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Mechanisms Linking White Matter Lesions, Tract Integrity, and Depression in Alzheimer Disease

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ABSTRACT

Objective: *Late-life depression involves the disconnection of white matter tracts that regulate mood. A pathogenic link between poor tract integrity and depressive symptoms is believed to be white matter lesions (WML), however the mechanisms linking tract integrity, WML, and depression remains unexplored. The authors sought to identify whether the association between reduced tract integrity and depressive symptoms is mediated by WML in patients with Alzheimer disease (AD), and whether individual characteristics moderate this effect.* ***Methods:*** *This was a cross-sectional study in a tertiary memory clinic. A total of 91 patients with mild AD and 79 healthy elderly, comparable in depressive symptoms, white matter hyperintensities (WMH) volume, cardiovascular risk, age, and sex were chosen. Tract integrity was assessed using diffusion tensor imaging, WML were indexed as WMH, measured using fluid-attenuation inversion recovery imaging, and depressive symptoms were measured with the informant-based Geriatric Depression Scale.* ***Results:*** *In patients with mild AD, reduced tract integrity in right hemispheric cortical-subcortical tracts and the genu of the corpus callosum was moderately associated with depressive symptoms. This association was fully mediated by WML. Moderation analysis indicated that old age strengthened the association between all tracts and depressive symptoms, as mediated by WML. In cognitively healthy elderly, neither tracts nor WML were related to depressive symptoms.* ***Conclusion:*** *Reduced tract integrity may be important but not sufficient for the manifestation of depressive symptoms in mild AD. Instead, WML may drive the*

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pathogenic link between reduced tract integrity and depressive symptoms. (Am J Geriatr Psychiatry 2019; ■■:■■−■■)

INTRODUCTION

Late-life depression is one of the most common mental illnesses in the aging population and its prevalence is exacerbated in those with dementia.[1] Onset of depressive symptoms in late life is precipitated by risk factors including cerebrovascular disease, old age, vulnerable genotypes, low socioeconomic status, and stressful life events.[2–4] Of these risks, the most studied has been cerebrovascular disease, which has been proposed by the vascular depression hypothesis to predispose, precipitate, and perpetuate late-life depression by altering cerebral white matter.[5]

The link between cerebrovascular disease and late-life depression has been supported by a large body of clinical and magnetic resonance imaging (MRI) studies. Clinically, cerebrovascular disease risk factors such as diabetes, high blood pressure, and atrial fibrillation frequently co-occur with depression and independently predict incidence of depressive symptoms.[6] However, this association between clinical markers of cerebrovascular disease and depression has been inconsistent,[7] and a more reliable link has been observed with MRI markers, such as white matter hyperintensities (WMH), chronic lacunes, and enlarged perivascular spaces.[8,9] WMH, in particular, have been shown to quadruple the odds of developing depressive symptoms in cognitively healthy elderly,[8] and in patients with dementia.[10]

WMH are believed to contribute to depression by disrupting white matter tracts that are central for mood regulation.[11] White matter tracts can be visualized using diffusion tensor imaging (DTI), which uses diffusion to measure the restriction of water movement through tissue due to structural abnormalities. Restricted mobility of water molecules is an indication of reduced tract integrity, caused by abnormal axonal membranes, myelin sheaths, and neurofibrils.[12] Reduced tract integrity plays an important role in depressive symptomology, discriminating between patients with and without symptoms[13] and predicting the incidence of late-life depression.[14] Tracts that play an important role in late-life depression involve those that link the frontal cortex with other mood-related cortical and subcortical areas, such as the amygdala and hypothalamus.[15] Alterations to these tracts disrupt the transfer of information between cortical and subcortical regions, lending support to the idea that depression may be a disconnection syndrome between cortical and subcortical regions.[13]

Tract integrity is influenced by individual characteristics that enhance or protect against structural abnormalities. For instance, reduced tract integrity has been associated with a greater accumulation of cardiovascular risk factors,[16] severe cognitive decline,[17] old age,[18] and the APOE-e4 gene.[19] Conversely, cognitive reserve, which is often characterized by high educational attainment and vocabulary knowledge, has been observed with healthier tract integrity.[17]

The direct relationships between depressive symptoms, WMH, tract integrity, and individual characteristics have been well established, however, what remains unclear is how WMH and tract integrity interact in the process of depression and under what conditions their relationship with depression is strongest. Based on the vascular depression hypothesis, we predict that the association between reduced tract integrity and depressive symptoms may be mediated by WMH and that this effect may be enhanced in individuals with a high load of cardiovascular risk factors, old age, lower educational attainment, impaired global cognition, and the APOE-e4 genotype. We applied this hypothesis to subsyndromal depressive symptoms given that most patients seen in memory clinics present with subsyndromal depressive symptoms.[20]

