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Brief Report

White Matter Integrity Underlying Depressive Symptoms in Dementia Caregivers

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ABSTRACT

Objective: *We sought to determine whether the aspects of white matter connectivity implicated in major depression also relate to mild depressive symptoms in family dementia caregivers (dCGs).* ***Methods:*** *Forty-one dCGs (average age=69 years, standard deviation=6.4) underwent a 7 Tesla 64-direction (12-minute) diffusion-weighted imaging sequence. We compared the fractional anisotropy (FA) of 11 white matter features between dCGs with (n=20) and without (n=21) depressive symptoms (Patient Health Questionnaire-9 scores ≥5).* ***Results:*** *Caregivers reporting depression symptoms had lower FA in tracts connecting to the posterior cingulate cortex (Cohen's d = −0.9) and connecting dorsolateral prefrontal with rostral cingulate regions (Cohen's d = −1.2).* ***Conclusions:*** *Posterior cingulate and dorsolateral prefrontal-to-rostral cingulate white matter, implicated in prior studies of major depression, appear relevant to mild depression in dCGs.* (Am J Geriatr Psychiatry 2020; 28:578–582)

Depression symptoms in dementia caregivers (dCGs) increase the risk of developing major depressive disorder.[1] While the neurobiology of depression in dCGs has only indirectly been examined,[2,3] numerous studies have examined the brain structural correlates of depression in older adults (without regard to caregiving). Patients with depression differ in several aspects of white matter connectivity[4] potentially partially due to cerebrovascular disease.[5] Meta-analytic[6] evidence demonstrates that people with affective disorders tend to have lower white matter integrity in frontolimbic, frontostriatal,

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and medial temporal networks. Mid-brain white matter[7] as well as connectivity in default mode and salience networks[8,9] are also implicated. Which aspects of brain structure relate to depressive symptoms in dCGs is unknown.

Identifying the aspects of brain connectivity related to depressive symptoms in dCGs is a step toward developing new biomarkers of depression vulnerability (that might improve risk stratification approaches) and its underlying mechanisms (that should be targeted via precise preventive interventions). We therefore aimed to identify aspects of brain connectivity that differ between dCGs with and without depressive symptoms. We also assessed the extent to which known correlations[10] between caregiving characteristics and depression symptoms could be attributed to these brain connectivity measures.

METHODS

Recruitment was conducted through outreach to caregiver support groups and 3 research registries (the local Alzheimer Disease Research Center; the Pittsburgh Regional Caregiver Survey; and the local Clinical and Translational Science Institute registry). Eligible caregivers were: ≥60 years old; providing unpaid care to someone with dementia; have experienced care-related stress/strain; living with their care recipient or providing ≥15 hours of care per week; having 9-item Patient Health Questionnaire scores <10; and able to undergo magnetic resonance imaging (MRI). Of the 239 potential participants screened, 86 were eligible, and 47 participated in the diffusion tensor imaging study; 6 of these participants did not contribute adequate diffusion tensor imaging data and were excluded (analytic n = 41).

MRI measures: We derived white matter FA in normal appearing tracts connecting to major nodes implicated in prior depression studies. Additional details of the MRI data acquisition and processing are provided in Supplemental Materials. Regions of interest (ROIs) were segmented using FreeSurfer 6.0 (FS; http://surfer.nmr.mgh.harvard.edu/) and included: the dorsolateral prefrontal cortex (combined labels for caudal middle frontal, rostral middle frontal, and superior frontal); the caudal cingulate; rostral cingulate; insula; medial temporal lobe (combined labels for the hippocampus, para-hippocampus, and entorhinal cortex); the posterior cingulate cortex; amygdala; and striatum (combined labels for the caudate, putamen, pallidum, and accumbens).

We examined white matter integrity, indexed by FA, for:[1] all white matter tracts connected to the abovementioned regions; and[2] white matter specifically connecting pairs of the aforementioned ROIs that were anatomically plausible as determined by a neuroanatomist (LB) and past research.[11–14] A list of targeted ROIs is provided in the Supplemental Table. We further restricted analysis to ROI pairs that were reliably tracked, that is, defined as being identified in every participant (those in Table 1). FA in right and left ROIs were averaged whenever possible (i.e., except if the tract was only reliably identified in 1 hemisphere).

