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Functional Connectivity Between Extrastriate Body Area and Default Mode Network Predicts Depersonalization Symptoms in Major Depression: Findings From an A Priori Specified Multinetwork Comparison

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ABSTRACT

BACKGROUND: Depersonalization/derealization disorder is a dissociative disorder characterized by feelings of unreality and detachment from the self and surroundings. Depersonalization/derealization disorder is classified as a primary disorder, but depersonalization symptoms are frequently observed in mood and anxiety disorders. In the context of major depressive disorder (MDD), depersonalization symptoms are associated with greater depressive severity as indexed by treatment resistance, inpatient visits, and duration of depressive episodes. In the current investigation, we tested four network-based, neural-functional hypotheses of depersonalization in MDD. These hypotheses were framed in terms of functional relationships between 1) extrastriate body area and default mode network (DMN); 2) hippocampus and DMN; 3) medial prefrontal cortex and ventral striatum; and 4) posterior and anterior insular cortex.

METHODS: We conducted functional magnetic resonance imaging during resting state on 28 female patients with MDD and 27 control subjects with no history of a psychiatric disorder. Functional connectivity between seed and target regions as specified by our network-level hypotheses was computed and correlated with scores on the Cambridge Depersonalization Scale. We used a conservative, unbiased bootstrapping procedure to test the significance of neural-behavioral correlations observed under each of the four models tested.

RESULTS: Of the four neural-functional models of depersonalization symptoms tested, only the model proposing that reduced connectivity between the extrastriate body area and DMN predicts higher levels of depersonalization symptoms in MDD was confirmed.

CONCLUSIONS: Our results indicate that depersonalization/derealization disorder symptoms in patients with depression are related to reduced functional connectivity between brain regions that are proposed to support processing of body-related (extrastriate body area) and autobiographical (DMN) information.

Keywords: Default mode network, Depersonalization/derealization disorder, Extrastriate body area, Functional connectivity, Major depressive disorder

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Depersonalization/derealization disorder (DPD) is a dissociative disorder characterized by a persistent and distressing sense of detachment from thoughts, feelings, bodily experiences, and the external world. Whereas DPD is a primary disorder (1) that can occur in the absence of other psychiatric illness, depersonalization symptoms (DPSs) also frequently occur as a comorbidity of mood and anxiety disorders at both clinically significant and subclinically elevated levels (2). Depersonalization additionally occurs with advancing severity of affective disorders (3–5); the comorbidity of DPD with major depressive disorder (MDD) is higher among inpatient than outpatient samples (4,6) and predicts heightened treatment resistance (7,8) and a longer duration of depressive episodes (9).

A small but consistent body of research exists on the neural underpinnings of primary and secondary depersonalization. Early work applying electrophysiological stimulation to identify loci of seizures indicated that functional abnormalities in the temporal lobes could undergird DPD (10). This formulation was subsequently supported by comparing regional glucose metabolism in the brain in DPD versus healthy samples (11). Furthermore, abnormalities in both gray matter and white matter in the temporal lobes have been identified in DPD (12,13). Augmenting these correlational findings, studies experimentally modulating temporal lobe activity by applying repetitive transcranial magnetic stimulation have shown small but consistent effects on DPSs (14–16).

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Extant work on neural accounts of DPD has largely applied a univariate, single-structure model. The dissociative aspects, however, are most readily construed in terms of alterations in functional connectivity between neural ensembles, and such accounts of depersonalization have been proposed (17,18). A frontolimbic inhibition hypothesis (17) suggests that hyperactivation of prefrontal regions implicated in emotion regulation results in a hypoactivation of limbic areas in DPD. Task-based functional magnetic resonance imaging (fMRI) studies examining neural responses to affective stimuli have provided tentative support for this model (19–22). However, a model that specifies such interregional interactions can be assessed effectively only by examining interactions in regional brain activity and relating them to DPD symptoms. Few studies have employed functional connectivity approaches in the investigation of DPSs. One study found longitudinal changes in connectivity of the extrastriate body area (EBA) with the rest of the primary visual network in adolescent subjects who chronically experienced dissociative states relative to subjects who did not (23). Another study identified abnormal functional connectivity between the periaqueductal gray and temporoparietal junction in patients with dissociative-subtype posttraumatic stress disorder relative to healthy control subjects and patients with nondissociative posttraumatic stress disorder (24).