METHODS

Participants

Ninety-one patients with mild Alzheimer disease (AD) and 79 cognitively healthy elderly were recruited into the study. Patients with mild AD were recruited from a tertiary neurology center in Singapore (National Neuroscience Institute) between 2013 and 2016. Diagnosis of mild probable AD was based on the National Institute on Aging-Alzheimer's Association Criteria[21] and included patients with a Clinical Dementia Rating Scale[22] of 1. Diagnosis was made by

cognitive neurologists using structural MRI as a supportive biomarker and a comprehensive neuropsychological evaluation. Healthy elderly were recruited at the National Neuroscience Institute, Singapore and National University Hospital, Singapore from 2010 −2016 and included elderly who were "cognitively normal," as determined by a comprehensive neuropsychological assessment, including a Mini-Mental State Exam (MMSE) score greater than 28, and had a Clinical Dementia Rating Scale of 0.

Exclusion criteria for all participants included 1) a current or history of alcohol or drug abuse; 2) comorbid neurodegenerative diseases (e.g., Parkinson disease); 3) history of acute clinical strokes; 4) cerebral amyloid angiopathy based on neuroimaging criteria; 5) participants with MRI contradictions; and 6) a current or known history of major depression (defined using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) or other psychiatric conditions. Therefore, reported depressive symptoms were subsyndromal and unrelated to a premorbid psychiatric disorder.

The study was approved by the SingHealth Centralized Institutional Review Board and conducted in accordance with Singhealth Centralized Institutional Review Board guidelines and the Declaration of Helsinki. Written informed consent was obtained from all participants or their next of kin if they were mentally incapable of giving consent.

Measures

Demographics were collected via clinical interview; cardiovascular risk profile was indexed using the Framingham office-based cardiovascular disease risk prediction model;[23] global cognition was indexed using the Montreal Cognitive Assessment[24] and the MMSE;[25] and APOE-e4 genotyping was performed using TaqMan SNP genotyping assay and ABI 7900HT PCR system (Applied Biosystems, Foster City, CA). Depressive symptoms were measured using the Geriatric Depression Scale-Short Form,[26] which is an informant-based questionnaire consisting of 15 yes/no items that has good validity ($r = -0.73$) and internal consistency (Cronbach $\alpha = 0.82$) in the elderly with an MMSE score greater than 10.[27] A cutoff of 5 points or more indicated significant depressive symptoms, as per locally validated norms.[28]

Target white matter tracts (Fig. 1) were chosen based on a literature review of the most frequently reported tracts from tract-based spatial statistics studies that analyzed the entire brain for group differences between depressed and nondepressed individuals, including patients with clinically diagnosed major depression[14,29,30] and subsyndromal depression,[31] and meta-analyses investigating the association between white matter tracts and late-life depression.[13] Total WMH burden was used instead of regional WMH because target tracts traverse across multiple cerebral regions.

FIGURE 1. The cortical-subcortical and cortical-cortical white matter tracts proposed to be associated with depressive symptoms. The tract skeleton was chosen using TBSS and the JHU atlas which was layered on top to identify individual tracts. Warm colors (red-orange) indicate right anatomic features, whereas cool colors (blue) indicate left anatomic features. AX: axial; CC: cingulum (cingulate gyrus); COR: coronal; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; JHU: John Hopkins University; PTR: posterior thalamic radiation; SAG: sagittal; SCR: superior corona radiata; SLF: superior longitudinal fasciculus; TBSS: Tract-Based Spatial Statistics; UF: uncinate fasciculus.

