Data supplement for Lebois et al., Persistent Dissociation and Its Neural Correlates in Predicting Outcomes After Trauma Exposure. Am J Psychiatry (doi: 10.1176/appi.ajp.21090911)

SUPPLEMENTAL METHODS

Measures

The Childhood Trauma Questionnaire – modified (CTQ). We measured childhood maltreatment severity at 2-weeks post-trauma using an abbreviated version of the CTQ (1) containing 11 items: 2 physical neglect, 2 emotional neglect, 2 emotional abuse, 2 physical abuse, and 3 sexual abuse items. The CTQ asks participants to indicate how often experiences occurred when they were growing up on a 5-point Likert scale ranging from “never true” to “very often true.” Items were summed to create a CTQ total score ranging from 0 to 44. Higher scores indicate greater childhood trauma severity. In our sample, the modified CTQ displayed very good internal consistency (α = 86). The modified CTQ total has a strong relationship with the full-length CTQ total in a different traumatized sample, $r = .99$, $p<.001$ ($N=127$; see data subset published in 22).

Brief Dissociative Experiences Scale – modified (DES-B). We measured persistent dissociation severity at 2-weeks post trauma using a 2-item abbreviated version of the DES-B (2). Participants were asked about feelings of detachment from their environment (derealization) by asking “how often during the past two weeks did”: 1) “People, objects, or the world around you seem strange or unreal”; 2) “You felt as though you were looking through a fog so that people and things seemed far away or unclear.” Responses were on a 5-point Likert scale ranging from “0, none of the time” to “4, all or almost all of the time.” Items were summed for a total score ranging from 0 to 8. Higher scores indicate more severe derealization symptoms. In our sample, the modified DES-B displayed very good internal consistency ($\alpha = .82$). The modified DES-B total has a strong relationship with the full-length DES depersonalization / derealization total in a different traumatized sample, $r = .92$, $p<.001$ ($N=127$; see data subset published in 22). Moreover, the full-length DES only has two derealization items (those that were included in our study). Therefore, the full-length DES derealization only score has a 1:1 correspondence with our DES-B derealization score.

PTSD checklist for DSM-5 (PCL-5). We measured posttraumatic stress symptom severity at 2-weeks and 3-months post trauma using the 20-item PCL-5 (3). The PCL-5 asks participants to indicate, “How much you were bothered by” various PTSD symptoms on a 5-point Likert scale ranging from “not at all” to “extremely.” The reference time was the past 2 weeks for the 2-week time point and the past 30 days for the 3-month time point. The total score ranges from 0 to 80. Higher scores indicate more severe PTSD symptoms. A cut point score of 28 was used to indicate a provisional PTSD diagnosis in this sample.

PROMIS Depression Short Form 8b scale. We measured depression symptom severity at 3-months post trauma using the 8-item PROMIS Depression short form (4). This scale asks participants to indicate "how often during [the past month] did you feel" various depression symptoms. Scores are converted to a T-score. A higher T-score indicates more severe depression symptoms. A cut point score of 60 was used to indicate a depression score that was 1 SD worse than average in this sample. We refer to this as a provisional depression diagnosis in our analyses that follow.

PROMIS Anxiety. We measured anxiety symptom severity at 3-months post trauma using an abbreviated version of the PROMIS Anxiety Bank containing 4-items (4). These items ask participants "how often during the past month did you" experience various anxiety symptoms using a 5-point Likert scale ranging from "none of the time" to "most of the time." The total score ranges from 0 to 16 with higher scores indicting more severe anxiety.

Pain Extent. We measured the extent of pain at 3-months post trauma by asking participants to indicate how many regions of the body had pain out of the 18 body regions listed in the Numeric Pain Rating Scale. The reference time was the past 30 days. The total score ranges from 0 to 18. Higher scores indicate greater extent of pain.