As results from myriad task-based functional neuroimaging studies have begun to cohere and stabilize into a functional map of the brain (25), we have a stronger, empirically based vantage point for developing neural-connectivity hypotheses of depersonalization. The phenomenology of DPSs suggests alterations at one or more psychological levels, potentially in parallel. The levels most strongly implicated include emotional valence, autobiographical memory, and bodily representation. With this in mind, we have formulated and tested four independent, nonexclusive neural-connectivity models of DPD symptoms in patients with MDD to better understand depersonalization symptoms secondary to MDD (hereafter abbreviated as DPSs in MDD). We briefly present each of these hypotheses below.

Reduced Functional Connectivity Between the EBA and the Default Mode Network

DPSs can be conceptualized as alterations in the integration of representations of the physical body into a sense of self, a process also referred to as embodiment (26). One region strongly implicated in bodily representation is the EBA, which responds to imagined and perceived body movements in addition to body-related information presented across sensory modalities (27). Current accounts of embodiment propose that processes supported by the EBA are integrated with information from sensory modalities into a representation of the self by the default mode network (DMN) (28), leading to an understanding of the self in the internal and external context. The EBA has been implicated in autoscopic hallucinations, the duplication of one's own body in extrapersonal space (29), which corresponds to experiences described by patients with DPD. Patients with MDD often report a dissociation between their physical body and their sense of self, describing their body as an obstacle, rather than as belonging to the self (30). Reduced integration of information about the physical body with the self could lead to these symptoms as well as DPSs in MDD. Alterations in DMN functionality have been proposed in both MDD (31,32) and DPD (23,31–33), and the EBA has been implicated in DPSs (23), but DMN-EBA functional connectivity has, to our knowledge, not been tested. We propose in the EBA-DMN model, therefore, that increasing DPSs in MDD are associated with decreasing EBA-DMN connectivity.

Reduced Functional Connectivity Between the Hippocampus and Primary Nodes of the DMN

Patients with DPD often report disturbances in their ability to recognize themselves and their surroundings (34), which could be due to a partial failure of recognition memory. To recognize an externally or internally generated stimulus as similar to one previously encountered, currently available and previously encountered stimuli must be compared and determined to be familiar or unfamiliar (35,36). The DMN is thought to be critical for this process (35,36). Posterior regions of the DMN, especially the hippocampus (HC), play a key role in the recognition of similarities between past and current stimuli and contexts (37,38), whereas anterior regions of the DMN are hypothesized to evaluate stimuli from an egocentric reference frame (37). Variability in the strength of functional connectivity between the HC and other regions of the DMN might therefore undergird variability in feelings of familiarity as conceptualized as the integration of previously encoded contexts and episodes with representations of the self.

Reduced functional connectivity between the HC and other nodes of the DMN has been observed in MDD (39,40) and could account for a partial failure in recognizing previously encountered stimuli, which might undergird elevated DPSs in MDD. Based on the role of the DMN in recognition memory, the disruption of recognition memory processes in MDD, and evidence for altered connectivity within the DMN in DPD (23), a HC-DMN model formulates that functional connectivity between these regions is reduced with advancing severity of DPS in MDD.

Reduced Functional Connectivity Between the Medial Prefrontal Cortex and Ventral Striatum

Depersonalization is characterized by deficits in affective valuation of stimuli (41), which might lead to feelings of emotional distancing or numbness. Valuation of stimuli is thought to be subserved by interactions between medial prefrontal cortex (mPFC) and ventral striatum (VS) (42). Specifically, it has been proposed that the VS codes for the prediction error associated with a potentially rewarding or aversive stimulus (43,44), and the mPFC translates this evaluation into a self-relational reference frame (45). Decreased connectivity between the VS and mPFC could therefore be associated with impaired assignment of hedonic tone to stimuli.