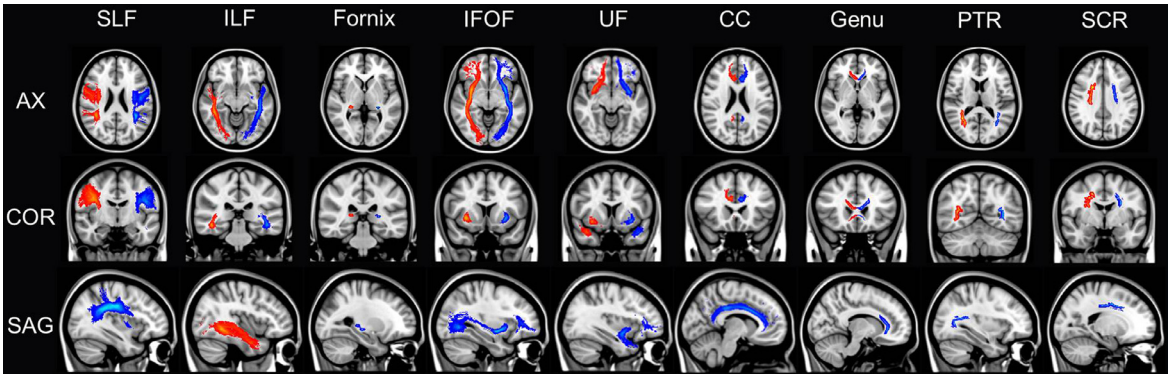


Image Protocol

Participants underwent MRI in a whole body magnetic resonance system. Participants undergoing study procedures before 2015 were scanned using a 3T Siemens Tim Trio system (Siemens, Erlangen, Germany), and participants recruited in 2015 and beyond were scanned using a 3T Siemens Prisma system (Siemens). Three-dimensional volumetric scans were obtained using a T1-weighted magnetization-prepared rapid gradient-echo sequence (repetition time 2300 ms, echo time 2.98 ms, matrix = 192 × 256 × 256, voxel = 1.0 mm isotropic) as per the AD Neuroimaging Initiative protocols (http://adni.loni.usc.edu/). Images were segmented into gray matter, white matter, and cerebrospinal fluid maps using a unified segmentation pipeline[32] including affine regularization to the International Consortium for Brain Mapping space template for East Asian brains. The generated gray matter and white matter maps were then used to generate global volumes of gray and white matter, respectively. Volumetric analysis of WMH was done in SPM8 (Wellcome Trust, London) using an existing workflow.[33] Fluid-attenuated inversion recovery sequences were co-registered with their corresponding Montreal Neurological Institute-normalized magnetization-prepared rapid gradient-echo sequences, and voxels of WMH were identified based on having an intensity of at least 1.4 times compared with the surrounding white matters.[34]

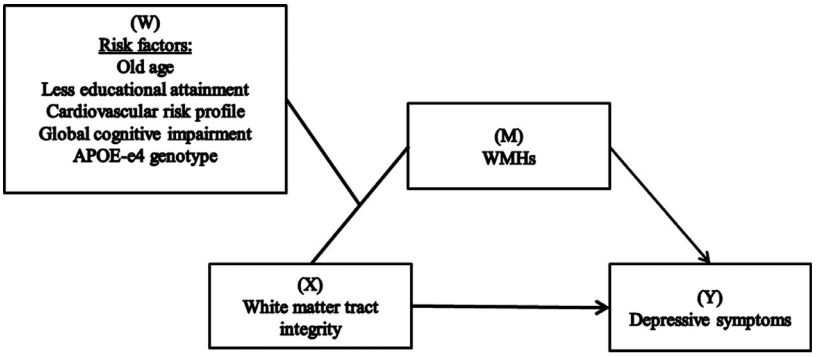
DTI sequences were acquired using a single-shot spin echo echo-planar sequence (repetition time 9600 ms, echo time 107 ms, matrix = 128 × 128, 54 slices, voxel = 2.0 mm isotropic, 30 diffusion directions, b = 1000 s/mm^2, and 6 b = 0 s/mm^2). The DTI data were preprocessed using FMRIB Software Library (University of Oxford, UK) (http://www.fmrib.ox.ac.uk/fsl). Following our previous approach,[35] each diffusion-weighted volume was aligned to the b = 0 image using EDDY current correction to correct for the distortions caused by eddy currents and head movements. Data were discarded if the maximum displacement relative to the first b = 0 volume was more than 3 mm. Diffusion gradients were rotated to improve consistency with the motion parameters. The DTI images were corrected for the geometric distortion caused by magnetic field inhomogeneity using FUGUE with gradient-echo field maps. Fractional anisotropy (FA) images were created by fitting a diffusion tensor model to the diffusion data at each voxel. We then applied tract-based spatial statistics[36] to carry out a voxel-wise analysis of FA data within major white matter pathways throughout the whole brain following our previous approach.[37] The mean FA of the predefined white matter tracts were extracted from individual tracts of interest (Fig. 1) located according to the Johns Hopkins University white matter tractography atlas and the Johns Hopkins University ICBM-DTI-81 white matter labels atlas.[38]

Statistical Analyses

Group differences in demographics, cognition, cardiovascular risk score, depressive symptoms, and MRI markers between patients with mild AD and healthy elderly were determined using a t test for continuous variables and the χ^2 test for categorical variables, or the Fisher's exact test for variables with small cell counts. For unequal variances, the Welch adjustment was used.