Sheehan Disability Scale (SDS). We measured functional impairment in work, family, and social life 3-months post trauma using the 3-item SDS (5). The SDS asks participants to indicate, "how much have symptoms related to your physical health or emotional problems disrupted" work/family/social life on a 11-point Likert scale ranging from "not at all disruptive" to "extremely disruptive." Items were summed to create a total score ranging from 0 to 30. Higher scores indicate more role impairment.

Magnetic Resonance Imaging

Acquisition. Brain scans were completed approximately 2-weeks after the emergency department visit at four different sites all using Siemens 3 Tesla MRI systems with an EP2d-BOLD sequence for functional scans and an MPRAGE T1-weighted (T1w) image for structural scans. The T1w image had 176 sagittal slices, interleaved, with a voxel size of $1mm^3$, TR=2530 ms, TE 1/2/3/4 = 1.74/3.6/5.46/7.32 ms, FA=7º. The fMRI scans were collected with 44 axial slices in a descending interleaved order, voxel size 3x3x2.5mm and a 0.5 mm slice gap, TR = 2360 ms, TE = 30 ms, FA = 70º. Sequence parameters were altered slightly to accommodate different models and software versions at each site. Previously published work detailed more information on site-specific sequence parameters (6, 8).

MRI Tasks. The MRI session included a resting-state scan and an emotion reactivity task (as well as two other tasks not reported here). During the 9-minute resting-state scan, participants were instructed to keep their eyes open and "Please try to clear your mind and focus on the little cross in the middle of the screen." The emotion reactivity task was designed to probe reactivity to social threat cues by having participants passively view fearful and neutral facial expressions (7). Faces were presented in a block design with 8 different faces of the same emotion (fear vs. neutral) within an 8 second block. Individual faces were presented for 500 ms each with a 500 ms interstimulus interval. Participants were given three 10 sec rest periods evenly distributed throughout the task. The 5 min task included 15 fear blocks and 15 neutral blocks presented in a pseudorandom order. The order was counterbalanced across participants.

Preprocessing. All data were preprocessed using a standardized pipeline via the FMRIPREP 1.2.2 software package, including EPI co-registration to the T1w image, spatial realignment, slice-time correction, and normalization to the 2009 ICBM-152 template using ANTs-based non-linear registration. We used ICA-AROMA in this pipeline to address volume-wise motion and other artifacts by regressing out artifact-related components. We also implemented a motion cutoff of 1mm FD and dropped runs with >15% of volumes exceeding this cutoff. The emotion reactivity task ICA-corrected images were smoothed with a 6mm FWHM gaussian kernel in SPM12. For the resting-state data, we also implemented a bandstop filter of >.01 Hz to address physiological noise. Furthermore, we discarded participants who had more than 15% of their scan volumes exceed 1 mm framewise displacement.

Emotion Reactivity Task First-level models and Region of Interest Extraction. We used SPM12 for the initial statistical models in the emotion reactivity task. We regressed out white matter, cerebral spinal fluid and global signal time courses to correct for motion/physiological noise while retaining signal quality (9). Emotion blocks were modeled with separate boxcar functions representing the onset and 8000 ms duration of each block, convolved with a canonical hemodynamic response function. We then extracted region of interest (ROI) data from the first-level fearful>neutral face contrast using AFNI version 20.0.24 (10). The extracted value was the average value from the whole ROI at each volume. Previous work in largely motor vehicle accident samples has associated ventromedial prefrontal cortex (vmPFC) activity with dissociative experiences during emotionally provocative tasks, using a dissociation measure with similar derealization items to our modified DES-B (11). Therefore, we derived our vmPFC ROI from this previous work using a 5mm sphere placed in left vmPFC (MNI coordinates -12, 50, 4).

Seed-based Resting-state connectivity. We used AFNI 20.0.24 to generate subject-level connectivity maps. First, we extracted the average value from subject-level resting-state data in our vmPFC seed region using the same 5mm sphere ROI placed in left vmPFC as the emotion reactivity task (MNI coordinates -12, 50, 4). Next, we correlated these values with the whole brain voxel time courses for each subject, and computed Fisher Z transformations to generate subject-level connectivity maps.

