Archival Report

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A Human Depression Circuit Derived From Focal Brain Lesions

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ABSTRACT

BACKGROUND: Focal brain lesions can lend insight into the causal neuroanatomical substrate of depression in the human brain. However, studies of lesion location have led to inconsistent results.

METHODS: Five independent datasets with different lesion etiologies and measures of postlesion depression were collated (N = 461). Each 3-dimensional lesion location was mapped to a common brain atlas. We used voxel lesion symptom mapping to test for associations between depression and lesion locations. Next, we computed the network of regions functionally connected to each lesion location using a large normative connectome dataset (N = 1000). We used these lesion network maps to test for associations between depression and connected brain circuits. Reproducibility was assessed using a rigorous leave-one-dataset-out validation. Finally, we tested whether lesion locations associated with depression fell within the same circuit as brain stimulation sites that were effective for improving poststroke depression.

RESULTS: Lesion locations associated with depression were highly heterogeneous, and no single brain region was consistently implicated. However, these same lesion locations mapped to a connected brain circuit, centered on the left dorsolateral prefrontal cortex. Results were robust to leave-one-dataset-out cross-validation. Finally, our depression circuit derived from brain lesions aligned with brain stimulation sites that were effective for improving poststroke depression.

CONCLUSIONS: Lesion locations associated with depression fail to map to a specific brain region but do map to a specific brain circuit. This circuit may have prognostic utility in identifying patients at risk for poststroke depression and therapeutic utility in refining brain stimulation targets.

Key Words: Depression, Functional connectivity, Functional MRI, Imaging, Lesion, Network, Stroke

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Patients with focal brain lesions can yield insight into the causal neuroanatomical substrate underlying neuropsychiatric symptoms (1,2). Several decades ago, an association between left frontal lesions and depression was reported for both stroke (3,4) and brain tumors (5,6). Subsequent work refined this association to lesions in the bilateral dorsolateral prefrontal cortex (DLPFC) (7). These lesion localization studies are important as depression is an independent predictor of morbidity and mortality poststroke (8). These lesion studies are also important for the insight they provide into the neuroanatomy underlying primary depression, including identification of treatment targets. For example, the first trials of transcranial magnetic stimulation (TMS) to the left DLPFC for treatment of primary depression were motivated partly by lesion data (9,10).

However, localization of depression based on focal brain lesions has been inconsistent. Even the early studies noted that most patients with poststroke depression had lesions outside the left frontal cortex (3,4). Work aimed at replicating this association found that it held true only for specific time points (11) or not at all (12). Multiple meta-analyses have failed to find an association between left frontal lesions and depression (13–16). Studies using newer methods such as voxel-based lesion-symptom mapping have also failed to find lesion locations significantly associated with depression (17,18).

One potential reason for these inconsistent findings is that lesions causing similar symptoms may localize to connected brain networks rather than to individual brain regions (19). Similarly, symptoms caused by focal brain lesions can arise from brain regions connected to the lesion location rather than from the lesion location itself, a phenomenon termed diaschisis (20,21). A recently validated technique called lesion network mapping can better account for these factors and incorporate them into lesion-based localization (19,22–25). This method uses lesion locations as seed regions in resting-state functional connectivity analyses, taking advantage of connectome data from large cohorts of healthy subjects. By comparing the

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functional connectivity profiles of lesions associated with a particular symptom, this method can identify brain regions or networks underlying a symptom of interest. This technique has proven useful for understanding hallucinations (19), delusions (22), criminality (26), and even disorders of free will (27).

In this study, we analyzed the association of lesion location with depression across 5 independent lesion datasets and several lesion etiologies (ischemic stroke, intracerebral hemorrhage, and penetrating traumatic brain injury) (7,17,28–30). We hypothesized that lesion location alone would not be significantly associated with depression but that resting-state functional connectivity between the lesion location and other brain regions would be.

METHODS AND MATERIALS

Subjects and Lesions

This study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center (Protocol No. 2018P000128). We performed a systematic literature search to identify lesion datasets containing depression assessments and wrote to investigators to request data (Supplemental Methods). Five independent lesion datasets totaling 461 patients were included with varied lesion etiologies, depression scales, and timing of depression assessment (Figure 1, Table 1; Supplemental Methods) (7,17,28–30). Our primary analysis focused on patients with moderate to severe depression (n = 58) versus patients with no depression (n = 300) (patients with depression are referred to subsequently as "depressed subjects" and those with no depression as "nondepressed control subjects") using established cutoffs for each depression scale (Table 1; Supplemental Methods) (7,17,31–36). We used a binary contrast of "depressed" versus "nondepressed" for our main analysis for 3 reasons. First, this maintains consistency with the poststroke depression literature, including studies whose findings we sought to replicate (7,37,38). Second, this enables combining datasets with different depression measures, each of which has established cutoffs for binary classification. Finally, because depression scales can be influenced by many factors, focusing on the extremes may be more likely to identify associations with lesion location. However, we also repeated our analyses on the full cohort of lesions (N = 461) treating depression as a continuous measure. To perform analyses across datasets, depression scores for subjects within each dataset were z-scored against other subjects within that same dataset, yielding a normalized continuous depression score for each subject.

