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Intrinsic Functional Network Connectivity Is Associated With Clinical Symptoms and Cognition in Late-Life Depression

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ABSTRACT

BACKGROUND: Late-life depression (LLD) has been associated with alterations in intrinsic functional networks, best characterized in the default mode network (DMN), cognitive control network (CCN), and salience network. However, these findings often derive from small samples, and it is not well understood how network findings relate to clinical and cognitive symptomatology.

METHODS: We studied 100 older adults (n = 79 with LLD, n = 21 nondepressed) and collected resting-state functional magnetic resonance imaging, clinical measures of depression, and performance on cognitive tests. We selected canonical network regions for each intrinsic functional network (DMN, CCN, and salience network) as seeds in seed-to-voxel analysis. We compared connectivity between the depressed and nondepressed groups and correlated connectivity with depression severity among depressed subjects. We then investigated whether the observed connectivity findings were associated with greater severity of common neuropsychiatric symptoms or poorer cognitive performance.

RESULTS: LLD was characterized by decreased DMN connectivity to the frontal pole, a CCN region (Wald χ^2_1 = 22.33, $p < .001$). No significant group differences in connectivity were found for the CCN or salience network. However, in the LLD group, increased CCN connectivity was associated with increased depression severity (Wald $\chi^2_1 > 20.14$, $p < .001$), greater anhedonia (Wald $\chi^2_1 = 7.02$, $p = .008$) and fatigue (Wald $\chi^2_1 = 6.31$, $p = .012$), and poorer performance on tests of episodic memory (Wald $\chi^2_1 > 4.65$, $p < .031$), executive function (Wald $\chi^2_1 = 7.18$, $p = .007$), and working memory (Wald $\chi^2_1 > 4.29$, $p < .038$).

CONCLUSIONS: LLD is characterized by differences in DMN connectivity, while CCN connectivity is associated with LLD symptomology, including poorer performance in several cognitive domains.

Keywords: Aging, Cognition, Cognitive control network, Default mode network, Functional connectivity, Geriatric

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Late-life depression (LLD), or major depressive disorder (MDD) in adults 60 years of age or older, is a clinically heterogeneous syndrome characterized by both neuropsychiatric symptoms and multidomain cognitive deficits (1). Converging evidence supports intrinsic brain network dysfunction as an underlying neural mechanism contributing to the pathogenesis of LLD (2). Specifically, adult MDD and LLD are associated with alterations in function and resting-state connectivity in intrinsic brain networks, best characterized in the default mode network (DMN), cognitive control network (CCN), and salience network (SN) (3). However, these findings often derive from small samples, and it is not well understood how network differences relate to clinical and cognitive symptomatology (4).

The DMN is a set of regions exhibiting increased activity during rest and decreased activity during externally driven attention-demanding tasks (5). The DMN is related to spontaneous or self-generated cognition, with its anterior hub contributing to self-referential processing and emotion regulation of present states and its posterior hub being associated with episodic memory retrieval and scene construction (6,7). Although DMN activity decreases during externally directed attention, in MDD, DMN activity is higher when assessing external stimuli (8) and during maladaptive ruminative self-focus (9). In both adult MDD and LLD, functional connectivity within the anterior and posterior hubs is increased (10–12), but there is reduced connectivity between the anterior and posterior DMN (13). DMN connectivity to other networks including the CCN is increased in LLD (4).

The CCN is engaged during externally directed cognitive tasks (14) and involved in attentional control, emotional regulation (15), and higher-order functions, including decision making and conflict resolution (14). In MDD, reduced CCN activity is observed at rest, in response to negative stimuli (16), and during attempts to regulate emotional responses (17). Although not universally observed (18), most studies of MDD and LLD demonstrate reduced within-network connectivity

(3,10,11). Additionally, CCN connectivity to the SN is increased in LLD and associated with greater depression severity (4).

The SN facilitates switching between the DMN and CCN as needed to shift attention from internal states to external stimuli. The SN is activated in response to various salient stimuli (19) and includes the insula, dorsal anterior cingulate cortex (dACC), and amygdala. In MDD, SN regions are generally overresponsive to affective challenges, particularly negatively valenced stimuli (20). MDD is characterized by altered SN connectivity of the amygdala and insula with frontal and ACC regions, but also with regions of the CCN and DMN (4,21,22).