Group-Level Statistical Analyses

Self-report data and Emotion Reactivity Task. Statistical analyses were completed using IBM SPSS version 28. We conducted Pearson correlation analyses to test associations between 2-week derealization, demographic variables and childhood maltreatment, and an ANOVA to test for differences in 2-week derealization between categorical race/ethnicity demographic variables. We then completed an exploratory analysis of sex differences in 2-week derealization using independent *t*-tests and a linear model.

Resting-state Connectivity. To test whether vmPFC connectivity was associated with derealization, we entered subject-level seed-based connectivity maps into a linear model using

AFNI 20.0.24 3dMVM program (12). We then used the residuals from our 3dMVM linear model to estimate the probability of false positive clusters using 3dClustSim. This version of ClustSim uses an estimated non-Gaussian autocorrelation function to avoid spurious false positives. This identified clusters of 70 voxels or larger to be significant at a voxel threshold of p = .002 and α = .05. These p and α levels were chosen following recommendations from Cox et al (21).

Manipulation Check Whole-Brain Analysis of Emotion Reactivity Task. To determine the effectiveness of the emotion reactivity task as a whole (without covariates), we completed a whole-brain analysis of the fear – neutral faces contrast using AFNI's 3dttest++ program. We then used 3dClustSim to estimate the probability of false positive clusters. This identified clusters of 70 voxels or larger to be significant at a voxel threshold of p = .002 and α = .05.

SUPPLEMENTAL RESULTS

Sample Characteristics. Participants were 1,618 adults who presented in the emergency department within 72 hours after a trauma exposure that involved actual or threatened serious injury, sexual violence, or death, either by direct exposure, witnessing or learning about it. A subset of these individuals also completed an MRI scan approximately 2-weeks after their emergency department visit (N = 197). Participants were excluded from the self-report analyses if they did not complete assessments of 2-week derealization (N = 154), leaving a final self-report N of 1,464. Participants were excluded from the MRI analysis if they did not pass quality control standards (N = 25) or if they were missing 2-week derealization scores (N = 27), leaving a final MRI sample of 145. All demographics and results reported in the SOM and main manuscript include only individuals who were not excluded.

Who experiences trauma-related persistent derealization? Persistent derealization was weakly associated with the total severity of childhood maltreatment, $r(1370)$ =.28, p < .001, and strongly associated with concurrent 2-week posttraumatic stress symptoms, $r(1374)$ =.68, p < .001. It was also weakly associated with age, $r(1464)$ = -.08, p = .002. There were no racial/ethnic differences in persistent derealization, $F(3, 1456)$ = 2.04, p = .106, but there was a sex difference in which female participants reported higher levels of 2-week persistent derealization compared to male participants, M_{diff} = -.28, SE = .11, $t(1113.78)$ = 2.47, p = .014.

However, female participants also reported higher levels of childhood maltreatment and 2-week posttraumatic stress symptoms compared to male participants in a series of t-tests, p's < .001. To test if differences in childhood maltreatment and 2-week posttraumatic stress symptoms were driving the sex difference in derealization, we ran a linear model with these variables and age as a covariate. The linear model revealed that there was a significant effect of sex on 2-week derealization after controlling for the effect of childhood maltreatment, 2-week posttraumatic stress symptoms, and age, $F(1,1289)$ = 8.90, p = .003. However, the sex effect was reversed, with males reporting higher levels of derealization when accounting for these other variables, M_{diff} = .27, robust SE = .09, $t(1292)$ = 3.12, p = .002.

MRI scanner effects. To determine if the relationship between vmPFC activity and derealization in the fear > neutral contrast varied as a function of MRI scanner, we also ran a follow-up linear model to those reported in the main manuscript under “Neural Correlates of Persistent Derealization” “Emotion Reactivity Task Activity.” This model included the interaction between MRI scanner and derealization in addition to controlling for sex, age, childhood maltreatment and 2-week posttraumatic stress symptoms. The interaction term was nonsignificant, $F(3,136) = 1.01$, $p = .391$, suggesting the relationship between derealization and vmPFC was robust to MRI scanner site effects.