In a psychiatric context, patients with MDD consistently demonstrate decreased valuation of rewarding stimuli (42), and mPFC dysfunction has been implicated in DPD (46). Reductions in functional connectivity of mPFC and VS could, furthermore, manifest as emotional numbing and detachment in promoting DPSs in MDD. Thus, an mPFC-VS model posits

that as connectivity between these regions decreases, DPSs in MDD will increase.

Reduced Functional Connectivity Along the Posterior-Anterior Insular Gradient

Some aspects of DPD and DPSs can be conceptualized as impairments in interoceptive processing, particularly in achieving conscious representations of internal bodily states. Patients with DPD have shown poor performance on a heartbeat detection task, indexing interoceptive sensitivity (47). Ascending spinothalamic tracts convey information from the body (48) to insular cortex (IC). Interoceptive processing and representation is thought to follow along a posterior-to-anterior insular gradient (48). Basic and fundamental representations of homeostatic processes are postulated to be formed in the posterior IC (49). The mid-IC is thought to complement these fundamental representations with information about the emotional salience of bodily stimuli (50). Finally, the anterior IC connects information from posterior and mid-IC with higher cognitive processes (49,51), leading to a conscious representation of bodily states.

Diminished interoceptive awareness has been observed in MDD (52,53), and functional abnormalities in both the posterior and anterior IC have been found in DPD (21,54,55). As interoceptive awareness is thought to result from the transmission of somatic information along the posterior-to-anterior IC gradient, we hypothesized in a posterior-to-anterior IC model that DPSs in MDD would increase with diminishing functional connectivity along this gradient.

Summary

In the present investigation, we tested and compared results from four neural-functional hypotheses of DPSs in MDD—namely, that reduced functional connectivity between 1) EBA-DMN, 2) HC-DMN, 3) mPFC-VS, or 4) posterior-to-anterior IC could account for increased DPSs in MDD. To test these neural hypotheses, we used fMRI data collected during the resting state (rsfMRI) to estimate levels of interregional functional connectivity and correlated these functional connectivity measures against clinical self-report measures of depersonalization.

METHODS AND MATERIALS

Participants

Study participants were recruited through advertisement at local outpatient treatment facilities and included 28 female patients (mean [SD] age = 37.04 [11.00] years) meeting DSM-IV criteria (56) for current, primary MDD and 27 demographically matched female healthy control subjects (mean [SD] age = 34.7 [12.48] years). All participants were assessed clinically by a trained interviewer with the Structured Clinical Interview for DSM-IV Axis I disorders (57). Exclusion criteria were standard MRI scanning contraindications (e.g., implanted ferrous metal, pregnancy, claustrophobia). Participants had to be free of all psychotropic medications in the 4 weeks before scanning. Additionally, the presence of another Axis I psychopathology (other than an anxiety disorder); of active suicidal ideation, intent, or behavior; or of psychosis to the extent that the participant was unable to provide informed consent led to exclusion from the MDD group. For healthy control subjects, personal or first-degree family history of any DSM Axis I disorder led to exclusion. In addition, individuals with a history of drug abuse or head trauma, medical conditions that could influence cerebral blood flow, or special education needs were excluded. The study was approved by the ethical committee of the Western Institutional Review Board (www.wirb.com), and all participants gave written consent to the scientific use of their data.

Eight participants with MDD were excluded from the analysis: 3 for not finishing the study, 4 owing to excessive movement during the rsfMRI scan (>0.2 mm per acquisition for 25% or more of the functional acquisitions), and 1 for being an outlier with respect to DPD severity (>2 SD from mean). From the control group, 4 participants were excluded owing to excessive movement during the scan. Thus, 20 patients with MDD and 23 healthy control subjects provided data for the findings presented.

Analysis Overview

Typically, neural-behavioral correlation analysis in psychiatry starts by identifying abnormalities in functional connectivity in patients relative to healthy control subjects and then correlating, in each group, functional connectivity from the abnormally connected region or regions to some behavioral index. Given that healthy individuals most often do not endorse any DPSs, we assessed neural-behavioral correlations only in the MDD sample for the current study. In follow-up analyses, we asked if networks showing significant neural-behavioral correlations in MDD showed evidence of abnormal connectivity relative to healthy control subjects. Importantly, this process also underscores recent recognition that associations between neural functioning and symptoms in psychiatric samples are of both theoretical (31) and therapeutic (58) significance, without reference to deviation from normal neural functioning.