Lesions were manually segmented based on computed tomography (7,29) or structural magnetic resonance imaging images (17,28,30), spatially normalized to Montreal Neurological Institute (MNI) 152 atlas space, and binarized, such that voxels within the lesion carried a value of 1 and all other voxels carried a value of 0. Lesion masks were added together to create lesion overlap maps (Supplemental Figure S1).

Analysis of Lesion Location

To identify any lesioned brain voxels associated with depression, we performed voxel-based lesion symptom mapping (VLSM) (1,2) using the MATLAB (MATLAB; The MathWorks, Inc., Natick, MA) package NiiStat (https://github.com/neurolabusc/NiiStat), controlling for lesion size and dataset as covariates (39) and using standard settings and statistical cutoffs (1,2) (Supplemental Methods). To maximize sensitivity, we focused our analysis on the bilateral DLPFC, defined using the Harvard Oxford atlas middle frontal gyrus (MFG) region and a cutoff of >0% probability. This focus was motivated by literature implicating the DLPFC in depression and its use as a treatment target for TMS. To ensure that results were not dependent on our choice of region of interest (ROI), we repeated our analysis using 2 other DLPFC ROIs used in prior studies of lesion location and depression (4,7) (Supplemental Figure S2). To ensure that we did not miss important results outside the DLPFC, we repeated our analysis using no mask (i.e., including the whole brain). Finally, we repeated analyses treating depression as a continuous rather than a binary variable and including all lesions (N = 461).

In addition to the above voxel-wise analyses, we also replicated ROI-based analyses from prior studies that reported positive associations between lesion location and depression (4,7) and tested for associations between depression and lesions to the left versus right hemisphere (Supplemental Methods, Supplemental Figure S2). In total, we tested 7 a priori hypotheses regarding lesion intersection with these ROIs.

Lesion Network Mapping

Using previously validated methods for lesion network mapping (19,22), we tested whether lesions associated with depression mapped to a connected brain circuit. Functional connectivity between each lesion location and all other brain voxels was computed using resting-state functional connectivity data from 1000 healthy subjects (40,41) (Figure 2; Supplemental Methods).

Unthresholded lesion network maps of depressed (n = 58) versus nondepressed control (n = 300) subjects were statistically compared using a general linear model and permutation testing (Permutation Analysis of Linear Models in FSL 3.2.0), including dataset and lesion size as covariates (42,43). The location of each lesion was not excluded from the corresponding lesion network map. As in our VLSM analysis, we searched for significant results within the Harvard Oxford bilateral MFG mask. We used a conservative voxel-level familywise error (FWE) correction for multiple comparisons, correcting for all brain voxels within our mask ($p_c < .05$). This is more stringent than the commonly used cluster-based correction that can be associated with false positives depending on the detection threshold (44). As with our VLSM analysis, we repeated our analysis using 2 other DLPFC masks and using no mask at all (Supplemental Methods).

Significant voxels from this analysis were extracted as a seed ROI, and the functional connectivity of this region to the rest of the brain was computed using the normative connectome of 1000 healthy subjects. By definition, this network map, which we term the "depression circuit," best encompasses lesion locations associated with depression while avoiding lesion locations that are not.

We repeated this analysis using the subset of lesions with a common lesion etiology (ischemic stroke, hemorrhagic stroke,

