VAN. Results also showed some distinct features differentiating the PTSD (Figure 2A) and ITRED-only (Figure 2B) groups from the TE-only group. Features differentiating PTSD participants from TE-only participants included CO-CO, CO-SN, DMN-DAN, and SN-VAN. Features differentiating ITRED-only from TE-only

Table 3. Scanner Information per Site

	Amsterdam, the Netherlands	Cape Town, South Africa	Groningen, the Netherlands	Minneapolis, Minnesota	Toledo, Ohio	Tours, France	Utrecht, the Netherlands	Columbia, New York	Milwaukee, Wisconsin
Scanner Type	Philips	Siemens	Siemens	Siemens	GE	Siemens	Philips	GE	GE
Scanner Model	Achieva 3T	Allegra or Skyra	MAGNETOM Trio TIM 3T	Trio 3T	Signa HDxt 3T	MAGNETOM Verio 3T	Achieva 3T	Premier 3T	MR750 3T
Coil Channels	32	4 or 32	12	12	8	12	8	32	32
Voxel Size, mm	3 × 3 × 3	3.8 × 3.8 × 4	3 × 3 × 3	3.4 × 3.4 × 4	3.75 × 3.75 × 3.5	3.3 × 3.3 × 3.3	4 × 4 × 3.6	3 × 3 × 4	3.5 × 3.5 × 3.5
FOV, mm	240 × 240	240 × 240	192 × 192	220 × 220	240 × 240	60 × 64	208 × 120 × 256	192 × 192	224 × 224
Order	Axial	Sagittal	Transverse	Axial	Axial interleaved	Transverse	Transverse	Interleaved	Sagittal
TR, Seconds	2	2	2.25	2	2	3	1.6	1.3	2
TE, ms	28	30	25	30	30	30	23	28	25
Flip Angle, °	76	77	80	90	90	80	72.5	60	77
Number of Slices	37	33	40	34	34	45	30	27	41
Scan Time, Minutes	8	8	5	6	8	6.38	8.75	6	8
Eyes Open or Closed	Open	Open	Open	Closed	Open	Closed	Open	Open	Open

FOV, field of view; TE, echo time; TR, repetition time.

participants included the CO-DMN, FPN-SC, SN-DAN, and VAN-FPN.

DISCUSSION

The present study explored brain-correlates of ITRED using rsFC data aggregated from 9 worldwide sites of the ENIGMA PTSD Consortium. We used RF ML to detect differences between PTSD participants, ITRED-only participants, and TE-only participants. Our RF classification performance was rigorously examined on both CV AUC and test AUC using a fully independent dataset. Our results showed that rsFC features differentiated TE-only participants from PTSD participants and ITRED-only participants with about 60% accuracy and medium effect sizes on the CV sample and test sample. As hypothesized, our results showed that rsFC features did not differentiate PTSD participants from ITRED-only participants, performing below chance level (i.e., 45%), even though the PTSD group had significantly higher symptom levels (i.e., CAPS scores) than the ITRED-only group. Exploring specific features differentiating TE-only participants from PTSD and ITRED-only participants revealed common features mostly involving connectivity with the DMN. Results also showed some unique features that emerged when comparing TE-only participants with PTSD participants but not when comparing TE-only with ITRED-only participants, and vice versa. Taken together, our findings support the concept of ITRED as a novel diagnostic conceptualization of posttrauma psychopathology that is neurobiologically based on functional brain network connectivity.