Questionnaires

This study was part of a larger study for which scores on a variety of questionnaires and tasks were collected. For the present study, only scores on the Beck Depression Inventory-II (BDI-II) (59), Beck Anxiety Inventory (BAI) (60), and Cambridge Depersonalization Scale (CDS) (61) were used. The CDS is a 29-item, self-report inventory assessing DPSs over the past 6 months. For each symptom assessed, two Likert scales query frequency (range: 0 [never] to 4 [all the time]) and duration (range: 1 [a few seconds] to 6 [more than a week]). Given that our intention was to assess DPSs over a short time interval in temporal proximity to MRI scanning, we asked about the frequency but not the duration of symptoms during the previous week, which overlapped with the MRI scanning session.

The CDS is a well-validated and well-explored instrument. We sought first to understand and optimize its factor structure with respect to our sample. Several exploratory factor analyses have revealed that the CDS comprises a number of distinct dimensions [e.g. (62–64)]. In the present study, we divided the CDS into the four factors determined by Fagioli *et al.* (62): detachment from self, anomalous bodily experiences, numbing, and temporal blunting. We excluded from further

consideration 1) the anomalous bodily experiences factor owing to its high skewedness toward zero and 2) all items that loaded on more than one factor, leading to the exclusion of seven CDS items. High correlations between these subscales (r = .70–.86) suggested a strong central theme in our sample. We therefore computed the first principal component of the subscales (using the pca function in MATLAB [The MathWorks, Inc., Natick, MA; www.mathworks.com]) accounting for 98% of the variance. Given this, we projected our data onto this dimension and included for further analysis only the first principal component as a representation of the central CDS construct (referred to hereafter as CDS_{core}). In addition, using SPSS Version 24.0 software (IBM Corporation, Armonk, NY), we examined the correlation of CDS_{core} with severity of depression (as assessed with the BDI-II) and anxiety (as assessed with the BAI) to determine whether to account for any associations between these measures in our neural-behavioral correlation analysis. As there were no significant correlations between CDS_{core} and BDI-II or BAI (both $p > .15$, two-tailed), we did not include either of these measures in the neural-behavioral regression. Results from control analyses that 1) used the CDS total score as opposed to CDS_{core}, 2) applied BDI-II scores as a covariate in the correlation analyses between CDS_{core} and functional connectivity indices, and 3) tested if other components of depressive psychopathology (i.e., anhedonia) were accounted for by our functional connectivity indices are presented in the Supplement.

Resting-State fMRI

Acquisition parameters and preprocessing steps of rsfMRI are described in the Supplement.

Functional Connectivity Analysis. Seed and target regions used in our analysis are depicted in Figure 1. Eight separate 5-mm-radius seed regions were defined within EBA, HC, mPFC, and posterior IC as determined by the senior author (JPH). Coordinates for the seed regions within these larger regions were determined by locating peak regions of reverse-inference–based meta-analytic associations with the search terms body, recognition memory, value, and interoceptive in the Neurosynth meta-analytic database (25). The seed regions used overlaid on the meta-analytic maps identified from Neurosynth using its default threshold are displayed in Supplemental Figures S1–S4. Target regions were the DMN, VS, and anterior IC; target masks were defined based on previous empirical work [DMN (65), VS (66), anterior IC (67)]. Voxelwise (i.e., preserving voxel-level information in the target region by not averaging across target-region voxels) seed-to-target region functional connectivity analysis was conducted