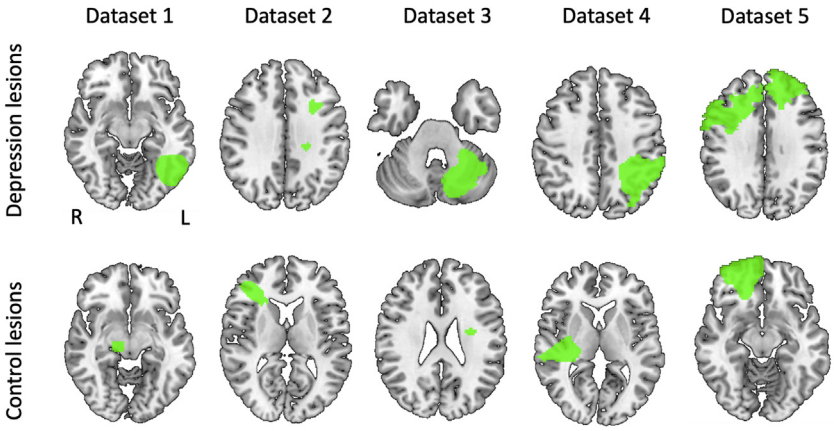

Figure 1. Lesions from depressed and nondepressed control subjects from each of our 5 datasets demonstrate heterogeneity in lesion location: Dataset 1: Naidech *et al.* (29) (intracerebral hemorrhage); Dataset 2: Corbetta *et al.* (28) (stroke); Dataset 3: Egorova *et al.* (30) (stroke); Dataset 4: Gozzi *et al.* (17) (stroke); Dataset 5: Koenigs *et al.* (7) (penetrating traumatic brain injury). L, left; R, right.

penetrating traumatic brain injury) and the subset of lesions with a confirmed lack of history of depression prelesion. Similarity to our primary circuit (n = 358) was assessed through spatial correlation (Supplemental Methods).

Leave-One-Dataset-Out Cross-Validation and Network Damage Scores. To ensure that our findings were not biased by any of our 5 datasets, and to test whether our depression circuit could predict depression in independent datasets, we performed a leave-one-dataset-out validation. We statistically compared the lesion network maps of depressed and control subjects 5 times, each time leaving out 1 of the 5 datasets. Each time, voxels that survived voxelwise FWE correction were extracted as ROIs (Figure 3A).

Then, we used each of these 5 ROIs as seeds and computed their functional connectivity with the rest of the brain using our normative connectome dataset (N = 1000). This generated 5 different depression circuit maps (Figure 3B, C). We then assigned each subject a "network damage score" using the depression circuit that was generated from the other 4 datasets to which the lesion did not belong (Figure 3). Each subject's network damage score was calculated by summing the intensity (t values) of those voxels in the depression circuit that overlapped with that subject's lesion. To avoid bias associated with a choice of threshold, network damage scores were computed using unthresholded depression circuit maps. To control for lesion size and dataset, we regressed this score against these variables and extracted the residuals to create an adjusted network damage score, which was used in all analyses.

First, we examined whether the network damage score differed between depressed and control subjects. Second, we examined whether subjects with higher network damage scores were more likely to have depression. Owing to the network damage score's nonnormality, statistical significance for these analyses were calculated using permutation testing with 1 million permutations, a nonparametric procedure that can be used on nonnormal data (45) (Supplemental Methods).

To ensure that results were not overly dependent on the cutoff values used to define control and depressed subjects, we performed additional analyses on the full cohort of subjects (N = 461) using the continuous depression score. We performed a Pearson's correlation between this score and the network damage score, using permutation testing to determine statistical significance due to nonnormality of both variables. We also examined whether lesion size predicted depression in binary and continuous models of depression.

We then divided subjects into 3 risk categories: low risk (network damage score $<$ 2 SD below the mean), high risk (network damage score $>$ 2 SD above the mean), and medium risk (the remaining subjects). Mean depression scores were compared across risk categories using 1-way analysis of variance (Figure 4A). Finally, we grouped subjects with mild or questionable depression along with control subjects and evaluated whether the prevalence of depression differed among the 3 risk categories using a χ^2 test (Figure 4B).

Poststroke Depression Treatment Targets

From the literature, we identified TMS targets that have successfully been used to treat depression following strokes (Supplemental Methods). We constructed 12-mm cone models of TMS activation for each TMS target and masked them against the MNI 152 brain, as described in prior work (46). As a control site, we also constructed a 12-mm cone model centered around the vertex (equivalent to Cz electrode location in the 10/20 electroencephalogram system), commonly used as a control target in trials of TMS and shown not to improve depression. Using normative connectome data, we assessed whether the successful TMS targets showed positive functional connectivity with the seed identified in our lesion network mapping analysis (see "LNM results" in Figure 2B). We then assessed whether the successful TMS targets showed significantly greater functional connectivity to the results of our lesion network mapping analysis than the vertex using Hotelling's t test (47) (Figure 5).

