Childhood trauma history is linked to abnormal brain connectivity in major depression

Meichen Yu[a,b], Kristin A. Linn[a,c], Russell T. Shinohara[a,c], Desmond J. Oathes[a,b], Philip A. Cook[a,d], Romain Duprat[a,b], Tyler M. Moore[e], Maria A. Oquendo[b], Mary L. Phillips[f], Melvin McInnis[g], Maurizio Fava[h], Madhukar H. Trivedi[i], Patrick McGrath[j], Ramin Parsey[k], Myrna M. Weissman[j], and Yvette I. Sheline[a,b,d,l,1]

[a]Center for Neuromodulation in Depression and Stress, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; [b]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; [c]Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; [d]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; [e]Brain and Behavior Laboratory, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104; [f]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15260; [g]Department of Psychiatry, University of Michigan School of Medicine, Ann Arbor, MI 48109; [h]Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114; [i]Center for Depression Research and Clinical Care, Peter O'Donnell Institute, University of Texas Southwestern Medical Center, Dallas, TX 75390; [j]Department of Psychiatry, Columbia University College of Physicians & Surgeons, New York, NY 10032; [k]Department of Psychiatry, Stony Brook University, Stony Brook, NY 11794; and [l]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104

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Patients with major depressive disorder (MDD) present with heterogeneous symptom profiles, while neurobiological mechanisms are still largely unknown. Brain network studies consistently report disruptions of resting-state networks (RSNs) in patients with MDD, including hypoconnectivity in the frontoparietal network (FPN), hyperconnectivity in the default mode network (DMN), and increased connection between the DMN and FPN. Using a large, multisite fMRI dataset (n = 189 patients with MDD, n = 39 controls), we investigated network connectivity differences within and between RSNs in patients with MDD and healthy controls. We found that MDD could be characterized by a network model with the following abnormalities relative to controls: (*i*) lower within-network connectivity in three task-positive RSNs [FPN, dorsal attention network (DAN), and cingulo-opercular network (CON)], (*ii*) higher within-network connectivity in two intrinsic networks [DMN and salience network (SAN)], and (*iii*) higher within-network connectivity in two sensory networks [sensorimotor network (SMN) and visual network (VIS)]. Furthermore, we found significant alterations in connectivity between a number of these networks. Among patients with MDD, a history of childhood trauma and current symptoms quantified by clinical assessments were associated with a multivariate pattern of seven different within- and between-network connectivities involving the DAN, FPN, CON, subcortical regions, ventral attention network (VAN), auditory network (AUD), VIS, and SMN. Overall, our study showed that traumatic childhood experiences and dimensional symptoms are linked to abnormal network architecture in MDD. Our results suggest that RSN connectivity may explain underlying neurobiological mechanisms of MDD symptoms and has the potential to serve as an effective diagnostic biomarker.

childhood trauma | dimensional symptoms | major depressive disorder | network connectivity | resting-state networks

Major depressive disorder (MDD) is a common mental disorder characterized by heterogeneous symptoms: persistently depressed mood, loss of interest, low self-esteem and energy level, weight change, insomnia or hypersomnia, and disturbance in cognitive functions such as attention and memory (1). These symptoms impair daily life function and increase the risk of suicide (2). According to the WHO, depression is the fourth leading cause of disability worldwide and is projected to be second by 2020 (3). In addition, experiences of childhood trauma, including physical, sexual, or emotional abuse, as well as physical or emotional neglect, have been found to be associated with the emergence and persistence of depressive and anxiety disorders (4). However, neurobiological mechanisms underlying the dimensional symptoms of MDD remain unclear (5, 6).

The human brain contains an estimated 100–1,000 trillion synapses. This complex neural system is amenable to scientific investigation from a network perspective by using modern network theory (7) to reveal resting-state networks (RSNs) (8, 9) that play important roles in brain function and disease, including major depression. MDD has been found to be associated with specific abnormalities in multiple RSNs compared with healthy controls (10). In particular, fMRI studies have consistently reported reduced functional connectivity (hypoconnectivity) within the frontoparietal network (FPN) (11, 12), increased connectivity (hyperconnectivity) within the default mode network (DMN) (13, 14), and hyperconnectivity between the DMN and FPN in patients with MDD. The FPN is involved in executive control of attention and emotion, while the DMN is involved in internally oriented attention and self-referential processing (15, 16). Dysfunction of these networks is integrally associated with MDD (5). A few studies also

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[1]To whom correspondence should be addressed. Email: sheline@pennmedicine.upenn.edu.

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Significance

The primary finding in this study was the dramatic primary association of brain resting-state network (RSN) connectivity abnormalities with a history of childhood trauma in major depressive disorder (MDD). Even though participants in this study were not selected for a history of trauma and the brain imaging took place decades after trauma occurrence, the scar of prior trauma was evident in functional dysconnectivity. In addition to childhood trauma, dimensions of MDD symptoms were related to abnormal network connectivity. Further, we found that a network model of MDD described within- and between-network connectivity differences from controls in multiple RSNs, including the default mode network, frontoparietal network, and attention and sensory systems.

found salience network (SAN) (17) and dorsal attention network (DAN) (18) dysfunction in MDD, but these findings are less frequently reported than those for the DMN and FPN. A recent large (556 patients with MDD and 518 healthy controls) meta-analysis of seed-based RSN studies confirmed alterations in functional connectivity in the DMN, FPN, SAN, and DAN among patients with MDD (19). Moreover, the abnormalities in network connectivity in MDD have been shown to be associated with depression severity (20), illness duration (18, 21), the number and length of episodes (13, 21), and treatment outcomes (22, 23). However, none of these studies used multivariate methods to simultaneously examine relationships among brain networks and item-level data from clinical assessments.