The purpose of this study was to examine differences in intrinsic functional network connectivity in LLD. Based on past work, in our primary analyses, we hypothesized that LLD and greater depression severity would be associated with higher DMN connectivity and with lower CCN connectivity. Exploratory analyses examined the SN. In further exploratory analyses, we hypothesized that connectivity findings would be clinically meaningful and associated with greater severity of neuropsychiatric symptoms or poorer cognitive performance. Because cognitive impairment in MDD and LLD has been hypothesized to be related to abnormal connectivity of the CCN and DMN (8,23), we further examined whether connectivity-cognition relationships differed between the depressed and nondepressed groups.

METHODS AND MATERIALS

Participants

Participants were recruited at Vanderbilt University Medical Center from clinical referrals and community advertisements as part of three research studies with common entry criteria. Core entry criteria focused on adults 60 years of age or older with a current DSM-IV-TR diagnosis of MDD and a Montgomery–Åsberg Depression Rating Scale (MADRS) (24) score of ≥15. Participants were also cognitively intact without a clinical diagnosis of mild cognitive impairment or dementia, plus a Montreal Cognitive Assessment (25) score of ≥24 or Mini-Mental State Exam score of ≥24.

Common exclusion criteria included 1) current or past diagnoses of other psychiatric disorders, except for anxiety symptoms occurring during a depressive episode; 2) history of alcohol or drug abuse over last 3 years; 3) acute grief; 4) acute suicidality; 5) current or past psychosis; 6) primary neurological disorders including dementia; 7) current psychotherapy; 8) electroconvulsive therapy in the last 2 months; and 9) contraindications to magnetic resonance imaging (MRI).

For two of the three studies, entry criteria specified no antidepressant use in the last 2 weeks. Antidepressant medications were allowed in one study, with 9 of 14 depressed participants taking antidepressant monotherapy at the time of MRI. For that study, participants taking antidepressant monotherapy needed to be on a stable dose for at least 8 weeks.

Eligible nondepressed participants adhered to similar age requirements and exclusion criteria. They had no lifetime history of psychiatric disorders and no history of psychotropic medication use, psychotherapy, or brain stimulation treatment.

All studies were approved by the Vanderbilt University Institutional Review Board. All participants provided written informed consent.

Clinical Assessments

Diagnostic and Medical Assessments. The Mini-International Neuropsychiatric Interview (version 5.0) (26) assessed current and lifetime depression and other psychiatric disorders. Diagnoses and duration of current episode were confirmed by clinical interview with a geriatric psychiatrist. Antidepressant treatment in the current episode was assessed using the Antidepressant Treatment History Form (27). Medical burden was quantified using the clinician-rated Cumulative Illness Rating Scale (28).

Mood and Neuropsychiatric Assessments. MADRS was assessed by the study psychiatrist on the day of MRI. For two studies (n = 56), additional neuropsychiatric symptoms were assessed in depressed participants through self-report questionnaires. Symptom domains and questionnaires included anhedonia, using the Snaith–Hamilton Pleasure Scale (29); anxiety, using the Penn State Worry Questionnaire (30); apathy, using the Apathy Evaluation Scale (31); fatigue, using the Fatigue Severity Scale (32); and rumination, using the Ruminative Response Scale, which includes a total score and subscales for depressive rumination, reflective rumination, and brooding rumination (33).

Cognitive Assessments. A total of 83 subjects (62 depressed, 21 nondepressed) completed paper-and-pencil neuropsychological test batteries. The specific tests probed specific cognitive domains affected by aging or impaired in LLD (34,35). Tests in each domain included the following:

- Episodic memory: word list memory recall (immediate and delayed), paragraph recall test, Constructional Praxis Test, and Benton Visual Retention Test.
- Executive function: Symbol-Digit Modalities Test, Trail Making Test Part B, and the Stroop Color and Word Test.
- Working memory: Digits Forward Test and Digits Backward Test.
- Processing speed: Stroop Color and Word Test, Trail Making Test Part A.
- Language processing: Stroop Word Reading Test and the Shipley Vocabulary Test.

