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Mapping the Relationship of White Matter Lesions to Depression in Multiple Sclerosis

Erica B. Baller, Elizabeth M. Sweeney, Matthew Cieslak, Timothy Robert-Fitzgerald, Sydney C. Covitz, Melissa L. Martin, Matthew K. Schindler, Amit Bar-Or, Ameena Elahi, Bart S. Larsen, Abigail R. Manning, Clyde E. Markowitz, Christopher M. Perrone, Victoria Rautman, Madeleine M. Seitz, John A. Detre, Michael D. Fox, Russell T. Shinohara, and Theodore D. Satterthwaite

ABSTRACT

BACKGROUND: Multiple sclerosis (MS) is an immune-mediated neurological disorder, and up to 50% of patients experience depression. We investigated how white matter network disruption is related to depression in MS.

METHODS: Using electronic health records, 380 participants with MS were identified. Depressed individuals (MS+Depression group; $n = 232$) included persons who had an ICD-10 depression diagnosis, had a prescription for antidepressant medication, or screened positive via Patient Health Questionnaire (PHQ)-2 or PHQ-9. Age- and sex-matched nondepressed individuals with MS (MS−Depression group; $n = 148$) included persons who had no prior depression diagnosis, had no psychiatric medication prescriptions, and were asymptomatic on PHQ-2 or PHQ-9. Research-quality 3T structural magnetic resonance imaging was obtained as part of routine care. We first evaluated whether lesions were preferentially located within the depression network compared with other brain regions. Next, we examined if MS+Depression patients had greater lesion burden and if this was driven by lesions in the depression network. Primary outcome measures were the burden of lesions (e.g., impacted fascicles) within a network and across the brain.

RESULTS: MS lesions preferentially affected fascicles within versus outside the depression network ($\beta = 0.09$, 95% CI = 0.08 to 0.10, $p < .001$). MS+Depression patients had more lesion burden ($\beta = 0.06$, 95% CI = 0.01 to 0.10, $p = .015$); this was driven by lesions within the depression network ($\beta = 0.02$, 95% CI = 0.003 to 0.040, $p = .020$).

CONCLUSIONS: We demonstrated that lesion location and burden may contribute to depression comorbidity in MS. MS lesions disproportionately impacted fascicles in the depression network. MS+Depression patients had more disease than MS−Depression patients, which was driven by disease within the depression network. Future studies relating lesion location to personalized depression interventions are warranted.

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Multiple sclerosis (MS) is an immune-mediated neurological disorder that is characterized by demyelinating white matter lesions in the central nervous system (1–3). Worldwide, 2.8 million people are estimated to have MS (4). Depression is highly comorbid with MS across international samples; up to 50% of patients with MS will experience a lifetime major depressive episode (5,6). Depression in MS is associated with suicide rates double that of persons without MS, with depressive symptoms mediating the relationship between disability and suicidal ideation (7–9). The rates of depression in MS are also higher than depression comorbidity in other chronic autoimmune diseases, suggesting that the neural pathophysiology of MS may confer increased depression risk (10). Despite the overlap between MS and depression, their association is not well understood (11). Scientists have conceptualized MS-related psychopathology as a reflection of underlying neural network dysfunction, where inflammation and neurodegeneration cause a disconnection syndrome that underlies psychiatric symptoms (12). Here, we evaluated whether lesions affecting white matter tracts that connect a brain network previously associated with depression contribute to depression in MS.

Previous studies of medically healthy participants with depression have described associations between white matter properties and depressive symptoms in numerous cortical and subcortical white matter fascicles, though the directionality and strength of associations are inconsistent (13,14). Depression has been associated with abnormal fractional anisotropy in the corpus callosum, cingulate, internal capsule, and thalamic radiations, suggesting that conduction through these fascicles is impacted. These fascicles connect functional brain networks that support complex cognition, mood, and movement. Classifiers using white matter measures as input features have outperformed functional magnetic resonance

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imaging (MRI) in discriminating between individuals with and without depression, though study design and symptom assessments vary (13,15,16).

However, research frequently excludes participants with intracranial pathology; results from these studies cannot be extrapolated to MS. Small MS studies that sought to identify fascicle damage associated with depression have also yielded mixed results (5,17–19); injury to the arcuate fasciculus; to thalamic radiations; and to the temporal, superior, and inferior frontal regions has been reported. Such heterogeneity may reflect study designs that evaluated fascicles individually rather than assessing how lesions in different anatomical locations within a functional network contribute to depressive symptoms. Exploring how depression is associated with heterogeneous white matter disease in connected brain networks is vital to fill in this gap.