In this study, we first compared differences in brain networks between patients with MDD and controls. Then, among the patients with MDD, we used multivariate methods to examine correlations between network measures and a large number of clinical variables that had first been grouped into clusters. In particular, we used a multisite fMRI dataset consisting of 189 patients with MDD and 39 healthy controls to investigate abnormalities in the system-level brain network architecture in patients with MDD relative to controls. Among the patients with MDD, we also studied relationships between brain networks and clinical symptoms, including depression (general and anhedonic depression), anxiety, personality (neuroticism, extraversion, openness, agreeableness, and conscientiousness), suicidality, and experiences of childhood trauma (physical abuse/neglect, emotional abuse/neglect, and sexual abuse), which were measured by 213 item-level survey questions. We hypothesized that (*i*) patients with MDD would present with abnormal connectivity patterns of RSNs, including the DMN and FPN, compared with controls, using a system-level connectivity analysis, and (*ii*) multivariate patterns of network connectivity within and between RSNs in patients with MDD would be associated with clinical symptoms, quantified by data-driven clustering of item-level survey data. To test our second hypothesis, we used canonical correlation analysis (CCA) to identify multivariate relationships between RSN connectivity measures and item-level clinical data in patients with MDD. Recent studies (20, 24) have shown that CCA, a powerful multivariate approach that seeks to identify clusters of maximal correlation between two groups of variables, can detect associations between structural or functional connectivity and behavioral measures. To our knowledge, our work is the first to apply CCA to study multivariate relationships between network connectivity and item-level clinical data in patients with MDD.

Results

Demographic and clinical characteristics of the study participants are presented in *SI Appendix*, Table S1. Distributions of age, sex, and educational level did not differ significantly between the two groups.

Network Modeling of MDD. We concentrated on 10 well-established, large-scale RSNs derived from the atlas of Power et al. (25): the DMN, FPN, SAN, cingulo-opercular network (CON), sensorimotor network (SMN), visual network (VIS), dorsal attention network (DAN), ventral attention network (VAN), auditory network (AUD), and subcortical network (SUB). We qualitatively characterized the average functional role of the 10 RSNs by mapping the group average within- and between-network connectivity into a 2D parameter space (Fig. 1 *A* and *B*; technical details are provided in *SI Appendix*). Connectivity was defined as temporal coherence of blood oxygen level-dependent signals in different regions (26). According to mean values of within- and between-network connectivity (depicted by the horizontal and vertical dotted lines in Fig. 1 *A*–*C*), eight RSNs from the two groups were concordantly classified into four network roles: cohesive connector (FPN and DMN), cohesive provincial (VIS and SMN), incohesive connector (DAN, SAN, and CON), and incohesive provincial (SUB). The VAN and AUD showed divergent roles in the two groups. Specifically, the VAN and AUD were incohesive connectors and provincial networks, respectively, in patients with MDD, and the opposite was found in controls.

Comparison of Network Connectivity in Patients with MDD Versus Controls. We tested for differences in the means of within- and between-network connectivity between patients with MDD and controls. Although the FPN and DMN were both cohesive connectors in the two groups (Fig. 1 *A* and *B*), the FPN showed significantly lower within-network connectivity and the DMN showed significantly higher within-network connectivity in patients with MDD compared with controls (Fig. 1 *F* and *G*). Similarly, although the DAN, SAN, and CON were incohesive connectors in both groups, patients with MDD had significantly higher SAN connectivity and lower DAN and CON connectivity relative to controls (Fig. 1 *F* and *G*). The VIS and SMN, two cohesive provincial networks that had the highest within-network connectivity overall in both groups (Fig. 1 *A* and *B*), showed significantly higher within-network connectivity in patients with MDD compared with controls (Fig. 1*F*). Patients with MDD also showed consistently higher one-versus-all-others-network connectivity in the DMN, FPN, SAN, and DAN compared with controls (Fig. 1*F*).

We computed pairwise between-network connectivity as the normalized mean connectivity between each pair of RSNs and compared the connectivity profiles of patients with MDD and controls. Fig. 1*F* shows that the pairwise between-network connectivity was significantly higher in patients with MDD in the following pairs: DMN-FPN, DMN-SAN, FPN-VIS, DAN-DMN, DAN-FPN, DAN-CON, and DAN-VIS. In contrast, patients demonstrated hypoconnectivity between the following pairs: DAN-SAN, DAN-AUD, and FPN-SAN. Fig. 1*G* illustrates the hyperconnected links between the DMN and FPN, as well as the FPN and DAN. Additional illustrations of between-group differences in other RSNs are provided in *SI Appendix*, Figs. S2 and S3. Fig. 2 summarizes the MDD network model estimated relative to healthy controls in a plot that we call a connectivity analysis of network dysfunction (CANDY) plot. The CANDY plot simultaneously displays abnormalities in patterns of within- and between-network connectivity. In our study, these abnormalities included three task-positive RSNs (FPN, DAN, and CON), two intrinsic networks (DMN and SAN), and three sensory networks (SMN, VIS, and AUD).