RESULTS

Analysis of Lesion Location

Across our 5 datasets (Table 1), lesions associated with moderate to severe depression and lesions associated with no depression occurred in various brain locations (Figure 1). Only 8 of 58 lesions associated with depression overlapped in any single location (Supplemental Figure S1A). Using voxel-based lesion-symptom mapping on the pooled data, no lesioned voxels were significantly associated with depression, either

Table 1. Subject Demographics

	Total Data	Naidech *et al.* (29)	Corbetta *et al.* (28)	Egorova *et al.* (30)	Gozzi *et al.* (17)	Koenigs *et al.* (7)
Total Subjects for Primary Analysis (Depressed/Nondepressed), *n*	358 (58/300)	33 (10/23)	87 (14/73)	49 (5/44)	45 (7/38)	144 (22/122)
Age, years, mean (SD)	59.3 (11.1)	58.6 (14.4)	53.8 (11.0)	68.1 (14.3)	63.5 (13.5)	58.5 (3.4)
Sex, *n* (%)	272 M (76), 86 F (24)	18 M (55), 15 F (45)	45 M (52), 42 F (48)	36 M (73), 13 F (27)	29 M (64), 16 F (36)	144 M (100)
Lesion etiology		Intracerebral hemorrhage	Stroke (ischemic or hemorrhagic)	Ischemic stroke	Stroke (ischemic or intracerebral hemorrhagic)	Penetrating traumatic brain injury
Depression scale		Neuro-QOL	GDSS	PHQ-9	HADS, followed by MINI	BDI-II
Depression threshold		Neuro-QOL *T* score $\geq$ 59.9 (equivalent to PHQ-9 $\geq$ 10)	GDSS $\geq$ 11	PHQ-9 $\geq$ 10	HADS $\geq$ 11, major depression per structured interview	BDI-II score $\geq$ 20
Threshold for nondepressed status		Neuro-QOL *T* score $\leq$ 50.5 (equivalent to PHQ-9 $\leq$ 4)	GDSS $\leq$ 5	PHQ-9 $\leq$ 4	HADS $<$ 11	BDI-II score $\leq$ 8
Time of depression assessment		Varied; 28 days, 3 months, or 12 months after hospital discharge	3 months after stroke	3 months after stroke	1 month after stroke	33–39 years following traumatic brain injury
Total Subjects for Continuous Analysis	461	51	100	63	51	196
Age, years, mean (SD)	59.3 (10.7)	61.1 (14.3)	53.6 (10.6)	67.5 (13.4)	62.6 (13.9)	58.3 (3.1)
Sex, *n* (%)	347 M (75), 114 F (25)	28 M (55), 23 F (45)	51 M (51), 49 F (49)	41 M (65), 22 F (35)	31 M (61), 20 F (39)	196 M (100)

BDI-II, Beck Depression Inventory II (36); F, female; GDSS, Geriatric Depression Score Short Form (32); HADS, Hospital Anxiety and Depression Scale (34); M, male; MINI, Mini-International Neuropsychiatric Interview (35); Neuro-QOL, Neuro-QOL Depression Scale (31); PHQ-9, Patient Health Questionnaire (33).