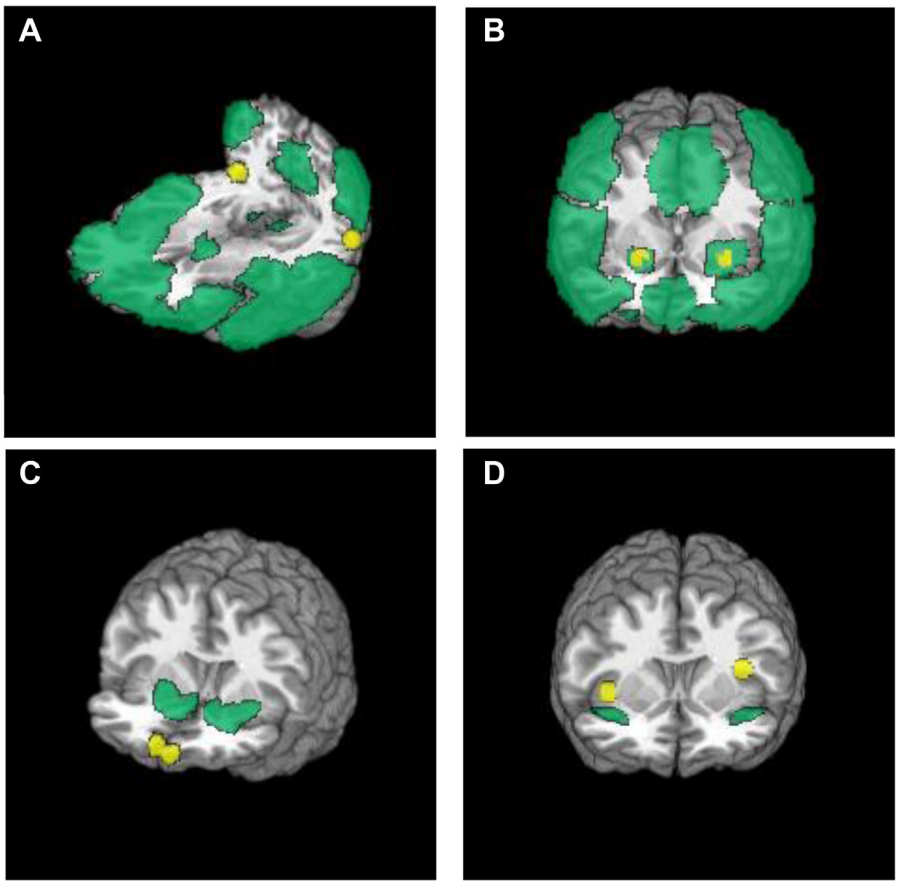

Figure 1. Seed (yellow) and target (green) regions of the voxelwise functional connectivity analyses conducted. Regions (seeds first, followed by targets) were extrastriate body area and default mode network **(A)**, hippocampus and default mode network **(B)**, medial prefrontal cortex and striatum **(C)**, and posterior and anterior insular cortex **(D)**.

Table 1. Descriptive and Inferential Statistics for CDS, BDI-II, and BAI in Depressed and Healthy Samples

	MDD (n = 20)		Healthy Control (n = 23)		Statistic	
Questionnaire	Mean (SD)	Range	Mean (SD)	Range	t_{41}	p
CDS	18.25 (12.58)	1–42	1.39 (2.37)	0–11	9.03	<.001
BDI-II	23.6 (11.33)	6–46	0.48 (1.38)	0–6	17.77	<.001
BAI	14.8 (10.6)	1–43	1.87 (2.32)	0–9	7.17	<.001

t values are based on independent samples tests, assuming equal variances. All raw data were log-transformed for the statistical tests owing to nonnormality of distributions in the healthy control group.

BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; CDS, Cambridge Depersonalization Scale (symptom frequency over last week based on all items of CDS); MDD, major depressive disorder.

for each participant and for each seed region relative to appropriate target regions by applying AFNI to the denoised rsfMRI data.

Neurobehavioral Correlation Analysis. We computed Spearman's rank correlation rho between seed-to-target functional connectivity—as indexed by beta values—and CDS_{core} voxelwise, using each of eight functional connectivity maps: four network models of DPD in MDD, one seed per hemisphere. Next, we used a novel approach to evaluate in an unbiased way the correlation maps associated with the four network models. We developed this approach because comparing spatial maps depicting correlations is challenging given that target regions are differently sized, affecting the likelihood of observing spuriously extreme correlation values. Further complicating this endeavor, intersubject variability in seed-to-target functional connectivity can also vary as a function of brain region, with corresponding effects on neurobehavioral correlations. To address these potential biasing effects, we applied statistical bootstrapping to determine for all eight correlation maps whether the average Spearman's rho across all target-region voxels was reliably different from zero. In a secondary, partially independent approach, we applied this same bootstrapping procedure to differences in area under the curve (AUC) for the negative-minus-positive tails of the distribution (corresponding to rho values with $p < .025$).