One powerful approach to relate heterogeneous lesions to the emergence of neuropsychiatric symptoms is lesion network mapping (LNM). LNM was developed to address a commonly observed phenomenon, in which lesions in heterogeneous areas were linked to a distinct neuropsychiatric syndrome (20,21). This created a challenge for 1-to-1 mapping between symptoms and lesion location, leading scientists to hypothesize that functionally connected lesions produced similar symptoms (20–24). LNM leverages normative human connectome data to identify functional circuits connected to a lesion and compares circuits between patients with and without the symptom (e.g., depression) (20). Recently, researchers demonstrated that strokes associated with depression are connected to a specific brain network (21,22). Brain stimulation at sites within this "depression network" also alleviated depression symptoms. Finally, MS lesions functionally connected to this network have been linked to depression (25). While white matter injury has been associated with overall disability in MS (26–28), prior work has not directly characterized how injury to white matter fascicles may be linked to depression in MS.

In this study, we assessed the relationship between depression and white matter lesion location and burden in a large sample of patients with MS. We hypothesized that MS lesions would preferentially target fascicles that connect the depression network. Furthermore, we predicted that MS patients with depression would have a greater lesion burden within the depression network than MS patients without depression.

METHODS AND MATERIALS

Participants

Participants with MS were identified from the electronic health record via the University of Pennsylvania Data Analytic Center, including demographics, ICD-10 diagnoses (29), medication lists, and depression screens including Patient Health Questionnaires (2-question form [PHQ-2] and 9-question form [PHQ-9]) (Figure 1) (30). The University of Pennsylvania Institutional Review Board approved this study.

MS Diagnosis. Participants 18 years of age and older were included if they received an ICD-10 MS diagnosis (G35) from a specialist at the Penn Medicine Multiple Sclerosis (MS) and Related Disorders Center and received 3T MRI under the University of Pennsylvania MS protocol (detailed below). This sample was stratified into samples of depressed patients with MS (MS+Depression group) and nondepressed patients with MS (MS−Depression). ICD-10 codes for MS do not specify progression subtype, which still lack imaging findings and biomarkers that reliably distinguish between clinical symptoms and predict disease trajectory, so all MS subtypes were considered together (31).

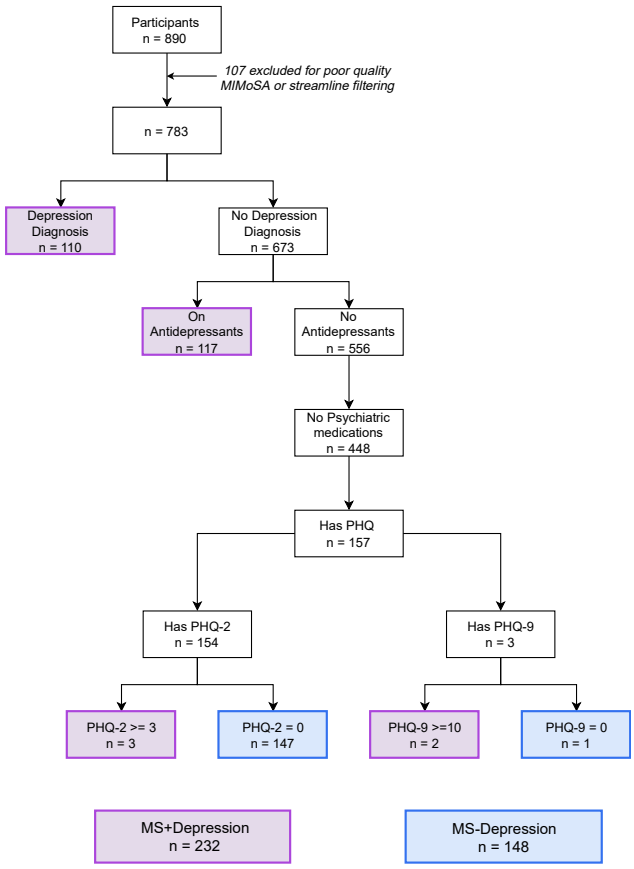

Figure 1. Flowchart of the study population. After excluding participants with poor-quality scans, patients with multiple sclerosis (MS) were stratified by depression diagnosis, prescription for psychiatric medications, and depression symptom screening. MIMoSA, Method for Inter-Modal Segmentation Analysis; MS+Depression, MS with depression; MS−Depression, MS without depression; PHQ, Patient Health Questionnaire (2- or 9-question version).