Linking vmPFC activity and connectivity. To test for possible links between these connectivity results and activity in the vmPFC ROI, we completed a series of exploratory correlations and linear models. First, we explored correlations between the vmPFC activity and connectivity Z scores to see if the extent of vmPFC activity in the fear > neutral face contrast was linked to connectivity between vmPFC and OFC or cerebellum. The correlations were not significant (p’s > .05). Next, we tested whether the level of connectivity between vmPFC and OFC or cerebellum influenced the relationship between vmPFC activity and our outcomes of interest: 2-week derealization, 3-month PTSD symptoms, 3-month depression symptoms. The interaction terms in these six linear models (3 for vmPFC activity x vmPFC-OFC connectivity, 3 for vmPFC activity x vmPFC-cerebellum connectivity) were not significant.

Manipulation Check Whole-Brain Analysis of Emotion Reactivity Task. To determine the effectiveness of the emotion reactivity task with no covariates, we completed a whole-brain group analysis of the fear – neutral contrast. Two regions survived multiple comparison correction. A cluster that spanned right amygdala and hippocampus was more active during fearful compared to neutral face conditions (cluster volume = 99, Peak $t = 5.15$, MNI coordinates for the peak t = 30, -7, -20). An area in right primary visual cortex near the calcarine sulcus was more active during neutral compared to fearful face conditions (cluster volume = 94, Peak $t = -3.99$, MNI coordinates for the peak t = 26, -55, 8). This analysis demonstrates the task as a whole was effective.

Predicting 3-Month PTSD and Depression Diagnosis. We were interested in the discrimination of both 2-week self-report derealization and vmPFC activity during the fearful > neutral faces task for 3-month diagnoses of PTSD and depression. Therefore, we converted our continuous PTSD and depression symptom outcomes into dichotomous PTSD or depression provisional “diagnosis” vs. no diagnosis variables as described in the supplement Methods. We then conducted a series of ROC curve analyses to compare discrimination across several models to determine if derealization and vmPFC improved predictive accuracy for PTSD and depression diagnoses.

First, we explored the predictive accuracy of 2-week derealization for PTSD and depression diagnosis by comparing three ROC curve models: 1) with 2-week derealization only; 2) without 2-week derealization but including our demographic/clinical covariates modeled in our continuous dependent variable analyses described in the main text (e.g., sex assigned at birth, childhood maltreatment etc.); and 3) with 2-week derealization and the demographic/clinical covariates.

The estimated areas under the ROC curves indicated acceptable discrimination for 2-week derealization alone (Model 1) but little improvement in discrimination when combined with other clinical predictors (Table S1).

We also identified the coordinates in each model associated with the highest diagnostic accuracy, defined as the average of sensitivity and specificity (Table S1). We then compared improvements in these metrics across models. Model 3 (derealization + demographic/clinical covariates) improved accuracy in PTSD diagnosis identification by 1% compared to the same model without derealization. Inclusion of 2-week derealization in the model did not improve the accuracy of depression diagnosis.

TABLE S1. ROC curve analyses for PTSD and depression provisional diagnosis with 2-week self-report derealization

ROC Model	Area under curve (CI)	Sensitivity	Specificity
PTSD diagnosis			
Model 1 Derealization only	0.75 (0.72, 0.78)	0.66	0.74
Model 2 Covariates only	0.86 (0.84, 0.88)	0.82	0.75
Model 3 Derealization and covariates	0.86 (0.84, 0.88)	0.84	0.74
Depression diagnosis			
Model 1 Derealization only	0.75 (0.72, 0.78)	0.66	0.74
Model 2 Covariates only	0.83 (0.81, 0.86)	0.74	0.78
Model 3 Derealization and covariates	0.84 (0.81, 0.87)	0.74	0.78

ROC = receiver operating characteristic; CI = confidence interval; cut-points for risk scores determining sensitivity and specificity were chosen to maximize the average of estimated sensitivity and estimated specificity. Covariates were age, sex, childhood maltreatment severity and PTSD symptom severity at two weeks.