Path analysis was used to examine the direct and indirect relationships between white matter and depressive symptoms. First, the direct relationship between predictor variables (tract integrity and WMH) and the outcome (depressive symptoms) was determined using independent regression analyses for each diagnostic group. Multicollinearity between all tracts and WMH was examined using variance inflation factors,[39] and normality was examined using skew and kurtosis, with log transformation where necessary. All analyses controlled for age, educational attainment, cardiovascular risk profile (Sex was included in the cardiovascular risk score; therefore, we did not include it as a separate covariate. Age and education also make up the cardiovascular risk score; however, because of their variability, we included them as covariates.), global cognition, APOE-e4 genotype, total gray matter volume, and MRI scanner type to control for the use of different scanners. Second, mediation analysis[40] determined whether the indirect relationship between tract integrity (X in Fig. 2) and depressive symptoms (Y in Fig. 2) could be explained by a mediating variable, WMH (M in Fig. 2). If the relationship between X-Y reduced in significance after including WMH, partial mediation was implied. Alternatively, if X-Y was no longer significant in the presence of WMH, full mediation was implied. Mediation analysis was carried out independently for each

FIGURE 2. The model implies that the relationship between reduced white matter tract integrity (X) and depressive symptoms (Y) may be driven by WMHs (M). The model additionally implies that individual risk factors (W) may moderate this indirect effect between tract integrity and depressive symptoms. Adapted from Hayes.[40]



diagnostic group, each white matter tract, and each hemisphere of each tract due to possible structural and functional hemispheric asymmetry.[41] To compare the structure of the regression models between diagnostic groups, Steiger's z test[42] was applied. First the predictive value for depressive symptoms was calculated for each diagnostic group; next the correlation between each predicted value and the criterion was determined to calculate Steiger's z. A simulated procedure using bootstrap methods corrected for multiple comparisons, which has been empirically validated to derive robust parameter estimates based on maximized power and limited type 1 error rates.[43] As a subanalysis, the mediation analyses were assessed in participants without significant depressive symptoms (Geriatric Depression Scale [GDS] score <5) to confirm consistency of results.

As a third step for significant mediation findings, a moderation analysis[40] was conducted to quantify whether the indirect relationship between tracts and depressive symptoms, via WMH, was enhanced or attenuated by individual characteristics, such as age, educational attainment, cardiovascular risk profile, global cognition, or the APOE-e4 genotype. Moderation was calculated by first z-scoring all variables then multiplying each tract (X in Fig. 2) with each risk factor (W in Fig. 2) to create the interaction variable (WX). If XW was significantly related to WMH (M in Fig. 2) (WX-M), and indirectly related to the outcome (Y in Fig. 2) (WX-M-Y), we noted that moderated mediation had occurred (for more detail see Supplementary Material).

Path analyses for both the mediation and moderation effect were conducted using SPSS Amos version 20 (SPSS, Inc, Chicago, IL). Model fit for each path analysis was determined using recommended criteria:[44] 1) χ^2 p value >0.05; 2) Bentler Comparative Fit Index (CFI >0.95); and 3) Root Mean Square Error of Approximation (RMSEA <0.06). Model fit was revised using modification indices. A bias corrected bootstrap estimation with 1,000 resamples was applied to both the mediation and moderation analyses as a nonparametric approach for effect-size estimation. Here, a 95% confidence interval that did not contain zero indicated a significant effect.[45] Effect sizes for the direct effects were indexed using the standardized coefficient of the slope (B), which is identical to the benchmark set for Pearsons r, 0.10 (small), 0.30 (moderate), and 0.50 (large).[46] Effect size for indirect effects were indexed by squaring Cohen's[46] estimations because indirect effects represent a product of two effects,[40] 0.01 (small), 0.09 (moderate), and 0.25 (large).

An exploratory analysis sought to verify the specificity of our model to mood-related white matter tracts by testing whether tracts outside of the mood network, such as motor tracts, were significant in our model. Specifically, we tested one cortical-subcortical tract, the cerebellar peduncle, which connects the cerebellum to the brainstem, and one interhemispheric tract, the splenium, which connects the motor regions of each hemisphere. We explored whether these motor-related tracts were directly and indirectly related to depression, as mediated by WMH.

RESULTS

Participants

The AD and healthy elderly groups did not differ in age, sex, race, cardiovascular risk profile, WMH volume, or severity of depressive symptoms (Table 1). Compared with the healthy elderly, patients with mild AD had lower educational attainment, greater global cognitive impairment, reduced gray matter volume, and higher prevalence of the APOE-e4 genotype. Patients with mild AD also exhibited reduced tract integrity compared with controls for all tracts except the right and left interior occipital fasciculus and left fornix (Supplementary Table S1).