Correlation Patterns of Network Connectivity with MDD Symptoms. Next, we performed CCA to link brain network connectivity measures with 213 item-level clinical survey responses in patients with MDD. To reduce the dimension of the clinical data, we derived four clinical summary variables using K-means clustering of the 213 item-level clinical data (details are provided in *Materials and*

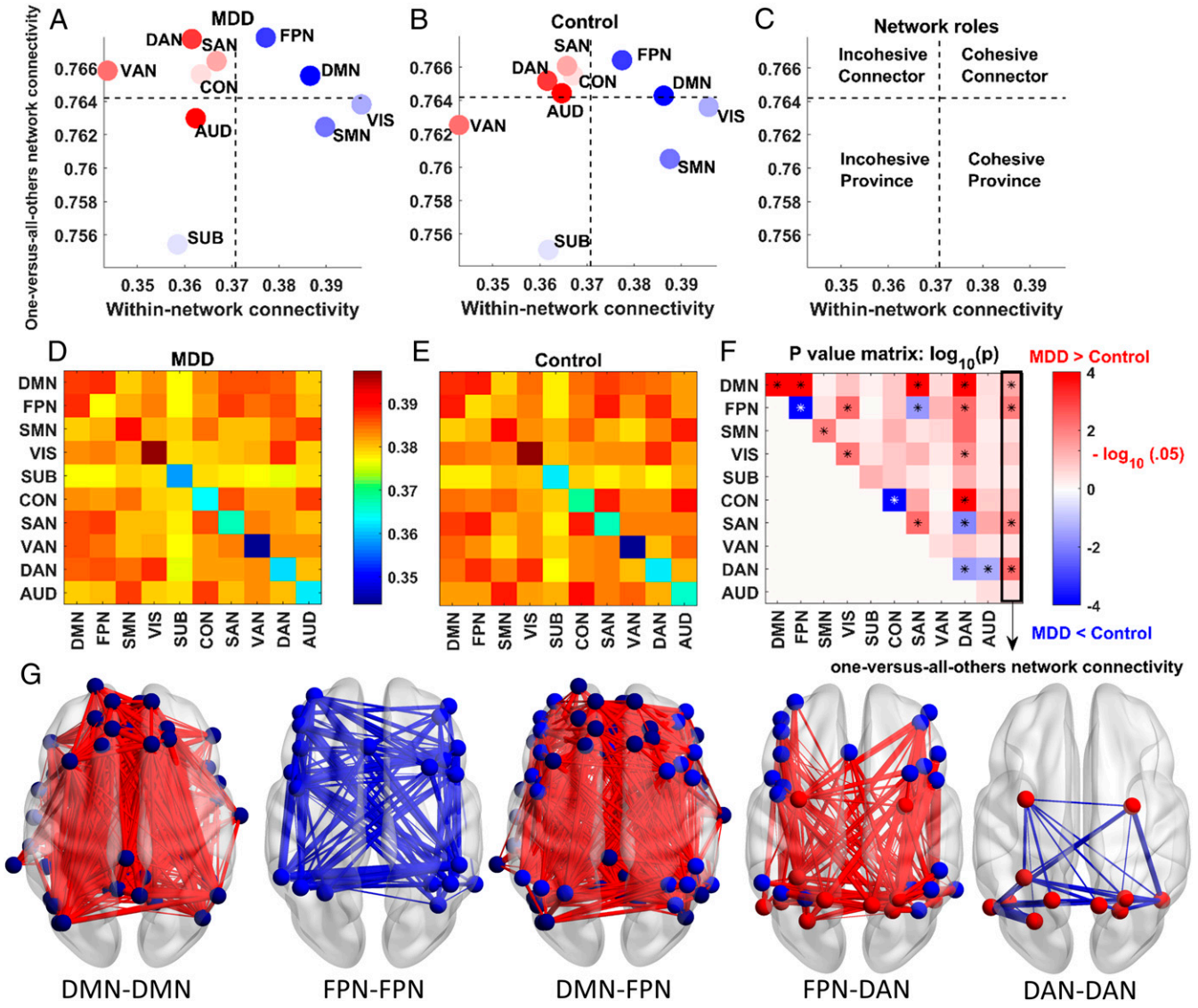

Fig. 1. Network roles (*C*) in brain networks of patients with MDD (*A*) and controls (*B*); within- and pairwise between-network connectivity matrices of patients with MDD (*D*) and controls (*E*); *P* value matrix of group differences in within-, one-versus-all-others-, and pairwise between-network connectivity (*F*); and cortical surface representation of the links that demonstrated significant between-group differences in several selected within- and between-network connectivity (*G*; corresponding results of other within- and between-network connectivity are provided in *SI Appendix*, Figs. S2 and S3) are illustrated. Note that the colors of the nodes in *G* correspond to those in *A*. The red and blue elements in *F* and the links in *G* represent MDD > control and MDD < control, respectively.