Bootstrapping procedures provide an alternative to standard approaches to statistical inference and are used when a parametric model has not been or cannot be determined analytically (68). In the present case, we computed the average target-region rho (or, secondarily, AUC) on each of 1000 bootstrapping iterations in which the primary data (seed-to-target functional connectivity and CDS_{core}) were sampled randomly with replacement. We considered a given network model of DPD in MDD to be substantiated if 1) 95% of the resulting average rho/AUC distribution was less than zero (all models predicted negative relationships between functional connectivity and CDS_{core}), and 2) this was observed for distributions resulting from seed regions from both hemispheres.

RESULTS

Questionnaire Data

Table 1 shows descriptive statistics of the CDS total scores, BDI-II, and BAI. For comparison, data from the demographically matched healthy control sample are shown. Scores on all clinical questionnaires were significantly higher in the MDD group compared with the control group (all $p < .001$).

Correlations Between Functional Connectivity and Depersonalization Metrics

Table 2 and Figure 2 summarize our findings from bootstrapping procedures applied to neurobehavioral correlation analyses. For both EBA seed regions, we observed that decreasing EBA-DMN functional connectivity was reliably associated with increased DPSs in MDD. The distributions of mean rho and AUC metrics derived during bootstrapping permutations of EBA-DMN-connectivity-by-CDS correlation were less than zero with >95% confidence. We did not observe reliable relationships between CDS_{core} and HC-DMN, mPFC-VS, or posterior-anterior insular functional connectivity. Supplemental Table S1 and Supplemental Figure S5 present results from voxelwise exploratory analyses of the locations of DMN regions for which functional connectivity with EBA was significantly related to CDS_{core}.

Follow-up Comparison of EBA-DMN Functional Connectivity in Depressed Versus Healthy Samples

To help us determine whether EBA-DMN functional connectivity was abnormal in MDD, we compared MDD and control samples voxelwise with respect to EBA functional connectivity within our DMN mask (two-sample t test, familywise error correction at $p = .05$, each EBA seed region tested independently). We observed no significant between-group differences

Table 2. Bootstrap-Derived p Values for Mean Spearman's Rho and AUC Metrics for Each Network Model

	Left Hemisphere		Right Hemisphere	
Network Model	Mean Rho (p)	AUC (p)	Mean Rho (p)	AUC (p)
Extrastriate Body Area–Default Mode Network (Body)	.018[a]	.009[a]	.047[a]	.022[a]
Hippocampus–Default Mode Network (Recognition Memory)	.646	.582	.267	.200
Medial Prefrontal Cortex–Ventral Striatum (Value)	.271	.214	.201	.177
Posterior-Anterior Insular (Interoceptive)	.834	.833	.734	.642

AUC, area under the curve.

[a]Significant at $p < .05$, one-tailed, given a priori–specified directionality of predictions.