Direct Relationships Between Tract Integrity, WMH, and Depressive Symptoms

For patients with mild AD, path analysis models testing the direct relationship between white matter tract integrity and depressive symptoms (X-Y association in Fig. 2), while controlling for all covariates and WMH had good model fit (χ^2 [14] <10, p >0.05, CFI >0.99 and RMSEA <0.09). Depressive symptoms were significantly related to the right side of the posterior thalamic radiation, uncinate fasciculus, inferior fronto-occipital fasciculus, fornix, superior corona radiate, and the genu of corpus callosum (Table 2). All relationships were negative with a moderate effect size, suggesting that as tract integrity decreased, severity of depressive symptoms increased. All left side tracts were not related to depressive symptoms.

TABLE 1. Participant Characteristics and Group Differences

Mean (SD)	Healthy Elderly (N = 79)	Mild AD (N = 91)	Test Statistic
Age (years)	62.85 (7.12)	69.25 (8.56)	0.16[a]
Sex (male, %)	33 (41%)	47 (52%)	1.65[d]
Years of education	13.33 (3.25)	9.72 (3.91)	3.23[a,f]
Race (%)			4.58[e]
Chinese	72 (91%)	85 (93%)	
Malay	1 (1%)	2 (2%)	
Indian	3 (4%)	3 (3%)	
Euroasian	3 (4%)	0	
Other	0	1 (2%)	
Medication (frequency, %)			
Cognitive enhancers	0	12 (13%)	2.16[d,f]
Antidepressants	2 (2%)	1 (1%)	1.60[d]
Antipsychotics	0	0	-
APOE-e4 carrier (%)	7 (9%)	41 (45%)	21.09[d,g]
MoCA (score range 0−30)	27.86 (1.83)	21.99 (5.27)	92.21[b,g]
MMSE (score range 0−30)	28.24 (1.55)	24.92 (4.09)	51.24[c,g]
Framingham score (score range 0−30)	12.84 (3.37)	14.98 (3.94)	0.85[a]
GDS Total (mean, SD, score range) (score range 0−15)	2.01 (2.68) range: 0−12	3.08 (2.53) range: 0−10	0.72[a]
GDS ≥5 (frequency, %)	9 (11%)	18 (20%)	1.49[d]
WMH volume	4.96 (6.53)	7.03 (9.10)	−1.67[a]
Gray matter volume	553.81 (60.69)	520.40 (62.14)	3.53[a,g]

Notes: MoCA: Montreal Cognitive Assessment; SD: standard deviation; WMH: white matter hyperintensities, cognitive enhancers included Donepezil.

[a] t test values with df = 168.

[b] Welch adjusted t test adjusted df = 119.89.

[c] Welch adjusted t test adjusted df = 118.59.

[d] The χ^2 test values with df = 1.

[e] Fisher's exact test values.

[f] p <0.01.

[g] p <0.001.

TABLE 2. Regression Path Analysis for the Direct Relationship Between Right White Matter Tracts and Depressive Symptoms in Mild AD and Healthy Elderly

	Healthy Elderly				Mild AD			
White Matter Tract	**B**	**SE**	**t Value**	**95% CI**	***B***	**SE**	**t Value**	**95% CI**
Superior longitudinal fasciculus	*−0.07*	0.11	−0.63	−0.22 to 0.75	*−0.29*	0.16	−1.81	−0.63 to 0.01
Inferior longitudinal fasciculus	*−0.05*	0.09	−0.55	−0.14 to 0.21	*−0.23*	0.16	−1.43	−0.49 to 0.05
Posterior thalamic radiation	*−0.10*	0.06	−1.66	−0.25 to 0.08	*−0.41*	0.14	−2.92	−0.65 to −0.15[a]
Uncinate fasciculus	*−0.19*	0.11	−1.72	−0.35 to 0.12	*−0.33*	0.16	−2.06	−0.57 to −0.04[a]
Cingulum cingulate	*−0.21*	0.13	−1.61	−0.46 to 0.09	*−0.11*	0.16	−0.68	−0.23 to 0.41
Inferior fronto-occipital fasciculus	*−0.13*	0.05	−2.60	−0.63 to 0.03	*−0.31*	0.15	−2.06	−0.56 to −0.03[a]
Fornix	*−0.16*	0.07	−2.28	−0.31 to −0.02	*−0.41*	0.15	−2.73	−0.65 to −0.15[a]
Genu of corpus callosum	*−0.30*	0.15	−2.00	−0.56 to −0.04[a]	*−0.41*	0.15	−2.73	−0.65 to 0.14[a]
Superior corona radiata	*−0.50*	0.28	−1.78	−0.54 to 0.42	*−0.29*	0.12	−2.41	−0.46 to −0.08[a]

Notes: Healthy elderly regression df = 69, mild AD regression df = 81. B: standardized beta coefficient; CI: confidence interval; SE: standard error. Values without a superscript "a" indicates not significant at $p > .05$.