Depression Diagnosis. Given heterogeneity in coding practices and known underdiagnosis of depression in medical populations (32), a multistep process was used to classify our MS+Depression and MS−Depression samples. The MS+Depression patients met one of the following 3 criteria: 1) ICD-10 code F32 (depressive episode), F33 (major depressive disorder), or F34 (persistent mood [affective] disorder); 2) screened positive for depression on PHQ-2 (score ≥ 3) or PHQ-9 (score ≥ 10); 3) previously prescribed an antidepressant medication (33). As the absence of an ICD-10 depression

diagnosis does not exclude a diagnosis of depression, all MS−Depression patients had no previous depression diagnosis, were asymptomatic on PHQ-2 or PHQ-9 (score = 0), and had no prescription history for psychiatric medications. Given that the depression network described by Siddiqi *et al.* (22) was generated from patients with major depressive disorder and that depression in bipolar disorder has been associated with discrete brain networks compared with major depressive disorder (34), patients with bipolar depression were excluded. Patients were also excluded if they had no psychiatric or medication history indicating depression but were never screened with PHQ-2 and/or PHQ-9, or if they were never evaluated by a Penn Medicine MS specialist.

To validate this classification, we evaluated group differences in the Patient-Reported Outcomes Measurement Information System (PROMIS) scores in a subset of patients (35). The PROMIS was not used in the definition of our groups and was well suited for group validation. The PROMIS assesses current symptom burden in 10 domains, including mental health and mood, emotional problems, quality of life, physical health, social activities satisfaction, carrying out social activities, carrying out physical activities, fatigue, overall physical impairment, and overall mental impairment. For patients who completed multiple PROMIS scales, the score most proximate to their imaging session was used.

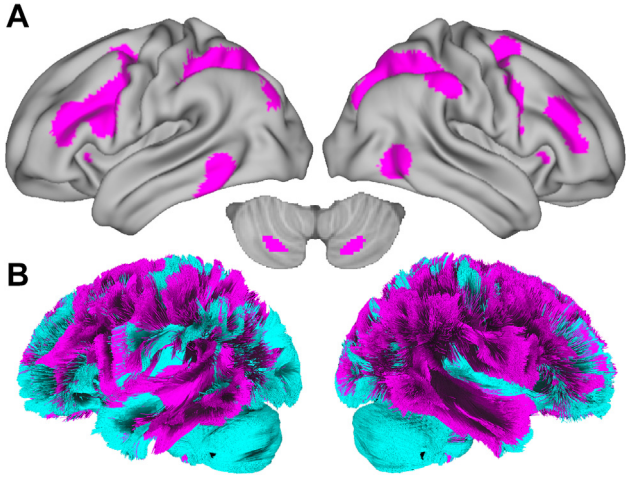

Figure 2. White matter depression network construction. **(A)** The gray matter depression network from Siddiqi *et al.* (22), thresholded at $t > 3.09$. **(B)** The white matter depression network was constructed from the top 25% of fascicles with the greatest volume of overlap with the gray matter depression network. Pink fascicles correspond to the depression network, whereas blue fascicles correspond to the nondepression network.

White Matter Depression Network Construction

To construct the white matter depression network, we identified fascicles that served as the structural backbone of a functional depression circuit map from Siddiqi *et al.* (22). Briefly, Siddiqi *et al.* evaluated correlations between depression and lesions or stimulation sites across 14 heterogeneous datasets and created an unthresholded mean correlation map. We first constructed a binary map by applying a threshold of $t > 3.09$ to identify voxels with a statistically significant positive association between depression symptoms and brain disease or stimulation. We then constructed the white matter depression network using tools from DSI Studio (36,37). We built 77 canonical fascicles spanning cortical and subcortical regions from an atlas that was derived from a large sample of high-quality diffusion MRI and verified by neuroanatomists to correspond to known neuroanatomy (36). We next calculated the volume (in voxels) that overlapped between the fascicle's individual fibers, or streamlines, and the binarized functional depression network. Fascicles were ranked by their volume of overlap with the functional depression network. Fascicles with the highest degree of overlap (top 25%, 19 fascicles) were considered to be in the white matter depression network (Figure 2; Table S1). The resulting white matter depression network included fascicles known to be commonly affected in MS, including the corpus callosum and thalamic projections. However, the superior longitudinal fasciculus and arcuate fasciculus, which support language and complex cognition, also comprised a substantial portion of the white matter network.

To ensure that our results were not driven by arbitrary thresholding decisions, we repeated our analyses using thresholds of $t > 2.3$ ($p < .01$) and $t > 2.6$ ($p < .005$). We also constructed and tested white matter depression networks using alternative overlap thresholds (e.g., the top 33% and 20%). We additionally repeated our primary analyses excluding the corpus callosum given the fascicle's large size compared with other fascicles. We summarized the lesion burden within each network (volume of impacted streamlines divided by the total volume of streamlines within each network).