Methods). The four clinical summary variables included the following: (*i*) anxious misery (including symptoms of depression, anhedonia, anxiety, neuroticism, and suicidality), (*ii*) positive traits (extraversion, openness, agreeableness, conscientiousness, and positive mood), (*iii*) physical and emotional neglect or abuse, and (*iv*) sexual abuse. Only the first pair of CCA modes was significantly correlated [Fig. 3*C*; canonical correlation: $r = 0.68$, $P = 0.005$ (permutation test), $P = 0.03$ (χ^2 statistic)]. In an effort to understand the composition of the first clinical CCA mode, we tested for univariate correlations with each of the four clinical summary variables. We found that the first clinical CCA mode was highly correlated with physical and emotional neglect or abuse scores ($r = -0.98$, $P < 0.0001$) and moderately correlated with anxious misery ($r = -0.41$, $P < 0.0001$), positive traits ($r = 0.34$, $P < 0.0001$), and sexual abuse ($r = -0.31$, $P < 0.0001$) scores (Fig. 3*A*). Patients with MDD and controls presented with significantly different childhood trauma experiences, including physical abuse ($P = 0.002$), physical neglect ($P < 0.0001$), emotional abuse ($P < 0.0001$), emotional neglect ($P < 0.0001$), and sexual abuse ($P = 0.0015$). All *P* values were false discovery rate (FDR)-corrected (more details are provided in *SI Appendix*, Fig. S7). As shown in Fig. 3*B*, the first network CCA mode was significantly associated with seven of the 55 original network variables, including within-network connectivity in the DAN and SUB, as well as between-network connectivity of the following network pairs: DAN-SMN, DAN-VAN, FPN-DAN, CON-AUD, and CON-VIS (Fig. 3*B*). We refer to these networks as CCA mode-related networks.

Heterogeneity Analyses by Sex and Age. The aforementioned network and CCA analyses were performed on individual data features that were orthogonal to age and sex, since we residualized the network variables with respect to age, sex, and motion and residualized the clinical variables with respect to age and sex (details are provided in *Materials and Methods*). Although we found that the results were similar whether or not age and sex were regressed out before performing the CCA (*SI*

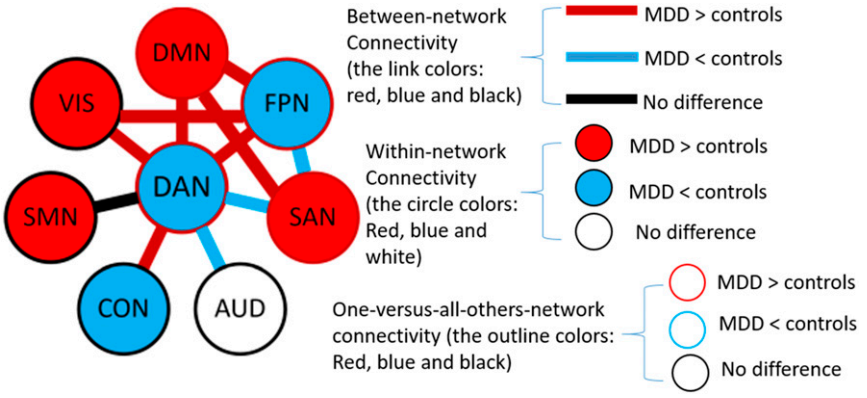

Fig. 2. CANDY plot displaying a network model of MDD. The brain networks of patients with MDD differed significantly from those of healthy controls in the DAN, FPN, DMN, SAN, CON, VIS, SMN, and AUD. Patients with MDD were characterized by within-network connectivity that was abnormally increased (MDD > controls; light red node) or decreased (MDD < controls; blue node) and between-network connectivity that was abnormally increased (MDD > controls; dark red link between nodes) or decreased (MDD < controls; blue link between nodes). A white node represents a nonsignificant difference in within-network connectivity between patients with MDD and controls. A black link represents a nonsignificant difference in between-network connectivity between patients with MDD and controls. The colors of the circles that outline each node represent differences in connectivity between that node and all of the other networks: dark red (MDD > controls) and black (no difference).

Appendix, Figs. S10 and S14), it is possible that multivariate effects of age and sex persist in both analyses. Importantly, estimation of a single multivariate correlation pattern using CCA conceals potential heterogeneity related to age and sex. Furthermore, females and males had significantly different childhood experiences, particularly with respect to sexual abuse (*SI Appendix*, Fig. S13). We thus sought to explore the multivariate relationships between network and clinical variables in females and males, as well as in younger and older participants, separately. These post hoc analyses were generally consistent subject to the limitations of small sample size (details are provided in *SI Appendix*, *CCA Analysis*).

Post hoc Correlation with Clinical Symptom Subsets. Our analysis detected a single significant CCA mode that correlated patterns of brain network connectivity with patterns of clinical symptoms derived from data-driven clusters of item-level data. However, the clinical clusters obtained from K-means clustering contained more specific information on multidimensional symptoms of MDD that is important for understanding heterogeneity of the disease. Therefore, we performed a post hoc correlation analysis to determine the direction and magnitude of associations between the first network CCA mode and subsets of symptoms (*SI Appendix*, Table S4) derived from the four clinical clusters. Specifically, we calculated Pearson's correlation between the first network CCA mode and the means of the symptom subsets (Fig. 4). We found that emotional abuse and neglect were most associated with increased network connectivity between the DAN and SMN; physical abuse and neglect were most associated with increased connectivity between the CON and VIS, as well as between the DAN and VAN (Fig. 4*A*). Within the anxious misery cluster (Fig. 4*B*), there were subsets of symptoms (depression, anhedonia, suicidality, neuroticism, and anxiety) all with primarily negative correlations with specific networks. Neuroticism was most associated with decreased connectivity within the subcortical structures (SUB). Anhedonia was associated with increased connectivity between the DAN and VAN, as well as between the DAN and SMN. Depression, anxiety, and suicidality were negatively associated with network connectivity between the DAN and FPN. In the positive trait cluster (Fig. 4*C*), positive mood and extraversion were both associated with increased within-SUB connectivity. Agreeableness and conscientiousness were most (negatively) correlated with network connectivity between the CON and VIS and between the CON and AUD, respectively. Openness was most associated with decreased connectivity between the DAN and VAN. The majority of the item-level sexual abuse questions were most associated with increased within-DAN connectivity (Fig. 4*D*).