Depressive symptom measure: Depressive symptoms were measured with the PHQ-9 and were dichotomized us a cutoff of ≥5 to indicate the presence of at least mild depressive symptoms.[15]

Known depression correlates: Subjective stress was measured the 10-item Perceived Stress Scale.[16] We measured caregiving burden using the Zarit Burden Interview.[17] We also measured morning inactivity as a composite of actigraphy-derived morning activity start times and levels (Supplemental Methods).

Statistical analysis: White matter integrity measures were compared between dCGs with and without mild depressive symptoms using *t*-tests and Cohen's d[18] as a measure of effect size. Next, we used logistic regression adjusting for basic caregiver characteristics (age, sex, and the relationship between the caregiver and care recipient) to examine the odds of having depression symptoms per standard deviation unit white matter measures. Finally, we assessed whether the odds of having mild depression were attenuated when adjusting for other relevant factors (caregiver characteristics or white matter).

RESULTS

About half the sample meets criteria for at least mild depressive symptoms (Table 1). Compared with the group that had no significant depressive symptoms, the group with mild depressive symptoms had significantly lower FA in white matter connecting:[1] to the posterior cingulate cortex (PCC; Supplemental Figure 1, left); and[2] connecting the right dorsolateral

TABLE 1. Characteristics of Dementia Caregivers With and Without at Least Mild Depressive Symptoms

	Caregivers Without Depressive Symptoms (n = 21, 51%)	Caregivers With Depressive Symptoms (n = 20, 49%)	Cohen's d	Test Statistic	p Value	FDR
Basic caregiver characteristics						
Age	71.5 (6.3)	68.2 (6.1)		1.71	0.09	
Female sex, % (n)	76[16]	80[16]		0.09	0.77	
Relationship to care recipient				0.01	0.91	
Spouse/partner, % (n)	66[14]	65[13]				
Child, % (n)	33[7]	35[7]				
Patient Health Questionnaire-9	2.4 (1.4)	8 (3.0)		−7.61	<0.0001	
Caregiver characteristics						
Zarit Burden Interview	15.9 (7.7)	20.9 (7.9)	0.6	−2.02	0.05	
Perceived stress scale	11.8 (8.5)	19.0 (6.6)	0.9	−3.33	0.002	
Morning inactivity score	−0.3 (1.1)	0.3 (0.8)	0.6	−1.8	0.07	
Inferential tests						
White matter hyperintensity volume	0.05 (1.1)	−0.06 (0.9)	0.1	0.35	0.73	-
Fractional anisotropy						
Dorsolateral prefrontal	0.0 (1.0)	0.0 (1.1)	0.0	0.14	0.89	0.97
Posterior cingulate	**0.4 (0.7)**	**−0.4 (1.1)**	**−0.9**	**2.92**	**0.006**	**0.03**
Dorsal cingulate	0.2 (0.7)	−0.2 (1.2)	−0.5	1.44	0.17	0.50
Medial temporal	−0.2 (0.7)	0.2 (1.2)	0.4	−1.38	0.18	0.50
Rostral cingulate	0.0 (1.0)	0.0 (1.0)	0.0	−0.04	0.97	0.97
Insula	0.1 (1.0)	−0.1 (1.0)	−0.2	0.50	0.62	0.97
Striatum	0.1 (1.1)	−0.1 (0.9)	−0.2	0.60	0.55	0.97
Amygdala	0.0 (1.1)	−0.1 (0.9)	−0.1	0.31	0.76	0.97
DLPFC-dCC	0.0 (1.1)	0.0 (0.9)	0.1	−0.17	0.87	0.97
Right DLPFC-rCC	**0.5 (0.7)**	**−0.5 (1.0)**	**−1.2**	**3.79**	**0.0005**	**0.006**
Insula-Amygdala	−0.2 (1.1)	0.2 (0.9)	0.3	−1.05	0.30	0.66

Notes: False discovery rate (FDR) calculated for fractional anisotropy variable comparisons using a Benjamini-Hochberg[23] multiple comparison correction. To facilitate interpretation, all continuous variables are standardized to a mean of zero and a standard deviation of one except for age and depressive symptom scores. Test statistics for continuous variables are *t*-values and p values are from *t*-tests where degrees of freedom are 39. For categorical variables, test statistics are chi-square tests with one degree of freedom. FDR, false discovery rate; DLPFC, dorsolateral prefrontal cortex; dCC, dorsal cingulate cortex; rCC, rostral cingulate cortex.