Image Acquisition and Processing

Structural 3T MRI was obtained as part of routine care using a research-quality protocol, including three-dimensional T1-weighted magnetization-prepared rapid acquisition gradient-echo (repetition time = 1.9 seconds, echo time = 2.48 ms, inversion time = 900 ms, flip angle = 9°, acquisition time = 4 minutes 18 seconds, 176 sagittal slices, resolution = 1 mm^3) and three-dimensional T2-weighted FLAIR (repetition time = 5 seconds, echo time = 398 ms, inversion time = 1.8 seconds, flip angle = 120°, acquisition time = 5 minutes 2 seconds, 160 sagittal slices, resolution = 1 mm^3) sequences. Images were processed using a previously described pipeline (38). N4 bias field correction was performed for T1-weighted and FLAIR images (39), extracerebral voxels were removed from the T1-weighted images using Multi-Atlas Skull-Stripping (40), T1-weighted images and their corresponding brain masks were registered to the corresponding FLAIR images, and intensity of skull-stripped FLAIR and aligned T1-weighted images was normalized using WhiteStripe (41). MRI was usually acquired within 6 months of presentation to the MS clinic.

Automated Lesion Segmentation and Streamline Filtering

Automated Lesion Segmentation. Fully automated lesion segmentation was performed with the Method for Inter-Modal Segmentation Analysis (MIMoSA) algorithm to obtain

binary maps of white matter lesions in a subject's native space (42). Prior work has demonstrated that this algorithm performs similarly to manual segmentation (42). The quality of all processed images and segmentations was assessed by an imaging scientist with 4 years of experience in MS imaging research.

Analysis of White Matter Fascicles. To assess the impact of white matter lesions on fascicles across subjects, we performed streamline filtering in DSI Studio (36,37,43). This required identifying whether individual streamlines within a fascicle were impacted (i.e., passed through a lesion) or spared (avoided a lesion). Delineating fascicles in a single diffusion MRI dataset is known to be error-prone (44), so we compared spatially normalized lesions to canonical fascicles in template space.

Individual lesion maps (Figure 3A) were normalized to the template space of the canonical fascicles (Montreal Neurological Institute 2009b Asymmetric template) (45) using the T1-weighted–based transform calculated by antsRegistration (Figure 3B) (46,47). Streamlines intersecting lesions at any point in their trajectory were considered injured and isolated from the rest of the fascicle. The total volume occupied by injured streamlines was calculated as the measure of disease burden in the fascicle (Figure 3C–E). This was repeated for each of the 77 fascicles. For each participant, we also calculated the relative disease burden across all white matter as the volume of injured streamlines divided by the complete volume of all fascicles.

Statistical Analyses

Primary Analyses. Given the high comorbidity of depression in MS, we first assessed whether MS lesions were randomly distributed throughout the brain or preferentially targeted fascicles within the depression network, irrespective of diagnosis. Next, we explored whether MS+Depression patients had more lesion burden than MS−Depression patients. We then evaluated whether there was an interaction between network location and diagnosis with a linear mixed-effects model (R package lme4 in R version 3.2.5; R Foundation for Statistical Computing) (37) that included fixed effects of network, diagnosis, network-by-diagnosis interaction, and a random intercept for participants.

Secondary Analyses. For our primary analyses, we defined the depression network as a binary map and assigned each fascicle to be either within or outside the depression network. However, it is possible that the relationship is continuous, and disease in fascicles with greater overlap with the functional depression network is more likely to contribute to differences in depression. To assess this, we evaluated disease within each fascicle separately. For each fascicle, we calculated the volume (in voxels) of overlap of the fascicle with the functional depression network. Next, we computed the effect size (*r*) from a Wilcoxon signed-rank test comparing volume of disease in that fascicle between MS+Depression patients versus MS−Depression patients. Finally, we used a linear model to test for an association between the overlap of each fascicle with the functional depression network and the effect size from the MS+Depression versus the MS−Depression analysis.

Sensitivity Analyses. Numerous biological and pharmacological factors may also contribute to depression in MS. Though our groups were matched on sex and age, we repeated the above analysis modeling sex and age as covariates. As age may be an indirect proxy for disease duration, which could contribute to higher rates of depression, we also tested for an age-by-diagnosis interaction. Medications used in the treatment of MS, specifically steroids and interferon beta, have been associated with psychiatric side effects (48,49). To address this potential confound, we repeated our analysis after removing participants on prednisone, methylprednisolone, and interferon beta.