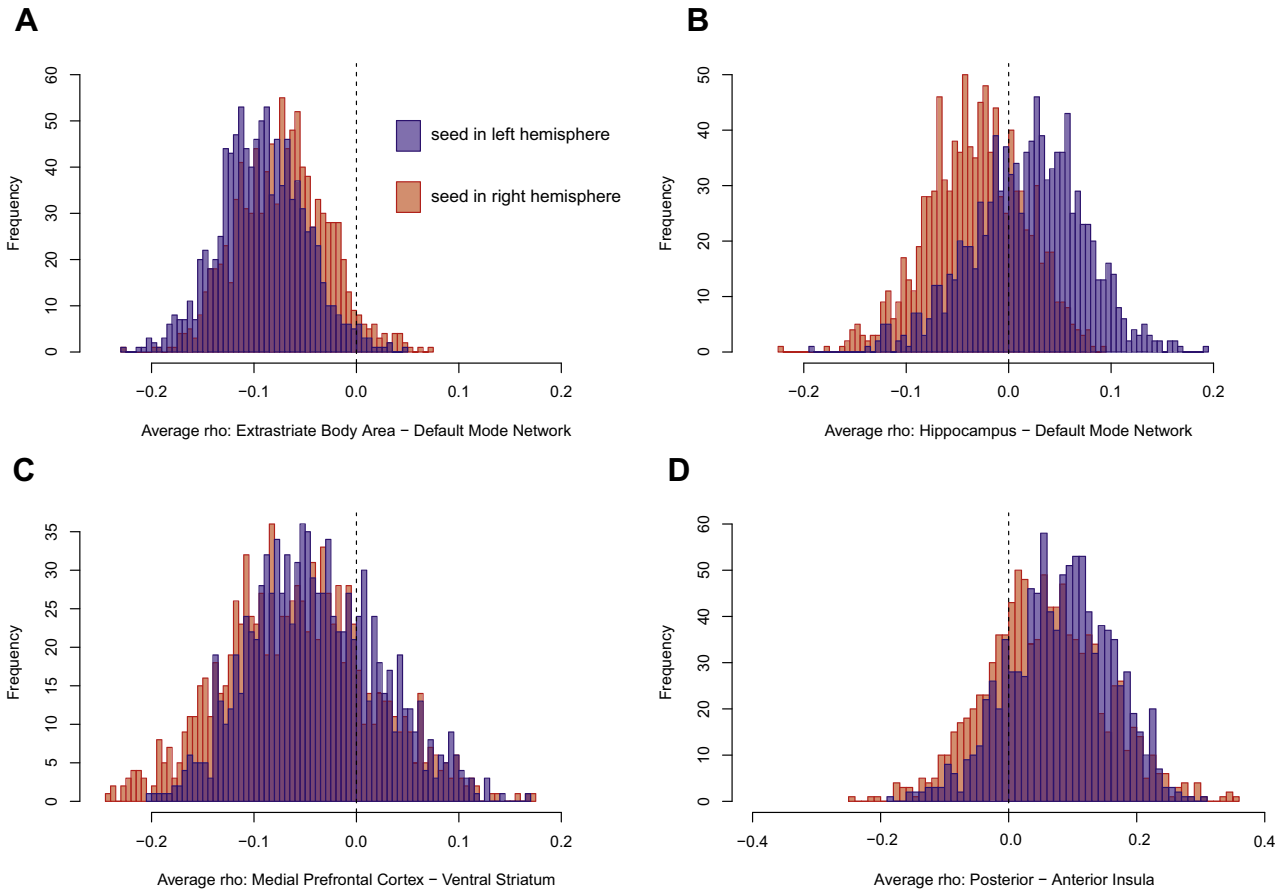

Figure 2. Histograms from 1000 bootstrap iterations computing mean within-target-region correlations between the first principal component of the Cambridge Depersonalization Scale and extrastriate body area to default mode network connectivity **(A)**, hippocampus to default mode network connectivity **(B)**, medial prefrontal cortex to ventral striatum connectivity **(C)**, and posterior to anterior insular connectivity **(D)**. Blue bars depict left hemisphere seeds, and red bars depict right hemisphere seeds.

in EBA-DMN functional connectivity. Supplemental Figure S6 depicts EBA-DMN connectivity in patient and control groups.

DISCUSSION

In the present study, we tested four neural-functional models of DPSs in depression. We found relatively strong empirical support for the EBA-DMN model, proposing that decreasing connectivity between EBA and DMN would predict increasing DPSs in patients with MDD. This significant association between EBA-DMN connectivity bilaterally and DPSs in MDD occurred in the absence of significant differences between MDD and control groups in EBA-DMN connectivity. We hypothesized that HC-DMN, mPFC-VS, and posterior-anterior IC connectivity could also predict DPSs in MDD; however, the data did not bear out any of these hypotheses. This was unexpected given that these regions have previously been implicated in primary DPD (55).