MRI Acquisition

Participants were scanned on a research-dedicated 3T Philips Achieva whole-body scanner (Philips Medical Systems, Best, the Netherlands) using body coil radiofrequency transmission and a 32-channel head coil for reception. Structural imaging included a whole-brain T1-weighted magnetization prepared rapid acquisition gradient-echo image (repetition time = 8.75 ms, echo time = 4.6 ms, flip angle = 9°, spatial resolution = 0.89 × 0.89 × 1.2 mm^3) plus fluid-attenuated inversion recovery (FLAIR) T2-weighted imaging (repetition time = 10,000 ms, echo time = 125 ms, inversion time = 2700 ms, flip angle = 90°, spatial resolution = 0.7 × 0.7 × 2.0 mm^3). Resting-state functional MRI was conducted with eyes open (repetition time = 2000 ms, echo time = 35 ms, flip angle = 77°, spatial resolution = 2.75 × 2.75 × 3.7 mm^3, 35 axial slices).

Functional MRI Analyses

Resting-state functional MRI images were preprocessed using the CONN toolbox (version 15.g) in SPM12, including realignment of the functional runs and correction for head motion, coregistration of functional and anatomical images for each participant, normalization of the anatomical and functional images to the standard Montreal Neurological Institute template, and spatial smoothing with a Gaussian filter (6 mm at full width at half maximum). Motion artifacts were further detected by applying the Artifact Detection Toolbox as implemented in CONN. We used a displacement threshold of 0.9 mm and a global signal threshold of Z = 5. To effectively mitigate the effects of head motion, denoising in CONN was conducted for white matter (five components extracted) and cerebrospinal fluid (five components extracted) signal, and realignment parameters (36) with outlier volumes identified by the Artifact Detection Toolbox. We retained all participants with >5 minutes of scan time after excluding outlier volumes. The resulting blood oxygen level–dependent time series were band-pass filtered (0.01 to 0.1 Hz) to further reduce noise and increase sensitivity.

We selected canonical network regions for each intrinsic functional network to use as key network seed regions of interest: 1) DMN seed [posterior cingulate cortex (PCC) (37)], 2) CCN seed [left dorsolateral prefrontal cortex (dlPFC) (14)], and 3) SN seed [right anterior insula (14)]. First-level whole-brain seed-to-voxel individual-subject functional connectivity maps were created for each network region of interest seed. We then conducted two second-level analyses. First, a second-level two-sided, two-sample *t* test examined differences in functional connectivity maps between diagnostic groups utilizing a false discovery rate of 0.05 and peak significance threshold of uncorrected $p < .001$. Second, a second-level linear regression examined the relationship of functional connectivity (both positive and negative connectivity) with depression severity (MADRS) among depressed subjects utilizing a false discovery rate of 0.05 and peak significance threshold of uncorrected $p < .001$. After identifying seed to cluster connectivity relationships using these methods, we extracted beta values (a measure of functional connectivity) for those seed-to-cluster pairs for use in subsequent statistical analyses.

Structural MRI Analyses

White matter hyperintensity (WMH) volumes, findings on T2-weighted or FLAIR images related to cerebral ischemia, were measured using the Lesion Segmentation Toolbox (38). These analyses, identical to those previously described (39), were implemented through the VBM8 toolbox in SPM8 using the threshold of 0.3. This threshold was selected based on data from a sample dataset, in which we compared segmented images with the native FLAIR image, examining a threshold range from 0 to 1 in increments of 0.05. In native space, each voxel on the T1 image is assigned as gray matter, white matter, or cerebrospinal fluid. After bias correction, the FLAIR is coregistered to the T1 image. The toolbox initially creates a conservative binary WMH map based on outlier values across the T1 and FLAIR images. Next, a lesion-growth algorithm using Markov random field modeling extends this conservative map to define the extent of the WMH. This lesion map is then used to calculate total cerebral WMH volume. We then applied FreeSurfer (version 6.0; https://surfer.nmr.mgh.harvard.edu) cortical parcellation of the T1 data to the WMH map, allowing us to calculate WMH volume for the frontal lobe.

Statistical Analysis

Statistical analyses examining demographic measures and extracted beta-value connectivity measures were conducted in SAS Studio 3.6 (SAS Institute, Cary, NC). Participant characteristics were summarized using mean ± SD for continuous variables and number and percentage for categorical variables and compared using two-tailed *t* tests for continuous variables and χ^2 test for categorical variables.