RESULTS

The analysis included 232 MS patients with depression (MS+Depression group; mean [SD] age = 49 [12] years, age

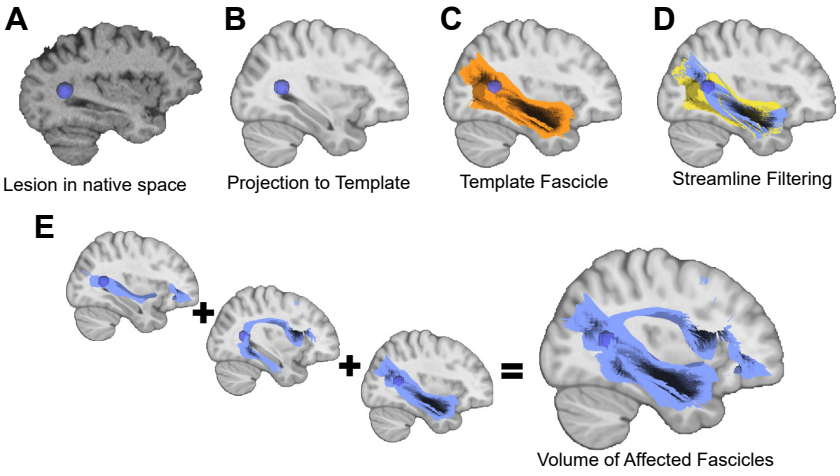

Figure 3. Fascicle analysis pipeline. **(A)** Lesions were segmented with the Method for Inter-Modal Segmentation Analysis (MIMoSA) algorithm and **(B)** normalized to the template space of the canonical fascicles (Montreal Neurological Institute 2009b Asymmetric template) (45). **(C, D)** For each fascicle, streamlines intersecting lesions at any point in their trajectory were considered injured and isolated from the rest of the fascicle (blue). The total volume occupied by injured streamlines was calculated as the measure of disease burden in the fascicle. **(E)** This was repeated at each of 77 fascicles to obtain measures of disease burden.

range = 21–72 years, 86% female) and 148 age- and sex-matched nondepressed MS patients (MS−Depression group; age = 47 [13], age range = 20–83 years, 79% female). As expected, MS+Depression patients had more depression symptoms than MS−Depression patients (Table S2). A subsample of participants completed the PROMIS scales (MS+Depression: n = 49; MS−Depression: n = 36); this scale was not used to construct our sample and allowed us to independently validate our diagnostic groups. MS+Depression patients were more impaired than the MS−Depression patients across 9 of 10 PROMIS measures (Table S3). There were no significant differences in fatigue between groups. We verified that there was no statistically significant difference in prevalence of depression in the subsample with PROMIS scores compared with the whole sample using a χ^2 test (χ^2_1 = 0.21, p = .65).

Lesion Burden Is Higher Both in the Depression Network and in MS+Depression Patients

Among all patients with MS, lesion burden preferentially affected fascicles within versus outside the white matter depression network (β = 0.09, 95% CI = 0.08 to 0.10, $p < .001$) (Figure 4). A main effect of diagnosis was also noted, where MS+Depression patients had more lesion burden across the whole brain compared with MS−Depression patients (β = 0.06, 95% CI = 0.01 to 0.10, p = .015) (Figure 5A). We next tested whether the diagnostic differences between MS+Depression and MS−Depression groups were network specific. We found a network-by-diagnosis interaction (β = 0.02, 95% CI = 0.003 to 0.040, p = .020) (Figure 5B), which was specifically driven by worse lesion burden in MS+Depression patients within the depression network. In addition to comparing disease burden between MS+Depression and MS−Depression groups at the network level, we compared fascicle-level burden between diagnostic groups (Figure 6A). We found that fascicles with more overlap with the depression network also had greater disease burden when comparing MS+Depression with MS−Depression patients (adjusted R^2 = 0.06, linear model p = .02) (Figure 6B).

Convergence Across Alternative Methods for Defining Gray and White Matter Depression Networks

To ensure that our results were not driven by the threshold we used to define the gray matter mask, we repeated the analyses at 2 additional thresholds, $t > 2.3$ ($p < .01$) and $t > 2.6$ ($p < .005$). Our results remained statistically significant and with the same directionality in all analyses. For the $t > 2.3$ threshold, we found a main effect of network (β = 0.05, 95% CI = 0.04 to 0.06, $p < .001$) and main effect of diagnosis (β = 0.05, 95% CI = 0.009 to 0.10, p = .02) (Table S4). For $t > 2.6$, our results were consistent (main effect of network: β = 0.08, 95% CI = 0.07 to 0.10, $p < .001$; main effect of diagnosis: β = 0.06, 95% CI = 0.01 to 0.10, p = .016) (Table S5).

We also tested the robustness of our results by repeating our analyses using alternate thresholds for assigning fascicles to the depression network (top 33% or top 20%). We also repeated our analysis excluding the corpus callosum given its large size compared with other fascicles. Our results remained significant across analyses. Using the 33% threshold, we found a main effect of network (β = 0.12, 95% CI = 0.11 to 0.14, $p < .001$) and a main effect of diagnosis (β = 0.06, 95% CI = 0.01 to 0.10, p = .015). With the 20% threshold, we found a main effect of network (β = 0.11, 95% CI = 0.10 to 0.12, $p < .001$) and a main effect of diagnosis (β = 0.06, 95% CI = 0.01 to 0.10, p = .015). Convergence was also seen in analyses that excluded the corpus callosum (main effect of network: β = 0.03, 95% CI = 0.02 to 0.05, $p < .001$; main effect of diagnosis: β = 0.06, 95% CI = 0.01 to 0.10, p = .013). Taken together, we demonstrated that our results were robust across multiple depression network definitions.