Discussion

Symptom-Specific Changes of Within- and Between-Network Connectivity in MDD. This data-driven study shows symptom-specific, system-level alterations of brain network connectivity in major depression. Our main findings are reflected in both network measures correlated with symptom clusters and connectivity abnormalities relative to controls. Previous studies that used the same subjects have found that several symptoms of major depression, such as anhedonia (27) (using task-fMRI data), anxiety (using clinical data) (28), and neuroticism (using EEG data) (29), were related to neural function and behavioral phenotyping in patients with MDD. However, these studies did not examine resting-state fMRI data and did not examine a full spectrum of data-driven behavioral brain network architectures. Several previous studies that examined brain network attributes have shown associations with depression and anxiety symptoms measured by various summary clinical scores (11, 13, 21, 30). Our study, however, investigates multivariate network-related associations with item-level data that characterize a broad range of dimensional symptoms: experiences of childhood trauma, depression, anxiety, anhedonia, neuroticism, suicidal tendency, and personality traits. Notably, we found that experiences of childhood trauma [not reported previously in association with brain networks in depression (5, 19)] had by far the strongest association among these patient symptom–brain network correlations. Traumatic experiences were correlated with within-network connectivity of the DAN and subcortical regions (SUB) and with between-network connectivity involving task-positive networks (DAN, FPN, and CON) and sensory systems (SMN, VIS, and AUD).

With estimates of ∼10% of all children in the United States having been subjected to child abuse, the significance of child maltreatment on brain morphology and function is an important consideration (31). The population attributable risk of adverse childhood experiences (ACEs) accounts for 67% of suicide attempts (32), and exposure to six or more ACEs was found to account for a 20-y reduction in lifespan (33). SMN connectivity with the DAN and VIS connectivity with the CON were especially indicative of emotional abuse/neglect and physical abuse/neglect,