As stated above, a similar test AUC emerged for classifying TE-only versus PTSD (60% test AUC) and vs. ITRED-only (59% test AUC). These classification rates might seem low when considering some single-site studies using rsFC that showed higher classification rates. However, large-scale imaging datasets, such as the one used here, show comparable results (around 62%) across different psychopathologies (32–34), including PTSD classification (X. Zhu, Ph.D., *et al.*, unpublished data, 2022). Importantly, ML studies using large-scale imaging datasets rectify some major limitations of single-site studies, especially data overfitting, which may result in overly optimistic results. Thus, using large-enough samples improves generalization beyond what can be achieved by independent datasets (35). The medium effect sizes of both the CV and test AUC data support the validity of current results. Unlike the results differentiating TE-only participants from both PTSD and from ITRED-only participants, the ML model differentiated between PTSD and ITRED-only participants below chance level (45% test AUC), despite the fact that the PTSD group showed significantly higher symptom levels than the ITRED-only group. These findings may suggest that participants with a traditional PTSD diagnosis and ITRED-only participants are more similar than dissimilar in their brain rsFC network features, providing additional support for ITRED as a simpler and more efficient diagnostic tool based on functional brain networks.

Exploring rsFC features common to distinguishing PTSD participants and ITRED-only participants from TE-only participants implicated the DMN as a central brain network, with 6 out of 9 common features including connections within the

Table 4. Sensitivity, Specificity, Accuracy, and AUC for Each Group Comparison

	PTSD vs. TE	ITRED vs. TE	PTSD vs. ITRED
CV Accuracy	0.62	0.68	0.68
CV AUC	0.63	0.61	0.42
Test Accuracy	0.60	0.59	0.48
Test AUC	0.60	0.61	0.45
Sensitivity	0.53	0.62	0.49
Specificity	0.68	0.57	0.45

AUC, area under the curve; CV, cross-validation; ITRED, intrusive traumatic re-experiencing domain; PTSD, posttraumatic stress disorder; TE, trauma exposed.

DMN and between the DMN and other brain areas (i.e., DMN-DMN, DMN-FPN, DMN-VAN, DMN-SC, DMN-SN, and DMN-VAN). The DMN is largely associated with self-referential processes, activated during resting states, and typically active in relationship with task or goal-directed states (36). In particular, hypoactive DMN connectivity has been strongly implicated in PTSD (37) and has been especially correlated with intrusions and dissociative symptoms (18). Furthermore, connectivity between DMN-related areas and other cortical and subcortical brain regions normalize following various exposure-based psychotherapies (38–40). Current findings also revealed a few unique features, namely features important for differentiating TE-only participants from one group but to a lesser extent from the other group: PTSD > ITRED-only (e.g., CO-SN, SN-VAN) or ITRED-only > PTSD (e.g., FPN-SC, VAN-FPN). Connectivity features that are unique to PTSD, but that are minimally present in ITRED, may be related to avoidance, hyperarousal, and/or changes in mood and cognition, which are not a part of ITRED symptom phenomenology. Connectivity features that are unique to ITRED, but that are less involved in PTSD, may represent intrusion-related connectivity features that failed to emerge when differentiating TE-only participants from PTSD participants, as both definitions (i.e., PTSD and ITRED) include intrusion symptoms (criterion B symptoms). A possible reason may be the increased focus of ITRED on intrusive re-experiencing, which may result in higher diagnosis homogeneity of the sample compared with that of the PTSD sample, flushing out additional connectivity patterns related to intrusive symptoms. Using the FPN as an example, while DMN-FPN connectivity emerged as a common feature of both PTSD and ITRED classifications, SC-FPN and VAN-FPN connectivity only emerged for differentiating ITRED-only from TE-only participants. Indeed, previous research has shown intrusive symptoms to be related to the FPN and FPN-DMN (15,41,42).