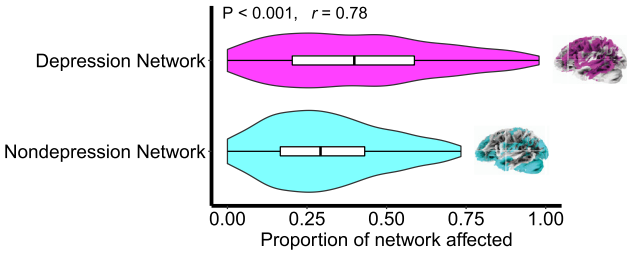

Figure 4. Multiple sclerosis lesions preferentially impacted white matter fascicles in the depression network. Patients with multiple sclerosis had enrichment of disease in fascicles that connect areas in the functional depression network ($p < .001$, r = 0.78).

Convergence When Accounting for Biological and Pharmacological Variables

As a final step, we repeated our analyses while accounting for sex, age, and MS medications. When covarying for sex, our results remained significant (main effect of network: β = 0.09,

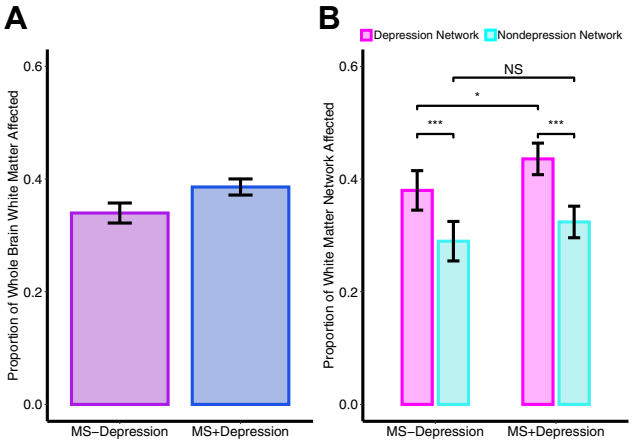

Figure 5. Multiple sclerosis (MS) patients with depression (MS+Depression) had more disease than MS patients without depression (MS−Depression) in the depression network. **(A)** Across the whole brain, MS+Depression patients had more white matter disease burden than MS−Depression patients (p = .04). **(B)** A network-by-diagnosis interaction was noted (p = .02), which was driven by worse disease in MS+Depression patients, specifically in the depression network. *$p < .05$, ***$p < .001$. NS, nonsignificant.

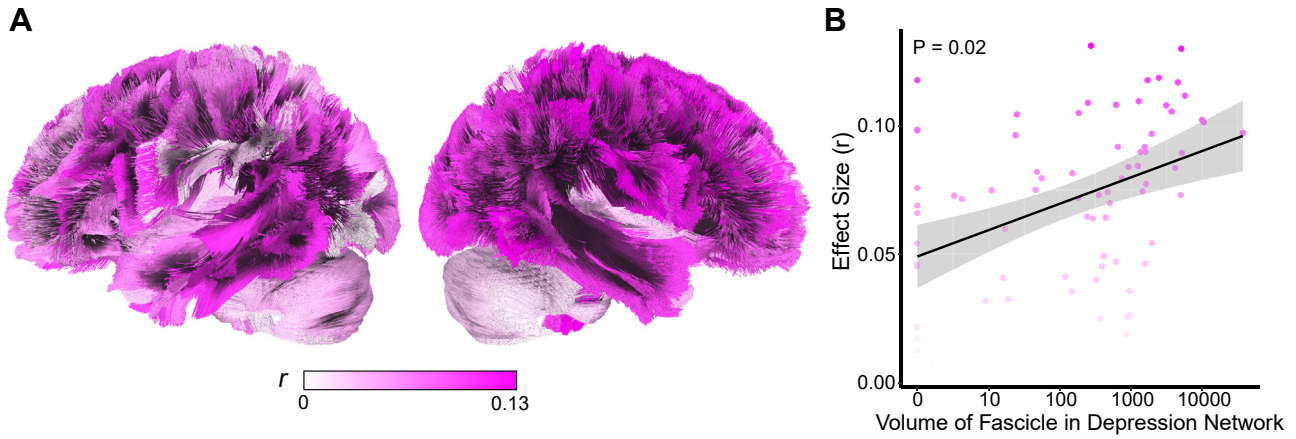

Figure 6. Differences in disease burden between diagnostic groups were larger in fascicles with greater overlap with the depression network. **(A)** Individual fascicles were colored by the effect size from a Wilcoxon signed rank test comparing disease burden in multiple sclerosis (MS) patients with depression (MS+Depression) vs. MS patients without depression (MS−Depression), with darker colors indicating more severe disease in MS+Depression patients. **(B)** Larger effect sizes in the between-diagnosis Wilcoxon signed rank test were associated with greater overlap of the fascicle with the depression network (p = .02). The x-axis is logarithmically scaled for visualization purposes.