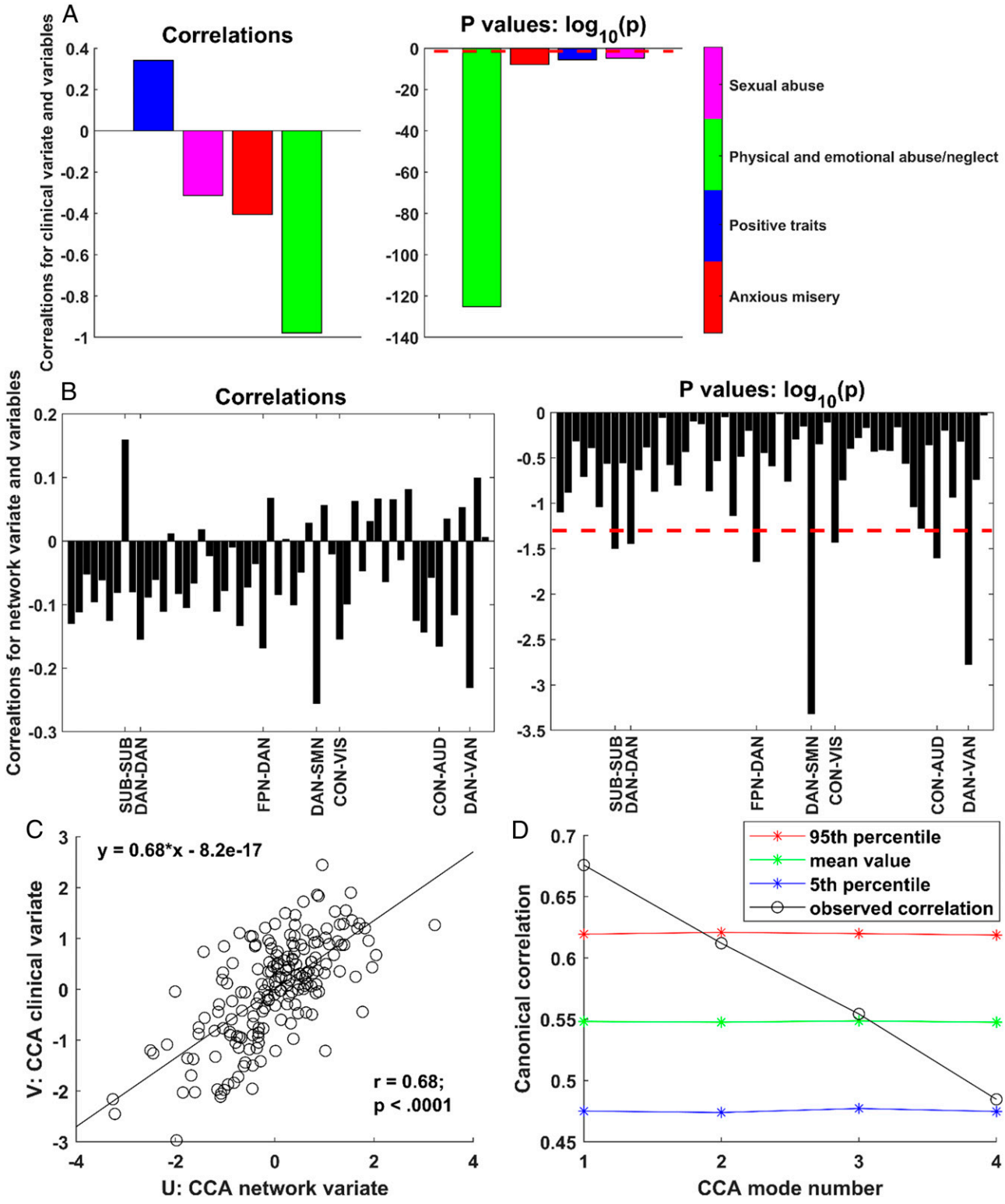

Fig. 3. Correlations and their significance between the following: the means of the four clusters of item-level variables and the first clinical CCA mode (*A*), within- and pairwise between-network variables and the first network CCA mode (*B*), and the first pair of CCA modes (*C*). (*D*) Observed CCA correlations, the mean, and the fifth to 95th percentiles of the null distribution of the permuted CCA correlations estimated via permutation testing across the four CCA modes. Note that the *P* values in *A* and *B*, but not *C*, have been $\log_{10}$-transformed. (*B*, *Right*) Note that the red dashed lines represent a $\log_{10}$-transformed *P* value of 0.05: $\log_{10}0.05 \approx -1.301$. U and V represent the CCA variates derived from the network and clinical variables, respectively; for details, see *SI Appendix, CCA Analysis*.

respectively. These systems have been related to treatment outcomes in affective disorders, risk, and family history of depression (34), and to functional domains, including error monitoring and top-down attentional control (35). We speculate that physical abuse/neglect and emotional abuse/neglect may have induced abnormal activation of sensory systems, such as the sensorimotor

Fig. 4. Radar plots showing patterns of association of network connectivity to subsets of physical and emotional abuse and neglect (*A*), anxious misery (*B*), positive traits (*C*), and sexual abuse (*D*). The values displayed by the dots in the radar plots are the absolute values of Pearson's correlation coefficients, negative coefficients are depicted by black nodes, and a table of the values is provided in *SI Appendix*, Table S5. ctq, child trauma questionnaire.

and visual cortex, and to have dysregulated connectivity with ventral and dorsal attention systems. Specifically, the increased DAN-SMN correlation with emotional abuse/neglect and increased CON-VIS and DAN-VAN correlations with physical abuse and neglect identified in our study can be interpreted in light of the role of the DAN in regulation of perceptual attention (36). How this alteration in connections occurs is not clear, but one hypothesis is that it might involve early developmental changes that are then impacted by experience. For example, the interhemispheric coherence within the DMN is already strong by the age of 6 y, but anterior-posterior coherence between the medial prefrontal cortex and parietal regions is relatively weak at this stage compared with future stages (37), suggesting an important experiential aspect in sculpting the DMN. Analogously, interhemispheric connectivity within the dorsal attention system may develop early, but anterior-posterior coherence may receive important experiential influences (e.g., ACEs), disrupting connectivity. This network sculpting may be affected by early-life stressors and trauma, which have been shown to predispose individuals to the development of depression (38), potentially through factors acting on neuroplasticity and connectivity (39). Another study (40) also found that childhood emotional maltreatment was associated with abnormal SUB and SAN connectivity.

Our findings regarding childhood trauma-related functional network abnormalities in MDD could also be interpreted alternatively. Both experimental (41, 42) and modeling (43) studies have demonstrated that functional networks are shaped by the underlying structural networks. Of note, previous studies have shown that patients who experienced repeated episodes of trauma had alterations in gray matter volumes and structural integrity of sensory systems (44–46). Thus, it is plausible that resting-state functional connectivity with sensory systems could be disrupted as sequelae of childhood maltreatment, as found in our study. A comprehensive review of the structural and functional consequences of childhood maltreatment (47) identified over 180 studies with findings of associated brain abnormalities, frequently manifested as structural abnormalities in subcortical regions. In the current study, we found that childhood trauma-related network connectivity abnormalities were preserved and

detected even well into adulthood. Therefore, our current study not only confirmed the important relationship between childhood trauma and major depression but also linked patients' experiences of childhood trauma with specific functional brain network abnormalities that suggest a possible environmental contributor to neurobiological clinical symptom profiles.

In addition, we found that depressive symptoms, personality traits, and sexual abuse were associated with subcortical and between-network connectivity involving the three task-positive networks (DAN, FPN, and CON) (48) and three sensory systems (SMN, VIS, and AUD), which is consistent with previous studies (5, 10, 49) and supports the idea that many brain network features contribute to broad clinical pathology. Several items of sexual abuse, as with physical and emotional abuse, were especially related to increased within-network DAN connectivity and network connectivity between the DAN and FPN. This system may be particularly related to regulation of perceptual attention (36, 50) with related consequences for depressed patients (51, 52), increasing negative attention bias. Neuroticism (negative correlation) and positive mood symptoms (positive correlation) were especially linked to within-SUB connectivity, which has a consistent precedent in the prior literature (53–55). As might be expected, opposite behavioral characteristics (suicidality and openness, anxiety and agreeableness) had opposite signs in their network correlations with DAN-VAN and CON-VIS, respectively. Moreover, the association between network connectivity involving the task-positive networks and sensory systems with dimensional depression symptoms and personality, such as FPN-DAN (negative correlation with depression), DAN-SMN (positive correlation with anhedonia), and CON-AUD (negative correlation with conscientiousness), further confirmed that disturbance of executive control (FPN/CON), external attention processing (DAN/VAN), and personality in patients with MDD could be characterized by abnormal information transfer between corresponding networks (10, 19, 56). Although the specific symptom and brain network domains were linked in a broad way across these measures in this cohort, the specific links between clinically relevant features and resting fMRI detailed here may guide research into additional patient populations that may share symptom and brain pathology profiles with MDD (57, 58).