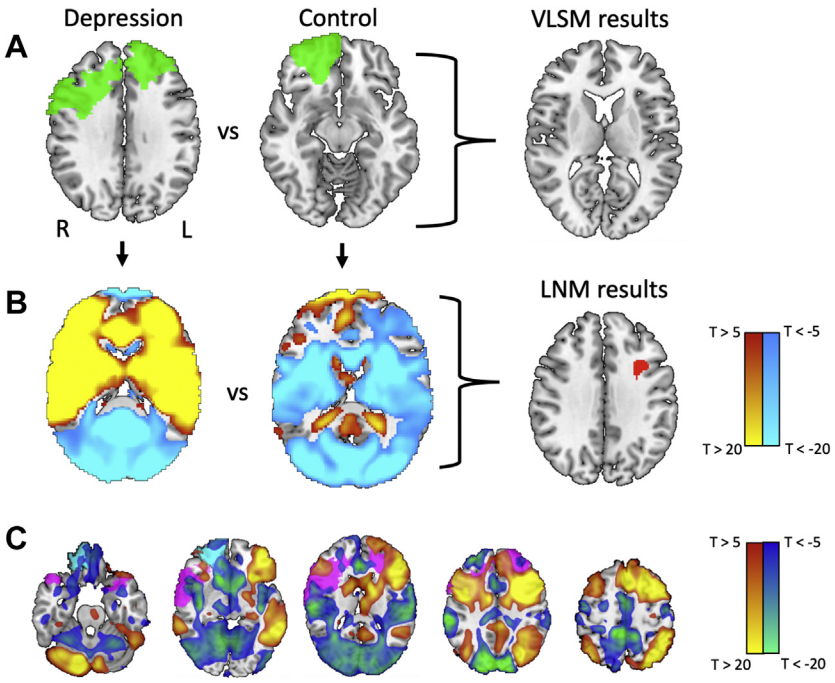

Figure 2. Lesion locations associated with depression intersect a connected brain circuit, not an individual brain region. **(A)** A sample lesion from a depressed subject and a nondepressed control subject are depicted in green. Standard voxel-based lesion-symptom mapping identified no lesioned voxels significantly associated with depression. **(B)** Functional connectivity of each lesion location to the rest of the brain was computed using resting-state functional connectivity data from 1000 healthy control subjects. A focal region in the left dorsolateral prefrontal cortex showed greater functional connectivity to lesions of depressed subjects than to lesions of nondepressed control subjects (depicted in red; voxel-level familywise error corrected: $p_c < .05$). **(C)** Using normative connectome data, we examined the whole-brain functional connectivity of this region, generating a depression circuit. By definition, lesions from depressed subjects will intersect positive nodes of this network (sample lesion shown in violet) while lesions from nondepressed control subjects will not (sample lesion shown in cyan). In panels **(B)** and **(C)**, the red-yellow coloration indicates regions positively connected to the region, while the blue-green coloration indicates regions negatively connected (anticorrelated) to the region. Network maps are thresholded at $T = \pm 5$ for ease of visualization (actual network maps were unthresholded). The z coordinates of slices in panel **(C)** are −25, −5, 15, 35, and 55. L, left; LNM, lesion network mapping; R, right; VLSM, voxel-based lesion symptom mapping.

inside our DLPFC ROIs or in a whole brain analysis (1) (Figure 2A; Supplemental Table S1). There were also no significant voxel-based associations when treating depression as a continuous variable ($N = 461$), either inside or outside our DLPFC ROIs.

Finally, we found no significant association between lesion location and depression when repeating ROI-based analyses from prior papers (4,7) or when performing laterality analyses (Supplement). Specifically, there was no difference in depression prevalence comparing left anterior versus left posterior lesions ($p = .36$), left anterior versus right anterior lesions ($p = .32$), right anterior versus right posterior lesions ($p = 1$), bilateral dorsal lateral prefrontal versus bilateral ventral medial prefrontal lesions ($p = 1$), or bilateral dorsal lateral prefrontal and nonprefrontal lesions ($p = .76$). There was also no difference in depression prevalence between left- and right-sided lesions in the cerebral hemispheres ($p = 1$) or between lesions falling within the Harvard Oxford left and right MFGs ($p = .44$) (Supplemental Table S2).

Lesion Network Mapping

Functional connectivity between each lesion location and the whole brain was computed using a normative connectome (Figure 2B). In contrast to analyses focused on lesion location alone, lesion connectivity was significantly associated with depression. Specifically, a focal region in the left DLPFC was significantly more connected to lesions of depressed subjects compared with nondepressed control subjects (159 voxels surviving voxel-level FWE correction, $p_c < .05$). The peak of this left DLPFC region was highly significant ($p_c = .005$) and located at the gray–white matter junction (MNI coordinates: x = −32, y = 12, z = 36) (Figure 2B). This result was independent of the specific DLPFC mask (Supplemental Figure S2), and the peak remained significant in a whole brain analysis ($p_c < .05$). No other significant peaks outside the left DLPFC were identified.

By definition, functional connectivity with this DLPFC region defines a human brain circuit that encompasses lesion locations associated with depression while avoiding lesion locations that are not (Figure 2C; Supplemental Table S3). Lesion locations from patients with depression will intersect positively connected brain regions in this circuit, while lesions from nondepressed control subjects will intersect neutral or negatively connected regions in this circuit. This lesion-based depression circuit was similar when restricted to cases of hemorrhagic stroke ($r = .66$), ischemic stroke ($r = .52$), penetrating traumatic brain injury ($r = .95$), or a documented lack of depression prior to the lesion ($r = .53$) (Supplemental Figures S3 and S4).

Leave-One-Dataset-Out Cross-Validation and Network Damage Scores. As a rigorous test of reproducibility, we repeated the above analysis 5 times, each time excluding 1 dataset. Lesions associated with depression were always more connected to a focal region in the left DLPFC ($p_c < .05$) that was similar no matter which dataset was excluded (Figure 3A). Connectivity with this left DLPFC ROI defined a brain circuit that was similar no matter which dataset was excluded (average spatial correlation: $r = .91$) (Figure 3B; Supplemental Table S4). Lesions associated with depression intersected this circuit to a significantly greater degree than control lesions did ($p = .0013$), as demonstrated by a higher network damage score. The degree to which lesions intersected this circuit predicted depression status (odds ratio = 1.62, $p = .0035$). Lesion size alone did not predict depression status (odds ratio = 1.14, $p = .31$).