[a] Bootstrapped $p < 0.05$.

The direct relationship between WMH and depressive symptoms (M-Y association in Fig. 1) was significant and of a small effect size (b = 0.06, SE = 0.03; 95% confidence interval: 0.01−0.15; $p < 0.05$), indicating that as WMH volume increased, severity of depressive symptoms increased.

The direct relationship between right white matter tracts and WMH (X-M association in Fig. 1) was significant and of a moderate to large effect size (Supplementary Table S1). All relationships were negative, indicating that as tract integrity reduced, WMH volume increased.

For healthy elderly, the direct relationship between white matter tract integrity and depressive symptoms (X-Y association in Fig. 1), while controlling for covariates and WMH, was only significant for the genu of corpus callosum, which was of a moderate effect size (Table 2).

The direct relationship between WMH and depressive symptoms (M-Y association in Fig. 1) was not significant.

The direct relationship between white matter tracts and WMH (X-M association in Fig. 1) was significant for the right side of the fornix, posterior thalamic radiation, and superior longitudinal fasciculus (Supplementary Table S2). All relationships were negative and of a small effect size.

Indirect Relationship Between Tract Integrity, WMH, and Depressive Symptoms

All models testing the indirect relationship between white matter tract integrity and depressive symptoms, as mediated by WMH, while controlling for covariates, had excellent model fit (χ^2 [13] <10; $p > 0.10$, CFI >0.99, and RMSEA <0.05). Table 3 displays that for patients with mild AD, WMH mediated the relationship between depressive symptoms and seven of the right hemispheric tracts, in addition to the genu of corpus callosum. Here, inferior fronto-occipital fasciculus exhibited the largest effect, whereas the inferior longitudinal fasciculus, superior longitudinal fasciculus, fornix, posterior thalamic radiation, and genu of corpus callosum exhibited moderate effect sizes. The uncinate fasciculus and superior corona radiata exhibited small effect sizes. The cingulum cingulate was not significantly mediated by WMH, nor were any of the left side tracts. All indirect associations were negative, suggesting that as the integrity of tracts decreased, the severity of depressive symptoms increased, as mediated by WMH. All effects involved full mediation as the direct relationship between tract integrity and depressive symptoms became insignificant when including the mediator. These findings remained consistent in a subanalysis with only participants exhibiting nonsignificant depressive symptoms (GDS <5) (Supplementary Table S3).

For healthy elderly, white matter tract integrity was not indirectly associated with depressive symptoms via WMH (Table 3). A Steiger's z test indicated that the structure of each mediation regression model was significantly different between the AD patients and healthy elderly (Supplementary Table S4). This suggests that the role of WMH and tract integrity in

TABLE 3. Regression Path Analysis Models for the Indirect Relationship Between White Matter Tracts and Depressive Symptoms as Mediated by WMH in Mild AD and Healthy Elderly

	Mild AD				Healthy Elderly			
Right Side Tract	**B**	**SE**	**t Value**	**BC 95% CI**	**B**	**SE**	**t Value**	**BC 95% CI**
Superior longitudinal fasciculus	−0.16	0.09	1.77	−0.38 to −0.03[b]	−0.04	0.08	−0.50	−0.13 to 0.36
Inferior longitudinal fasciculus	−0.24	0.12	−2.00	−0.48 to −0.05[a]	−0.01	0.02	−0.50	−0.11 to 0.23
Fornix	−0.22	0.12	−1.83	−0.42 to −0.04[a]	−0.00	0.02	0.00	−0.07 to 0.31
Posterior thalamic radiation	−0.22	0.12	−1.83	−0.42 to −0.04[a]	−0.01	0.09	−0.11	−0.05 to 0.04
Uncinate fasciculus	−0.06	0.04	−1.50	−0.13 to −0.01[a]	−0.01	0.02	−0.50	−0.04 to 0.67
Cingulum cingulate	−0.03	0.04	−0.75	−0.19 to 0.00	−0.01	0.03	−0.33	−0.06 to 0.66
Inferior fronto-occipital fasciculus	−0.31	0.16	−1.93	−0.65 to −0.07[a]	−0.00	0.02	0.00	−0.06 to 0.02
Genu of corpus callosum	−0.22	0.12	−1.83	−0.41 to −0.03[a]	−0.01	0.02	−0.50	−0.06 to 0.37
Superior corona radiata	−0.04	0.05	−0.80	−0.10 to −0.01[b]	−0.04	0.07	−0.57	−0.17 to 0.04

Notes: Healthy elderly regression df = 68, mild AD regression df = 80. B: standardized beta coefficient; BC: bias corrected; CI: confidence interval; SE: standard error.
[a] Bootstrapped p <0.05.
[b] Bootstrapped p <0.01.

depressive symptoms were significantly different across patients with AD and healthy elderly.