Difference in Within- and Between-Network Connectivity in Patients with MDD Compared with Controls. We identified a network model of patients with MDD relative to controls that corroborates the abnormal within-network connectivity of DMN and FPN that has consistently been reported by previous experimental studies (11, 13, 14) and by a recent large meta-analysis (19). However, our study also identified less frequently reported abnormal within-network connectivity in the DAN (18), SAN (17), and CON (59). Of note, increased DMN connectivity and decreased FPN, CON, and DAN connectivity have been found in other studies to be related to higher levels of maladaptive rumination (11) and goal-oriented attention deficits in MDD (19), respectively. Overall, the interpretation of the current findings can be placed in a broader context supporting network imbalance between the task-positive (FPN, CON, and DAN) and intrinsic (DMN and SAN) networks that results in the cognitive and executive dysfunction, as well as emotional dysregulation, that characterize MDD (60).

In addition to different within-network connectivity from controls, we identified abnormal between-network connectivity. These network abnormalities occur in both task-positive and task-negative systems. Task-positive networks (i.e., the FPN, CON, DAN) are primarily involved in executive control and external attention. Our results suggest that the abnormal connectivity patterns of these networks are related to dysfunction of executive control (as reflected by decreased FPN and CON connectivity) (61, 62) and external attention (as related to decreased DAN connectivity) (63). In contrast, the DMN plays an important role in internal attention and self-referential thinking when external demands for attention are minimal (8, 16). The increased connectivity of the DMN, with its focus on internal states, could exacerbate the tendency for patients to dwell or ruminate on negative feelings and events (11, 14, 64). Moreover, the prominent role of the SAN in emotion regulation for salient events and sensory experiences might explain how the abnormal increased within-network connectivity (segregation) in the SAN could contribute to ruminative responses to negative mood states and life events in patients with MDD (65). Thus, our results provide further evidence for the integrative role of DMN and FPN in cognitive processing and for further understanding the neurocircuitry basis of major depression. In summary, we provide evidence for brain network abnormalities in patients with MDD compared with controls and for multivariate patient symptom–brain network associations that are most notably driven by experiences of childhood trauma.

Future Directions. In this study, our primary focus was on the multivariate correlation patterns between symptom profiles in major depression and brain networks. In future work, these multivariate patient symptom–brain network associations can be extended to other patient samples with depressive symptoms and other samples with a history of childhood trauma to determine whether these associations generalize. Further, CCA can be employed more generally to investigate multivariate correlation profiles in other psychiatric disorders.

Materials and Methods

The Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study consists of 200 unmedicated depressed patients with MDD and 40 healthy subjects. Several papers (27, 29, 66) have published analyses of the EMBARC task fMRI, structural MRI, and EEG data. In this study, we used the EMBARC resting-state fMRI data to study brain network differences between patients with MDD and controls and multivariate correlations between network measures and item-level clinical measures in MDD. The participants were recruited and scans were acquired at four clinical sites: Columbia University, Massachusetts General Hospital, the University of Texas Southwestern Medical Center, and the University of Michigan. Institutional review boards from the four clinical sites approved all study procedures. Participants provided written informed consent. In this study, 11 depressed patients and one healthy individual were excluded due to excessive motion (>4 mm), low slice signal-to-noise ratio (<80), and severe slice artifacts in MRI data. The final sample for comparison of network measures between groups included 189 patients with MDD and 39 healthy individuals (*SI Appendix*, Fig. S1). Resting-state fMRI images were acquired in 2 × 6-min blocks (12 min total) for each participant. Following preprocessing, the network connectivity measures of the two scans were first computed separately and then averaged; the participant-level network measures were used in the CCA analysis. Details of the network and CCA analyses are provided in the following sections. Detailed descriptions of the samples, acquisition parameters, data preprocessing (including procedures for motion correction), network and clinical measures, K-means clustering, CCA, harmonization procedures, and software used for the statistical analyses are provided in *SI Appendix*.

Functional Network Analysis. We used the atlas of Power et al. (25) to partition the brain of each participant into 264 cortical and subcortical areas. Wavelet coherence (26, 67) was used to estimate the functional connectivity between all pairs of regions of interest for both patients with MDD and controls. The functional connectivity matrices were corrected for site effects using the ComBat harmonization approach (66, 68). Subsequently, network connectivity was calculated within 10 RSNs defined by previous fMRI studies (25, 48). We also calculated network connectivity between all pairs of the 10 RSNs, as well as between each RSN and all other RSNs (one-versus-all-others).

Group Comparisons of Demographic Characteristics and Network Metrics. Statistical comparisons of demographic characteristics and network metrics between patients with MDD and controls were performed using a significance level of $P < 0.05$ for all tests. Age and educational level were compared using two-sample, two-tailed t tests. Differences in the distribution of sex between the two groups was assessed using a χ^2 test. A detailed description of the study participants is provided in *SI Appendix*. Before computing the

network metrics, the resting-state time series data from each participant were processed using the XCP Engine (69, 70), which uses an optimized confound regression procedure to reduce the influence of subject motion (71, 72). In particular, the XCP Engine can substantially eliminate potential distance-dependent motion artifacts in fMRI network connectivity measurements. A detailed description of motion correction procedures is provided in *SI Appendix*. Each network metric (within-, one-versus-all-others-, and pairwise between-network connectivity) was compared across groups using generalized linear model (GLM) analysis adjusting for age, sex, and in-scanner motion [mean relative displacement averaged over two imaging sessions (68)] as covariates. All P values were adjusted for multiple comparisons (10 within-network metrics + 10 one-versus-all-others-network metrics + 45 pairwise between-network metrics = 65 comparisons) by controlling the FDR (73).