To ensure that these results were not dependent on the cutoffs used to classify patients as "depressed" or "not

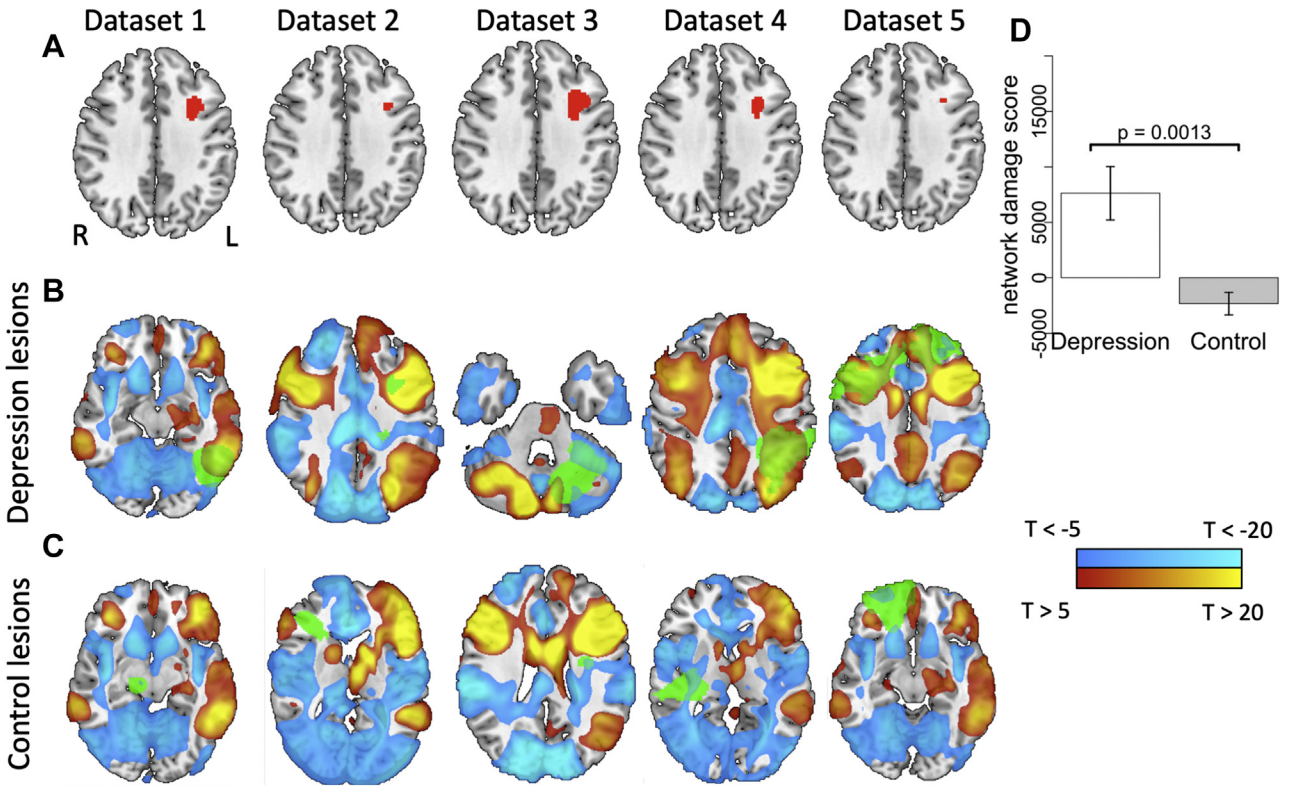

Figure 3. Lesion locations associated with depression intersect a brain circuit derived from independent lesion datasets. **(A)** The analysis shown in Figure 2B was repeated 5 times, each time leaving out 1 of the 5 datasets. In all 5 analyses, a similar region in the left dorsolateral prefrontal cortex was significantly more connected to lesions of depressed subjects than to lesions of nondepressed control subjects (depicted in red; voxel-level familywise error corrected: $p_c < .05$). **(B, C)** The functional connectivity of each of these regions to the remainder of the brain was computed using a normative connectome of 1000 healthy subjects, generating 5 depression circuits. The red-yellow and blue-cyan coloration depict positive connectivity and negative connectivity (anticorrelation) to the region, respectively, while green coloration depicts sample lesion locations from the excluded dataset. Depression circuits are thresholded at $T = \pm 5$ for ease of visualization (actual depression circuits for analysis are unthresholded). **(D)** Network damage scores, representing intersection of each lesion with the depression circuit generated from the other lesion datasets, was significantly higher for depressed subjects than for control subjects. L, left; R, right.

depressed," we repeated this analysis of circuit intersection on our full cohort of patients with lesions (N = 461), treating depression as a continuous rather than a binary variable. Intersection with our depression circuit (defined using the other 4 datasets) was a significant predictor of continuous depression severity (r = .13, p = .0040). Lesion size alone did not predict continuous depression severity (r = .061, p = .19).