Some limitations of this study should be noted. First, while the ITRED-only group included exclusively participants not meeting a PTSD diagnosis, the present study did not include a group of participants with solely a PTSD diagnosis, without concurrent ITRED, as all of those in the PTSD group also met criteria for ITRED. This is not surprising, given the need to meet criterion B for a PTSD diagnosis, per the DSM-IV and DSM-5 (1). While including such a group may further enhance current efforts in exploring similarities and differences between PTSD and ITRED, this would not be an easy, or even feasible, task due to very low prevalence rates (7). Thus, we could not include these participants as a separate group in our analysis. Second, due to the nature of this ENIGMA PTSD project (i.e., data are collected independently in each site and then aggregated retrospectively), there were site variabilities in the way the data were collected. For example, as types of comorbid psychopathologies were not consistently recorded across all participating sites, we could not assess, or control for, the effects of each comorbid condition. This was also true for other demographic characteristics of the sample such as ethnicity, socioeconomic status, and education. Finally, this was also true for ensuring interrater variability across sites. Nonetheless, we did correct for these variables, when possible, in our data and analysis. Third, our study focused on rsFC data using the Power atlas (24). While the Power atlas covers all the areas of interest identified in PTSD, future studies could consider using other atlases [e.g., (43,44)] with whole brain overlapping coverage. In addition, due to the nature of the ML algorithms, it is important to recognize that while the results suggest similar brain connectivity maps between ITRED and PTSD, this finding cannot be fully ascertained. Future studies could replicate the current results while expanding to other magnetic resonance imaging modalities, such as structural or task-based magnetic resonance imaging, to further investigate ITRED and PTSD. Fourth, ITRED-related studies, including this one, have shown a different percentage of TE individuals who fail to meet the DSM criteria for PTSD but meet ITRED criteria. A possible

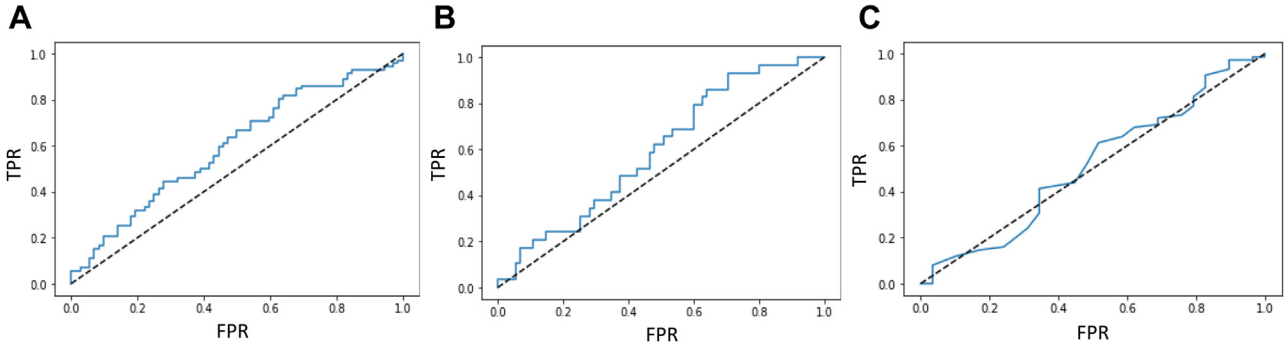

Figure 1. Test area under the curve of **(A)** posttraumatic stress disorder vs. trauma exposed, **(B)** intrusive traumatic re-experiencing domain vs. trauma exposed; and **(C)** posttraumatic stress disorder vs. intrusive traumatic re-experiencing domain. FPR, false positive rate; TPR, true positive rate.