Clustering Analysis of Item-Level Clinical Data. Patients' clinical symptoms and history were evaluated using a total of 213 item-level variables from nine questionnaires (a detailed description of item-level clinical measures is provided in *SI Appendix*). Six of 189 patients with MDD were excluded due to missing item-level clinical data; therefore, 183 patients were used in the downstream analyses (*SI Appendix*, Fig. S1). All 213 item-level variables were residualized with respect to age and sex using GLMs before performing subsequent analyses.

We used K-means clustering (74) to group the 213 item-level variables into homogeneous variable subgroups. Critically, the Childhood Trauma Questionnaire (CTQ) (75) measures childhood experiences of trauma, whereas the other clinical items characterize patients' current clinical symptoms. In light of this inherent dichotomization, we applied K-means clustering separately to the item-level CTQ scores and the remaining item-level clinical items. Details about our implementation of K-means are provided in *SI Appendix*. K-means clustering of CTQ scores resulted in two clusters: (*i*) sexual abuse (five items) and (*ii*) physical and emotional abuse and neglect (20 items). The other clinical measures were also grouped into two clusters: (*i*) an anxious misery cluster consisting of 13 Hamilton Depression Rating Scale (HAMD), 14 Smith–Hamilton Pleasure Scale, 10 Spielberger State-Trait Anxiety Inventory (STAI), 12 NEO-Five Factor Inventory II (NEO; neuroticism), 16 Concise Health Risk Tracking Scale, 13 Concise Associated Symptoms Tracking Scale (CAST), 16 Quick Inventory for Depression Symptomatology, and 29 Mood and Anxiety Symptom Questionnaire (MASQ) items (123 items in total), and (*ii*) a cluster of positive traits consisting of 48 NEO (extraversion, openness, agreeableness, and conscientiousness), 10 STAI, 2 HAMD, 4 CAST, and 1 MASQ items (65 items in total). Each item's description (i.e., from the questionnaires) and cluster assignment are provided in *SI Appendix*, Table S3. To investigate the sensitivity of the results to our clustering approach, we also applied a single K-means clustering to all of the item-level clinical measures together, which resulted in four similar (Rand index = 0.73) (76) clinical clusters (*SI Appendix*, Fig. S8 and Table S3).

CCA Analysis. We used CCA to link clinical data and RSN connectivity in patients with MDD. One set of variables included within- and pairwise between-network connectivity, individually residualized with respect to age, sex, and in-scanner motion using linear models (a detailed description of motion correction procedures is provided in *SI Appendix*). The other set consisted of each patient's four mean values that resulted from averaging over the item-level variables that made up each of the four clinical clusters. Before performing the CCA analysis, both sets of variables were standardized using a z-score transformation to make the scale comparable across all variables. A schematic illustration of the CCA analysis is provided in *SI Appendix*, Fig. S5, with technical details given in *SI Appendix*. The CCA provided a set of modes that maximally correlated the network variables and clinical cluster summaries. For each CCA mode, we used a permutation testing procedure to test the significance of the corresponding canonical correlation (24, 77), details of which are provided in *SI Appendix*. The P values for the correlation of each CCA mode pair were explicitly corrected for multiple testing across all CCA mode pairs estimated [i.e., against the maximum correlation value (24)]. More strictly, Bartlett's χ^2 statistic (78, 79) was performed to assess the significance of the full multivariate distribution. A CCA mode pair was considered to be significantly correlated only if both tests rejected the null hypothesis of no association at the level of $P < 0.05$. Given a significant CCA mode, we next assessed Pearson's correlation between the CCA mode and the corresponding set of original variables of which it consisted. More specifically, we correlated the multivariate projection of the network variables with the original, univariate network variables, and, similarly, we correlated the multivariate projection of the clinical cluster summaries with the individual clinical cluster summaries. These tests helped quantify the strength of contribution of the individual network and clinical cluster summaries to the corresponding CCA mode(s). To test that our CCA analysis was not driven by separating CTQ measures from other clinical measures in the K-means clustering analysis approach, we repeated the CCA using the clusters from a single K-means clustering analysis applied to all of the clinical measures together (*SI Appendix*, Table S3); the results of the two CCA analyses were comparable (Fig. 3 and *SI Appendix*, Fig. S9).

Next, we further divided each clinical cluster of items into more symptom-specific groups of item-level data to better characterize the multidimensional nature of MDD symptoms (details are provided in *SI Appendix*, Table S4). For example, the anxious misery cluster was subdivided into five subsets of depressive symptoms, including depression, anhedonia, anxiety, neuroticism, and suicidality. Similarly, the positive traits cluster was subdivided into extraversion, openness, agreeableness, conscientiousness, and positive mood. For each symptom subset, we computed Pearson's correlation between the mean of the item-level data in the subset and the first brain network CCA mode. Finally, the correlation coefficients were visualized using the radar plots in Fig. 4. For the sexual abuse cluster, we note that this post hoc correlation analysis was performed using the five individual items.

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