Binning all 461 subjects into 3 risk categories based on circuit intersection revealed a significant difference in continuous depression scores ($F_{2,458}$ = 4.8, p = .0036) (Figure 4A) and depression prevalence (χ^2 = 7.2, p = .019) (Figure 4B). Prevalence of depression was 4 times higher (35.7%) in the high-risk category than in the low-risk category (8.3%).

Poststroke Depression Treatment Targets

We identified 3 TMS targets with evidence of efficacy in treating poststroke depression (Figure 5). These included the 5-cm target traditionally also used in treatment of primary depression (48,49), the left F3 electrode location on the scalp using the 10/20 electroencephalogram coordinate system (50,51), and the center of the left MFG (52). All 3 targets fell within our depression circuit derived from focal brain lesions, defined by positive connectivity to our node in the left DLPFC (r = .23 for the 5-cm target, r = .14 for the electroencephalogram F3 target, and r = .20 for the center of the MFG; all $p < .00001$). All 3 TMS targets were significantly more connected to this DLPFC node than our control site in the vertex ($p < .0001$ for all comparisons).

DISCUSSION

Our results define a depression circuit in the human brain based on brain lesions. First, we found that lesion location alone was not significantly associated with depression. Second, we showed that functional connectivity between lesion locations and the left DLPFC was strongly associated with depression, independent of lesion etiology, lesion size, or dataset. Third, we validated our depression circuit by predicting depression status and depression severity in independent lesion cohorts. Finally, we showed that our circuit derived from brain lesions associated with depression aligns with brain stimulation sites that improve depression, suggesting therapeutic utility. Although we used binary cutoffs for our main analysis, our findings are not dependent on these cutoffs and were reproducible when treating depression as a continuous measure.

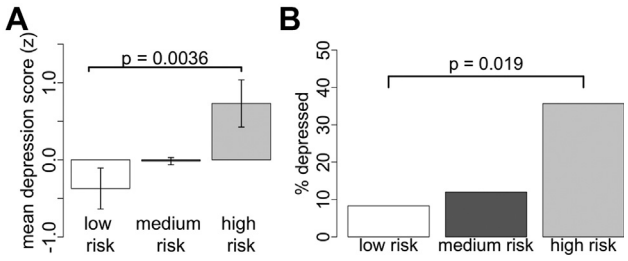

Figure 4. Network damage score is associated with depression severity and prevalence. **(A)** All subjects were divided into 3 risk categories based on their network damage score. Mean depression score significantly differed across the risk categories and was highest in the high-risk group. **(B)** Prevalence of depression significantly differed across the risk categories and was highest in the high-risk group.

Lesion Location and Depression

We did not find an association between lesion location and depression anywhere in the brain either using VLSM or when replicating prior positive analyses from the literature (4,7). While it is possible that significant associations would have become apparent with more lesions and statistical power, this study is the largest VLSM analysis of depression to date, about twice the size of the next largest study (18). Other studies approaching the size of our study, but classifying lesion location based on rough anatomical descriptions rather than lesioned voxels, have also been negative (53), including multiple meta-analyses (12–15). Collectively, these results suggest that lesions associated with depression do not localize to any specific brain region.

Lesion Network Mapping, Frontal Connectivity, and Depression

In contrast to the negative results regarding lesion location, functional connectivity between lesion locations and the rest of the brain was a significant predictor of depression. This finding is consistent with a growing literature suggesting that symptoms localize to connected brain circuits, not to single brain lesions (19,22,54–56).

Functional connectivity between lesion location and a region within the left DLPFC was higher in depressed than in nondepressed control subjects, a finding that remained significant even in a conservative whole-brain analysis with voxelwise FWE correction. Because this analysis compared lesions from individuals with depression with individuals with no depression, we controlled for the possibility that the DLPFC is simply a hub connected to all lesion locations. These findings are consistent with lesion studies implicating the DLPFC in depression (4,7). However, our findings also help explain why multiple lesion studies, including the present study, failed to see such relationships (12–15). Specifically, our results suggest that lesions located outside the DLPFC, but functionally connected to this area, can also cause depression.

Connectivity with the DLPFC defines a human brain circuit that best encompasses lesion locations associated with depression. This circuit was independent of lesion etiology, dataset, or scale used to measure depression. Intersection between lesion location and this circuit predicted prevalence and severity of depression in independent lesion cohorts. As such, this circuit might be used to identify patients who are at elevated risk of depression after a stroke or brain injury. Clinicians could examine the overlap between a patient's lesion and our depression circuit, and patients at elevated risk could then be directed toward early psychiatric evaluation and treatment.