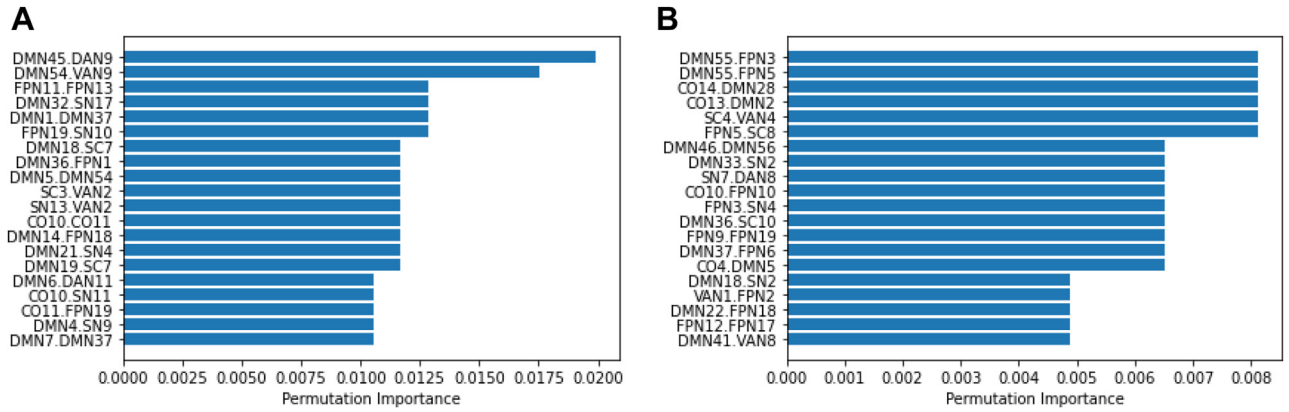

Figure 2. Gini importance feature importance distinguishing **(A)** posttraumatic stress disorder vs. trauma exposed and **(B)** intrusive traumatic re-experiencing domain vs. trauma exposed. The figure only shows the top features, out of all the possible pairs, that contributed to the classifiers of each group pair. CO, cingulo-opercular network; DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; SC, subcortical network; SN, salience network; VAN, ventral attention network.

reason for this between-samples divergence is the homogeneity/heterogeneity of the samples explored. All previous samples were from single sites—participants were all from the same country and culture. Moreover, most previous samples were also homogeneous regarding trauma type. In the present ENIGMA study, the sample comprised 9 different sites from several different countries (e.g., United States, Denmark, the Netherlands), with different populations and trauma types across sites (e.g., civilian with mixed trauma types, civilian with motor vehicle accident trauma types, military with combat-related trauma types). Additionally, the number of traumas and trauma specificity, as well as other demographic variables, might also differentiate the present sample from previous ones. Unfortunately, these were not consistently recorded in all the sites and could not be explored in detail in the present study. Future studies could explore these differences in ITRED percentages based on country, culture, population, sex, and trauma type. Last, as our study focused on predicting diagnosis using ML procedures, it did not explore longitudinal progression or treatment response. Furthermore, our study focused on the re-experiencing symptoms of PTSD, without looking at other domain-specific criteria for hyperarousal, mood, and avoidance. However, unlike other psychiatric conditions, PTSD is still the only diagnosis in the DSM necessitating an actual traumatic experience that occurred in real life. Hence, in PTSD, re-experiencing is connected directly to that event (i.e., the re-experiencing is of the event itself). This is not necessarily the case in other psychopathologies, especially those with overlapping symptoms of hyperarousal, mood dysregulation, and avoidance (e.g., in obsessive-compulsive disorder, intrusive thoughts [i.e., obsessions] are typically focused on dreaded or feared situations that may be only weakly connected to external reality). These commonalities and differences across psychopathologies and treatment response could be addressed in future studies using ITRED.

We provide preliminary neural evidence supporting the ITRED concept as a new and concise diagnostic construct of posttraumatic psychopathology. A narrow focus on re-experiencing symptoms can complement existing PTSD diagnostic tools. Incorporating the ITRED concept in common psychiatric services could enhance the field in two important ways. First, ITRED could provide a simpler, faster, and more cohesive framework for diagnosing posttraumatic psychopathology, as it picks up approximately 95% of the cases. More importantly, ITRED can be used to identify TE individuals experiencing severe re-experiencing symptoms but who are ineligible for a PTSD diagnosis in its present formulation (around 10.5%; range, 7.3%–14.2%) (7), which in some instances, might preclude formal health care services and benefits. Overall, ITRED and its associated neurobiological processes can offer an alternative perspective for developing augmentative therapies that may focus on re-experiencing symptoms.

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