Moderators of the Relationship Between White Matter and Depressive Symptoms

For patients with mild AD, all models testing whether individual characteristics moderated the indirect effects between white matter tracts and depressive symptoms, via WMH, had good model fit (χ^2 [47] <70; p >0.05, CFI >0.95, and RMSEA <0.04). The only significant moderator was old age for all tracts, except for the inferior longitudinal fasciculus (Table 4). The effect suggests that patients older than 65 years exhibited the strongest association between low tract integrity and severity of depressive symptoms.

For healthy elderly, no significant moderation was observed.

Exploratory Analysis with Non-Mood Related White Matter Tracts

Motor-related tracts, namely the cerebellar peduncle and the splenium, were not directly or indirectly related to depressive symptoms, as mediated by WMH in patients with mild AD (Supplementary Table S5), supporting the specificity of our model to mood-related tracts.

DISCUSSION

Main Findings

In patients with mild AD, we observed that reduced integrity in mood-related white matter tracts was important but not sufficient for the manifestation of subsyndromal depressive symptoms. Instead, WMH were the catalyst that connected reduced tract

TABLE 4. Regression Path Analysis Models for Age (≥65 years) as a Moderator for the Indirect Relationship Between White Matter Tracts and Depressive Symptoms via WMH for AD

Right Side Tract	**B**	**SE**	**t value**	**BC 95% CI**
Superior longitudinal fasciculus	−0.08	0.02	−4.00	−0.17 to −0.01[a]
Inferior longitudinal fasciculus	−0.01	0.02	−0.50	−0.09 to 0.05
Fornix	−0.04	0.02	−2.00	−0.11 to −0.01[a]
Posterior thalamic radiation	−0.05	0.03	−1.66	−0.12 to −0.01[a]
Uncinate fasciculus	−0.05	0.03	−1.66	−0.11 to −0.01[a]
Inferior fronto-occipital fasciculus	−0.04	0.03	−1.33	−0.12 to −0.01[a]
Genu body	−0.69	0.47	−1.46	−1.63 to −0.10[a]
Superior corona radiata	−0.54	0.29	−1.86	−1.36 to −0.20[a]

Notes: Healthy elderly regression df = 63, mild AD regression df = 75. B: standardized beta coefficient; BC: bias corrected; CI: confidence interval; SE: standard error.
[a] Bootstrapped p <0.05.

integrity to depressive symptoms. Patients with AD were found to be most vulnerable to this effect, whereas reduced tract integrity and WMH played a limited role in subsyndromal depressive symptoms in cognitively healthy elderly comparable on age, sex, cardiovascular risk profile, WMH volume, and severity of depressive symptoms. We further observed that depressive symptoms may not just involve a disconnection between cortical-subcortical tracts, which was localized to the right hemisphere, but also a disconnection between the interhemispheric tracts. Finally, we observed the association between white matter and depressive symptoms was strongest in elderly older than 65 years.

Theoretical and Clinical Implications

Consistent with previous findings in cognitively normal elderly with major depression,[47] we observed that reduced white matter tract integrity was directly related to depressive symptoms; however after the inclusion of WMH, this association was no longer significant. WMH is a macrostructural representation of neuronal loss, demyelination, and gliosis[48] and represents the most advanced stage of white matter degeneration. Alternatively, DTI metrics provide a microstructural representation of fiber density and axon diameter and represent subtle early stages of white matter degeneration. Therefore, our findings suggest that subtle changes in mood-related tracts may only be associated with depressive symptoms when the overall severity of white matter damage is advanced. Our findings are supported by previous research demonstrating that depression severity correlates strongest with white matter tracts intersected by white matter lesions,[29] and that a direct relationship between tract integrity and depressive symptoms is commonly observed in elderly with cerebrovascular disease,[49] but not in healthy elderly without cerebrovascular disease.[50] Further research is required to determine whether severe white matter damage located specifically in target tracts is driving this effect.

Consistent with previous perspectives,[5] we observed that mood-related cortical-subcortical tracts were implicated in subsyndromal depressive symptoms, however, we further found that interhemispheric tracts may be of equal clinical relevance. Specifically, the genu of the corpus callosum exhibited the largest association with depressive symptoms, and was the only tract significantly related to depressive symptoms in cognitively healthy elderly. The corpus callosum transfers information between the two hemispheres and the genu connects the prefrontal with orbitofrontal regions.[51] This significance of the genu of the corpus callosum in depressive symptomology converges with previous findings[13] and signifies the importance of disrupted information transfer between frontal hemispheres in depression. With regards to cortical-subcortical tracts, we observed that only the right hemisphere tracts were associated with depressive symptoms in patients with mild AD, which is consistent with the growing evidence that the right side of the brain may have a primary role for depressive symptoms in the elderly.[52] Importantly, we verified the specificity of our model to mood-related tracts by demonstrating that motor-related cortical-subcortical and interhemispheric tracts were not significant predictors of depression in patients with mild AD.