Our circuit derived from brain lesions associated with depression aligned with stimulation sites that were found to improve depression in poststroke depression. Although previous work has suggested therapeutic relevance of lesion network mapping results (57–59), this is the first study to show that lesions causing a symptom are part of the same brain circuit as stimulation sites improving that symptom in lesion patients. While the peak of our lesion-based depression circuit is in the left DLPFC, TMS to secondary nodes in this circuit may also be beneficial, although this remains a testable hypothesis for future work. These results support the use of lesion network mapping to identify therapeutic brain stimulation targets for improving lesion-induced symptoms.

It is likely that our depression circuit has implications for understanding and treating primary depression not caused by focal brain lesions. While depression has not consistently been associated with changes in DLPFC activity (60,61), increases in DLPFC activity have been associated with antidepressant response (62), especially improvement in the cognitive symptoms of depression (63). However, it is now widely recognized that primary depression is associated with circuit abnormalities that extend beyond the DLPFC (64,65). Our circuit, based on causal brain lesions, may help refine circuit models of primary depression.

Finally, our results may help inform treatment targets in primary depression. The DLPFC region was initially chosen as a TMS target for primary depression based partly on lesion studies (66). Our current depression circuit may help refine this target and motivate new strategies for

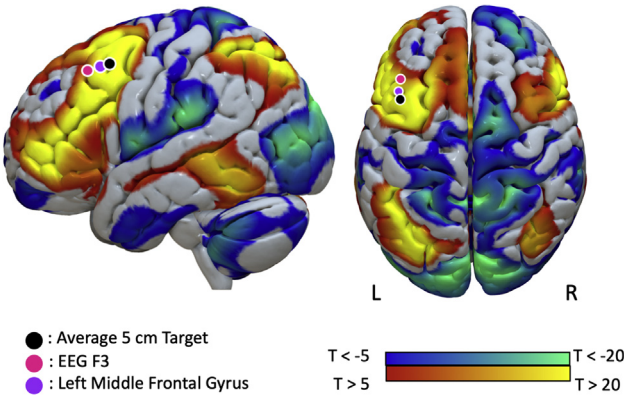

Figure 5. Our lesion-based depression circuit aligns with transcranial magnetic stimulation sites used to treat poststroke depression. Spheres indicate the stimulation locations used by prior transcranial magnetic stimulation studies that have successfully treated poststroke depression. Our depression circuit is displayed on the cortical surface and thresholded at $T = \pm 5$ for ease of visualization (actual network is unthresholded). EEG, electroencephalogram; L, left; R, right.

neuromodulation that target a brain circuit rather than a single brain region (67,68).

Limitations and Future Directions

There are several limitations. First, as previously discussed (22), lesion network mapping using a normative dataset assumes that the patterns of connectivity in healthy individuals are approximately the same as for an individual patient prior to their brain lesion. This assumption appears reasonable given the success of lesion network mapping across numerous symptoms (19,22–25) and the fact that prior work using a connectome age-matched to lesion patients had no effect on results (19). In similar work on TMS or deep brain stimulation electrodes, disease matching the connectomes also had no effect on results (25,69). Second, the current study focused only on lesion location and connectivity to explain lesion-associated depression. We did not account for compensatory network adaptations that may occur following a lesion, nor did we account for many other factors that contribute to postlesion depression such as genetics, psychosocial situation, degree of disability, or comorbid diagnosis (14). Third, lesions were treated as functionally homogeneous units regardless of their size. A potential approach to address this limitation could involve deconstructing lesions into functionally homogeneous seeds using an atlas, and then using these seeds to generate multiple lesion network maps for each subject. However, as this potential approach has not been standardized, we elected to pursue our previously validated approach.

Fourth, we did not have complete information about psychiatric comorbidities or prelesion history of depression. Substance dependence and posttraumatic stress disorder can be significant comorbidities in veterans with penetrating traumatic brain injury, for example. Additionally, the time point of depression assessment relative to the lesion was variable across datasets, limiting our ability to make strong causal inferences. At least some patients in this study likely had depression that was unrelated to the location of their brain damage. However, a depression circuit created from the subset of individuals who had a documented lack of depression prior to their lesion was similar to our primary depression circuit (r = .53). Fifth, depression is a syndrome composed of many different symptoms with potentially distinct neuroanatomical correlates. Future work applying this technique to individual symptoms of depression is needed. Sixth, our results should not be interpreted as specific to the left DLPFC relative to the right DLPFC. Although connectivity to the left DLPFC was the only significant finding in our full cohort, some subcohorts showed similar findings in the right DLPFC (Supplemental Figures S3 and S4). Finally, there is certain to be some error in lesion tracing and atlas registrations. However, it is important to note that all of these limitations should bias us against the present findings, namely consistent localization of lesions associated with depression to a specific brain circuit across datasets and lesion etiologies.

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