Next, we explored the predictive accuracy of vmPFC activity during the fearful > neutral faces task for PTSD and depression diagnosis by comparing the same three ROC curve analyses just discussed, namely: 1) with vmPFC activity only; 2) without vmPFC but including our demographic/clinical covariates modeled in our continuous dependent variable analyses described in the main text (e.g., sex, childhood maltreatment, scan site etc.); and 3) with vmPFC and the demographic/clinical covariates.

The estimated areas under the ROC curves indicated less than acceptable discrimination for vmPFC activity alone and only slight improvement in discrimination when combined with other clinical predictors (Table S2).

We also identified the coordinates in each model associated with the highest diagnostic accuracy (i.e., the highest value when sensitivity and specificity were averaged; Table S2). Including vmPFC activity in addition to other clinical predictors improved accuracy of PTSD diagnosis identification by 3% and accuracy of depression diagnosis by 2%.

TABLE S2. ROC curve analyses for PTSD and depression provisional diagnosis with vmPFC ROI activity during fear > neutral face contrast

ROC Model	Area under curve (CI)	Sensitivity	Specificity
PTSD diagnosis			
Model 1 vmPFC only	0.62 (0.51, 0.72)	0.63	0.63
Model 2 Covariates only	0.80 (0.72, 0.88)	0.80	0.68
Model 3 vmPFC and covariates	0.81 (0.73, 0.89)	0.85	0.69
Depression diagnosis			
Model 1 vmPFC only	0.65 (0.55, 0.76)	0.83	0.49
Model 2 Covariates only	0.87 (0.77, 0.97)	0.92	0.81
Model 3 vmPFC and covariates	0.88 (0.88, 0.98)	0.92	0.78

ROC = receiver operating characteristic; CI = confidence interval; cut-points for risk scores determining sensitivity and specificity were chosen to maximize the average of estimated sensitivity and estimated specificity. Covariates were MRI scan site, age, sex, childhood maltreatment severity and PTSD symptom severity at two weeks.

SUPPLEMENTAL DISCUSSION

A critical descriptive finding in our study is that rates of persistent derealization in the aftermath of an acute trauma were remarkably high – around 50% of people reported mild to severe levels of derealization. Given that 2-week derealization was correlated with more severe PTSD, anxiety, depression, pain extent, and impairment at 3 months, it is crucial for medical and clinical personnel to assess for dissociation, and derealization symptoms in particular, in the weeks following traumatic events.

Furthermore, we found that a history of childhood maltreatment, younger age, and female sex were associated with higher levels of persistent derealization. Some prior work has also found a small negative association between age and dissociative symptom severity (13), and other work suggests dissociation declines with age as a natural part of development (14). Moreover, a large body of work across clinical and nonclinical samples has reported a strong relationship between trauma and dissociation (15). In particular, experiences of severe childhood maltreatment are associated with severe levels of dissociative symptomatology (16). In these contexts, ongoing dissociation may serve to preserve attachment bonds with caregivers who are abusive, but necessary for the child's survival (17).
Additionally, across nonclinical and clinical samples of children and adults, most prior work has also found high rates of dissociation among females (13, 18, 19). However, these results are confounded by differences in diagnosis incidence across genders (13), and by greater exposure among females to traumatic exposures that are strongly associated with dissociative symptoms (e.g., sexual trauma) (18, 19). To address some of these confounds, we controlled for childhood maltreatment and concurrent PTSD symptom severity and found that the sex effect was reversed. That is, males reported higher levels of derealization when controlling for these variables. An international epidemiological survey study also found males to have higher rates of PTSD with depersonalization/derealization dissociation compared to females (20). It is yet unclear if sex assigned at birth is an independent risk for dissociation following trauma, and if so, further work

is necessary to determine the direction of that risk. Taken together, our results replicate and extend previous findings in dissociation, suggesting a profile of individual differences more likely to be associated with persistent derealization symptoms in the aftermath of an acute traumatic event – younger age, females, and those with a history of childhood maltreatment.

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