The EBA responds not only to images of human body parts (69) but also to one's own bodily movement regardless of whether the movement is actually performed or only imagined (70), suggesting that the EBA integrates information across sensory modalities. The DMN is postulated to encode information in terms of an egocentric frame of reference (36,37), generating a conscious representation of the self (71). Given that depressed and healthy groups did not differ in terms of EBA-DMN connectivity, we propose that the low end of natural variability in nonpathological EBA-DMN connectivity marks reduced integration of physical body–related information (EBA) into the sense of self (DMN), which could lead to DPSs within the context of a depressive episode. It is also possible that the kinds of information mediated by DMN-EBA connectivity change toward dissociative in the context of a depressive episode. In such a scenario, functional connectivity can remain unchanged in MDD, while still accounting for variability in DPSs. We have proposed similar hypotheses to account for relationships between DMN-to-subgenual-cingulate connectivity and ruminative tendencies in MDD (31).

To our knowledge, the present findings are the first to address the neural underpinnings of DPSs in MDD. Furthermore, these findings are the first to implicate the EBA in depression and its comorbidities. The novelty of this EBA-related finding could be attributed to the relative novelty of examining DPSs in major depression and/or that such findings have been masked by the common methodological decision to identify neural abnormalities in psychiatric samples (relative to

healthy control samples) before approaching questions about neural-behavioral correlations. Based on the current findings and previous work (31,58), we suggest that future work incorporating the same approach could be fruitful in developing neural-functional models of psychiatric disorders and their common comorbidities.

Several studies using task-based fMRI have investigated DPD as a primary or secondary disorder [for reviews see (21,55)], either with comorbid MDD symptoms (3,20,21,23,24) or with clinically significant depression explicitly eliminated (46). Although these studies employed an exploratory, task-based fMRI approach in contrast to our confirmatory, functional connectivity paradigm, it is still noteworthy that some of these studies identified neural response abnormalities in regions of the DMN (3,20,23,33). This, along with the present findings, indicates at least that DMN-mediated processes could constitute a neural mechanism of depersonalization. Neural investigations of primary DPD and DPSs have reliably implicated the temporal lobes, with a trend toward the temporoparietal junction specifically (16,24). While none of the neural-functional hypotheses tested involved the temporoparietal junction directly, this region sits adjacent to EBA (Supplemental Figure S10). This suggests that polymodal sensory integration regions could play an important role in DPSs more broadly.

Limitations and Future Directions

Owing to the relatively small sample size, effect sizes had to be high and reliable for an effect to be considered significant. It is not possible to conclude with certainty, therefore, that the unsupported hypotheses presented here would not be significant in a better powered study. Furthermore, whereas we contend in the present investigation that we are now better situated in psychiatric neuroimaging to start testing explicit, a priori–defined, neural-functional models, it is nonetheless possible that there are tenable neural models of DPSs in MDD that we have failed to specify and test in the current investigation. In addition, we intentionally omitted the duration scale of the CDS to account for symptom prevalence over a given week; including both frequency and duration scales might have captured DPD symptoms more accurately. Finally, even though commonalities between DPD and psychotic disorders have been suggested (72), we did not assess psychotic symptoms in the present study and therefore cannot draw any conclusions as to their relationship to the neural correlates of DPSs in MDD.

We undertook the current cross-sectional investigation of a priori–formulated models of DPSs in MDD because of a common occurrence of DPSs in the context of comorbidities with mood and anxiety disorders. We are eager to see if the current effects are seen in primary DPD as well as in other psychiatric disorders, such as panic disorder, that have a high DPD comorbidity. We also look forward to future work that tests and better specifies the current findings within more artificial and experimental contexts by, for example, examining effects on EBA-DMN functional connectivity of ketamine administration, which frequently evokes dissociative states (73,74). Conversely, assessing effects on DPSs in MDD by selectively disrupting EBA-DMN connectivity through transcranial magnetic stimulation applied to the EBA (which is near the cortical surface) is another route for identifying causal mechanisms within the framework supported here.

Conclusions

Despite the frequent comorbidity of DPSs and MDD, little is known about the neural-functional substrates of DPSs in depression. We formulated several a priori hypotheses of how variability in functional connectivity could account for DPSs in MDD. We found consistent support for the model specifying that reduced connectivity between the EBA and DMN predicts increasing DPSs in MDD. The results of this study could be considered a first step in developing a more mechanistic neuroscience of DPSs in MDD and more broadly.

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