prefrontal cortex (DLPFC) and rostral cingulate cortex (rCC; Supplemental Figure 1, right). These associations were large (see Cohen's d) and statistically significant after correction for multiple comparisons. Adjusting for basic caregiver characteristics, each standard deviation higher on these white matter measures was associated with substantially lower odds of having depression symptoms (Supplemental Table 2, Model 1: PCC odds ratio = 0.34, 95% confidence interval: 0.14, 0.83; Model 2: DLPFC-right rCC odds ratio = 0.10, 95% confidence interval: 0.02, 0.44). These odds ratios were not strongly attenuated (<10%) when adjusting for caregiving burden, perceived stress, or morning inactivity. In contrast, the higher odds of having depression symptoms associated with caregiver burden and morning inactivity were attenuated by 42% and 21%, respectively, when adjusting for PCC FA (see odds ratios in Supplemental Table 2 Models 3–4 and 9–10).

DISCUSSION

Our data demonstrate that 2 aspects of white matter, previously associated with major depression, are also associated with mild depressive symptoms in caregivers. Caregivers with depressive symptoms had lower white matter integrity (as measured with FA) in tracts connecting to the PCC and in right-hemisphere tracts connecting the DLPFC to the rCC. By specifying the depression-relevance of white matter connecting to the PCC, and connecting the right DLPFC to the rCC, our study indicates that the function subserved by these connections may be particularly relevant to depression in dCGs.

The PCC is involved in autobiographical memory and future planning.[19] Witnessing a family member, typically a major attachment figure (spouse or parent), lose their memories and other key functions can

make it challenging to maintain/recall positive self-memories. Caregivers also need to be highly effective planners to successfully anticipate and navigate challenges ahead. Links between DLPFC-rostral cingulate white matter and depressive symptoms are also plausible. The DLPFC is critical for re-evaluating stimuli[20] and the rostral cingulate has a role in down-regulating emotional conflict.[21] Compromised information transfer between these regions may be related to difficulty consciously re-appraising negative emotions related to watching a loved one suffer losses from dementia. Future studies are needed to investigate the role of these psychological functions in relation to depression and its neurobiological basis in dCGs.

Furthermore, we found that the integrity of PCC white matter connections explained considerable portions of associations between 2 known risk factors (caregiver burden and morning inactivity) with depression symptoms. Thus, caregiving burden and morning inactivity explain variance in depression symptoms that is shared with PCC connectivity. However, the cross-sectional design prohibits us from making statistical inferences regarding the temporal relations between white matter connections, the functions they serve, and depression. Both temporal sequences are plausible. Lower integrity PCC connections could have functional consequences (e.g., nonspecific autobiographical memory or impaired future planning) that lead to morning inactivity, subjective burden, and depression. Alternatively, maintaining morning activity engagement and low levels of caregiver burden may require engaging functions (subserved by PCC connections), in turn strengthening these circuits, and protecting mood. While white matter has traditionally been considered static in adults, evidence suggests changes in white matter can occur after as little as weeks of training.[22] Experimental studies will be needed to determine whether modifying these factors (e.g., boosting morning activity) influences PCC white matter; if so, on what time scale occurs; and if this reduces depression vulnerability.

Additional limitations include that the sample was relatively small. Future studies are needed to confirm the potential roles of these biomarkers. We did not include participants with major depression and did not assess other disorders; therefore, we cannot evaluate the role of these biomarkers across spectrums of severity, disease course, or comorbidity. Although we identified some white matter measures related to depressive symptoms in dCGs, we were unable to reliably tract other plausible connections; for example, we did not reliably measure left DLPFC-rCC tracts; therefore, these data do not indicate the right hemisphere connections are more relevant. We likely still have an incomplete picture of how brain connectivity underlies depression in dCGs. Our analyses identified regions to which the integrity of connecting white matter associated with depressive symptoms; additional research is needed to specify the exact nature of these connections, their impact on brain function, the psychological/behavioral functions that link them with depression, and how these pathways can be modified.

In summary, this report provides initial evidence that mild depressive symptoms in dCGs—a marker of vulnerability to develop major depressive disorder—are related to differences in specific aspects of brain connectivity. Pending replication, the integrity of certain white matter connections could serve as biomarkers of depression vulnerability in dCGs. Future studies are needed to determine if experimentally manipulating the correlates of depression (e.g., morning activity or caregiving burden) influences white matter biomarkers.

DISCLOSURE

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There are no disclosures to report.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2019.11.010.

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