95% CI = 0.08 to 0.10, $p < .001$; main effect of diagnosis: β = 0.06, 95% CI = 0.01 to 0.10, p = .012). There was no effect of sex (β = 0.02, 95% CI = −0.06 to 0.02, p = .32). Convergence was also present when we modeled age as a covariate (main effect of network: β = 0.09, 95% CI = 0.08 to 0.10, $p < .001$; main effect of diagnosis: β = 0.05, 95% CI = 0.004 to 0.09, p = .035). Though higher age was associated with worse disease burden (β = 0.004, 95% CI = 0.002 to 0.006, $p < .001$), there was no age-by-diagnosis interaction ($\beta = -2.7 \times 10^{-4}$, 95% CI = −0.003 to 0.0020, p = .84), suggesting that the accumulation of disease alone does not account for depression. When we removed participants on methylprednisolone, prednisone, and interferon beta, our results remained significant (main effect of network: β = 0.09, 95% CI = 0.08 to 0.11, $p < .001$; main effect of diagnosis: β = 0.05, 95% CI = 0.001 to 0.10, p = .046). Statistics for supplementary analyses are provided in Table S6.

DISCUSSION

Using a novel approach for assessing the relationship between white matter lesions and brain networks implicated in depression, we provide new evidence supporting an association between white matter lesion location and depression in MS. Regardless of depression diagnosis, patients with MS had greater disease burden within the white matter depression network. This anatomical predilection may create a vulnerability to depression comorbidity in MS; MS+Depression patients had higher disease burden across the whole brain than MS−Depression patients and greater burden specifically within the white matter depression network. MS+Depression patients had greater injury in fascicles with more overlap with the depression network. Additionally, MS+Depression patients had greater functional impairment than MS−Depression patients in our subsample with PROMIS scores. Taken together, these data demonstrate that injury to white matter fascicles that structurally support a previously defined functional depression network (22) are associated with depression in MS.

Numerous conceptual and methodological challenges have limited the field's understanding of how MS lesions may increase vulnerability to depression. Prior studies built on the assumption that depression symptoms are caused by lesions in the same anatomic location have yielded inconsistent findings, indicating that spatially distributed lesions can lead to a common phenotype (6,18,50). However, few studies have directly explored whether heterogeneous lesions of the same network, rather than the same location, contribute to depression. Large sample sizes are necessary to identify complex relationships between distributed white matter lesions and depression, but previous studies often employed manual lesion segmentation to extract white matter lesions from brain scans, which is time-intensive and subject to bias (39). Given the high resolution necessary for segmentation, prior work often relied on research scans, increasing costs and effort for recruitment (50,51). Together, these constraints have limited efforts to disentangle the complex relationship between MS and depression.

To address these limitations, our analysis coupled automated lesion segmentation in clinical scans with white matter LNM to show that lesions in white matter fascicles connecting the depression network are associated with depression in patients with MS. These fascicles connect a previously described functional depression network that includes the frontoparietal and dorsal attention networks, which support executive function and attention. Importantly, planning and concentration difficulties are core deficits in depression (52,53). Furthermore, the dorsolateral prefrontal cortex, a central brain region in the frontoparietal network, is a structural target for transcranial magnetic stimulation and electroconvulsive therapy for severe depression (54,55). Disease in these fascicles may therefore impact treatment outcomes and warrant further study.

In recent work, Siddiqi *et al.* (25) builds upon LNM studies by using normative data to estimate the relationship between blood oxygen level–dependent signal in MS white matter lesions and the functional depression network. In a sample in which variation in depressive symptoms was captured dimensionally in patients with MS not diagnosed with depression, the authors showed that the normative blood oxygen level–dependent signal in MS lesions was functionally connected to a brain network that overlapped with the previously defined functional depression network. We extend this literature by using white matter lesions to define participant-specific, disconnected white matter networks and directly tested whether structural injury to key fascicles relates to a history of clinically impairing depression. Additionally, we capitalized on a new dataset of research-quality clinical scans to increase sample size and generalizability. Lastly, our conceptual framework complements recent literature showing that MS-associated structural disruptions are associated with disability and disease progression (26,56,57).