In our study, cognitively healthy elderly and AD patients had comparable WMH volumes and severity of depressive symptoms. Despite this, poor white matter health was only associated with subsyndromal depression in patients with AD. This implies the manifestation of subsyndromal depressive symptoms in cognitively healthy elderly may be independent of white matter health and the vascular depression hypothesis may have limited applicability for this population. A significant finding only in the AD group suggests that AD pathology may have provided a vulnerable context for poor white matter health to cause observable abnormalities. Amyloid has previously been shown to compromise the integrity of white matter tracts[53] and greater AD pathology has been associated with greater WMH accumulation.[54] Therefore, late-life subsyndromal depressive symptoms may involve an interaction between the pathophysiological changes of depression and changes initiated by other diseases, such as AD.[55] We note that mechanisms other than cerebrovascular disease may degrade white matter structures in AD, such as inflammatory processes,[56] and further research is required to understand these mechanisms.

We have demonstrated that the vascular depression hypothesis, originally intended for understanding late-life major depression,[55] may also be generalized to understand subsyndromal depressive

symptoms. This is particularly important given subsyndromal symptoms are more prevalent in the elderly than major depression[20] and are a risk for neurodegeneration of AD-related brain regions,[57] greater conversion to AD,[58] and poorer functional outcomes.[59] By excluding patients with major depression, our findings suggest that subsyndromal depressive symptoms in AD may have a comparable etiology to major depression in AD. Therefore, implications from the vascular depression hypothesis[55] may be useful to guide assessment and treatment strategies for subsyndromal depressive symptoms in mild AD. We note, however, that subsyndromal depression may involve unique etiologies not observed in major depression and the vascular depression hypothesis may only describe one potential mechanism. Pathologies other than WMH may be contributing to poor tract integrity as previous research has demonstrated that even after removing WMH, reduced white matter tract integrity was still associated with depressive symptoms in the elderly.[60] Other pathologies such as inflammatory demyelinating disease[61] and amyloid deposition[53] have been associated with poorer tract integrity and should be investigated in future research.

Our exploratory analysis identified that the link between tract integrity and subsyndromal depressive symptoms was strongest in AD patients over the age of 65 years. The size of this modulatory effect was small for most tracts except for the inferior fronto-occipital fasciculus and genu of the corpus callosum, suggesting that not all tracts are equally affected by age-related changes. Interestingly, a high cardiovascular risk profile did not moderate the association between white matter health and symptom severity in AD. Although cardiovascular risk factors contribute to the development of poor white matter health,[16] it appears to have limited effects on moderating whether poor white matter health manifests as subsyndromal depression.

Limitations and Future Directions

We note that our cross-sectional data cannot prove causation, only association. Future research may benefit from exploring the causal links between tract integrity, WMH, AD pathology, and depressive symptoms. We note that we included total WMH in our model instead of regional WMH given that tracts explored in this study transversed across multiple regions. Indeed, regional WMH plays a discriminatory role in late-life depression,[62] however, most WMH observed in patients with late-life depression[8] and with mild AD[63] are often found in the frontal regions. Furthermore, in patients with mild AD, WMH in all regions have been found to have consequences on frontal hypometabolism.[63] As a result, we propose that including regional WMH in our model may unlikely change the findings, however, this speculation should be tested in future research with tract-based spatial statistics of each tract as it travels across various regions. We further note that three participants (2%) were on antidepressants. These participants did not present as outliers with their GDS scores (the GDS score range for these three participants was 0−6), thus we did not exclude them, nor did we feel they would affect the results. Future research may further benefit from investigating how different DTI metrics are mediated by WMH to influence symptom severity.

CONCLUSION

Reduced tract integrity may be important but not sufficient for the manifestation of depressive symptoms in mild AD. Instead, WMH may drive the pathogenic link between reduced tract integrity and depressive symptoms, and Alzheimer pathology may provide a vulnerable context for poor white matter health to manifest symptomatically. We further found that depression in mild AD may not just involve a disconnection between cortical-subcortical tracts, localized to the right hemisphere, but also between the interhemispheric tract genu of corpus callosum. Finally, we demonstrated that after the age of 65 years, the association between white matter and depressive symptoms may be strengthened. Implications of this study reinforce the need for vascular control in the management of subsyndromal depressive symptoms in AD.

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SUPPLEMENTARY MATERIALS

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