Limitations

Our study has several limitations. As our study uses ICD-10 for phenotyping, we rely on ICD-10 diagnostic coding for both depression and MS. For depression phenotyping, ICD-10 diagnosis reflects a lifetime history of depression rather than symptoms at the time of scan. Depression is underdiagnosed in medical populations—the absence of an ICD-10 depression code does not preclude the presence of depression (32). Our rigorous, multistep depression phenotyping that incorporated medications and symptom screenings aimed to address this limitation and was validated by an independent measure not used in group construction (i.e., PROMIS). Previous research has suggested that depression may mediate the relationship between disease burden and disability, which may be reflected in our PROMIS subsample data (9). Future prospective studies with structured depression assessments that relate active or gadolinium-enhancing lesions with depression symptoms concurrently will be critical to testing for causal relationships between the two.

In MS research, participants are often clustered by clinical progression subtype, duration of disease, and disease severity as summarized by the Expanded Disability Status Scale. However, the electronic health record codes MS via the ICD-10 code G35, which does not specify either clinical subtype or disease duration. There is ongoing debate regarding the meaning of clinical MS phenotyping given that biological correlates have not been reliably associated with disease progression, leading some to conceptualize MS clinical phenotypes as a continuum (58). Furthermore, the Expanded Disability Status Scale is a research scale that was designed to measure outcomes in clinical trials and often is not part of clinical standard of care; it was not available for our sample. Critiques of the Expanded Disability Status Scale often highlight that it does not sufficiently assess mood and cognitive function (59). While data from our PROMIS subsample suggest that MS patients with depression have more functional impairment than MS patients without depression, the above-mentioned limitations highlight the need for rigorous clinical and cognitive phenotyping in conjunction with neuroimaging and measures of functional impairment to further disentangle these relationships. Lastly, though this study characterizes MS as a disease of white matter, MS is also associated with gray matter atrophy (60,61). Incorporating measures of gray matter disease into future studies of MS and depression will likely be informative.

Generalizability

We demonstrated that lesions to white matter fascicles can contribute to depression. Our work highlights opportunities to combine clinical imaging and electronic health record data to capture individual variation related to depression. Our study was performed using data from a single institution, which may limit its generalizability to other populations. However, by using automated white matter lesion segmentation, we have provided a scalable solution for expanding this work to bigger datasets as well as datasets outside our hospital system. Additionally, our template-based approach does not require diffusion-weighted MRI, allowing for wider use.

Conclusions

In this retrospective case-control study, we explored the high comorbidity between MS and depression using white matter LNM. We identified key relationships between white matter lesions in the depression network and depression. MS lesions preferentially targeted white matter fascicles that connect the depression network irrespective of depression diagnosis. Furthermore, MS patients with depression had more disease burden than MS patients without depression, which was specifically driven by more disease burden within the white matter depression network. This approach holds promise for understanding not only depression in the context of MS, but also the role of abnormalities in white matter as a mechanism for depression more broadly.

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EBB, RTS, and TDS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. EBB, EMS, MC, MKS, RTS, and TDS were responsible for concept and design of the study. EBB, EMS, MC, SCC, MLM, MKS, AB-O, ARM, CEM, CMP, VR, JAD, MDF, RTS, and TDS were responsible for acquisition, analysis, or interpretation of data. EBB and TDS wrote the original draft of the manuscript. EBB, EMS, MC, MKS, RTS, and TDS were responsible for critical revision of the manuscript for important intellectual content. EBB and EMS performed the statistical analysis. EBB, RTS, and TDS obtained funding. AE, VR, and MMS provided administrative, technical, or material support. RTS and TDS supervised the study.

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Code and instructions for replicating all analyses can be found at https://pennlinc.github.io/msdepression/.

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ARTICLE INFORMATION

From the Penn Lifespan Informatics and Neuroimaging Center, Philadelphia, Pennsylvania (EBB, MC, SCC, BSL, MMS, TDS); Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania (EBB, MC, SCC, BSL, MMS, TDS); Penn Statistics in Imaging and Visualization Center, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania (EMS, TR-F, MLM, ARM, MMS, RTS); Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania (MKS, AB-O, CEM, CMP, JAD); Center for Neuroinflammation and Neurotherapeutics, University of Pennsylvania, Philadelphia, Pennsylvania (MKS, AB-O, CEM, CMP); Department of Information Services, University of Pennsylvania, Philadelphia, Pennsylvania (AE, VR); Center for Brain Circuit Therapeutics, Department of Neurology, Psychiatry, and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (MDF); and Center for Biomedical Image Computing and Analytics, University of Pennsylvania, Philadelphia, Pennsylvania (RTS, TDS).

RTS and TDS contributed equally to this work as joint senior authors.

Address correspondence to Theodore D. Satterthwaite, M.D., at sattertt@pennmedicine.upenn.edu.

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