Seed-to-voxel relationships among functional connectivity, diagnosis of depression, and depression severity by MADRS were identified using CONN. After extracting the connectivity beta values, initial statistical models confirmed our second-level seed-to-voxel analyses testing for differences between diagnostic groups and relationships with depression severity. For group differences, we created a regression model with functional connectivity as the dependent variable and diagnostic group, age, sex, and medical morbidity by the Cumulative Illness Rating Scale as the independent variables. For depression severity, using only the depressed group, we created a regression model with MADRS as the dependent variable and functional connectivity, age, sex, and medical morbidity as the independent variables. We also examined whether the subsample of participants on antidepressant medications at time of MRI ($n = 9$) influenced our findings. We reran the statistical models described above without those participants to determine whether they affected the results.

As WMH volume is associated with altered network functional connectivity (40,41), we examined whether WMHs were associated with observed regional connectivity measures. We constructed regression models with functional connectivity as the dependent variable and whole-brain or frontal lobe WMH volume as independent variables with additional covariates of age, sex, diagnostic group, and medical morbidity.

Final analyses examined the relationship between observed connectivity measures and clinical and cognitive measures.

Table 1. Demographics

	Depressed ($n = 79$)	Nondepressed ($n = 21$)	Test Statistic	*p* Value
Age, Years	66.3 ± 5.9	68.3 ± 5.7	$t_{98} = 1.41$	.169
Sex, Female	27 (34)	9 (43)	$\chi^2_1 = 0.54$	.461
Education, Years	16.5 ± 2.3	16.4 ± 1.7	$t_{98} = 0.24$	.808
MADRS Score	27.3 ± 4.7	0.4 ± 0.7	$t_{98} = 49.41$	<.001
ATHF Score	2.5 ± 3.0	—	—	—
CIRS Score	5.1 ± 3.1	4.4 ± 2.4	$t_{98} = 1.16$	.255
WMH, Total Cerebral, mL	7.0 ± 13.2	3.9 ± 1.5	$t_{84.9} = 1.67$	.099
WMH, Frontal, mL	2.2 ± 4.9	1.0 ± 1.4	$t_{97.1} = 1.94$	.055

Values are mean ± SD or *n* (%). Categorical variables compared using χ^2 test. Analyses of continuous variables used pooled, two-tailed *t* tests, except for analyses of white matter hyperintensity (WMH), which used Satterthwaite *t* tests owing to unequal variance.

ATHF, Antidepressant Treatment History Form; CIRS, Cumulative Illness Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

For the subset of depressed subjects with neuropsychiatric symptom data, we constructed models with each neuropsychiatric symptom as the dependent variable and functional connectivity, age, sex, medical morbidity, and MADRS score as independent variables. For the subset of subjects with neuropsychological test data, we examined how functional connectivity measures were related to cognitive performance. To test for group differences in the connectivity-cognitive performance relationships, we constructed models for each test with a group by connectivity (beta value) interaction term, controlling for age, sex, medical morbidity, and education. For those cognitive tests without a significant interaction effect, we removed the interaction term and reran the model to test for primary effects of connectivity. If the interaction term was statistically significant, we conducted post hoc analyses within each diagnostic group.

RESULTS

The study included 100 subjects, 79 depressed and 21 never-depressed elderly adults. There were no significant differences between diagnostic groups in demographic measures or medical morbidity (Table 1). The sample was cognitively intact, with a mean Mini-Mental State Exam score of 28.9 ± 1.31 (range = 26–30; n = 86) and mean Montreal Cognitive Assessment score of 27.9 ± 1.46 (range = 25–30; n = 14). There was no significant difference in Mini-Mental State Exam score between diagnostic groups (t_{82} = 0.82, p = .414). Per the Antidepressant Treatment History Form, the sample could not overall be considered treatment resistant, although there were exceptions, as the score ranged from 0 to 18.

A subset of 83 subjects (n = 62 depressed, n = 21 nondepressed) completed neuropsychological testing. After controlling for covariates, the depressed group exhibited significantly poorer performance on measures of episodic memory, executive function, working memory, processing speed, and language processing (Table 2). However, in the depressed group, performance on cognitive tests was not associated with variability in depression severity, except on the Digits Forward test (Table 2).

Diagnostic Group Differences in Resting-State Functional Connectivity and Relationship With Depression Severity

In whole-brain seed-to-voxel analyses, no CCN or SN regions exhibited statistically significant group differences in connectivity. Examining the DMN, depressed subjects exhibited lower positive resting functional connectivity between the PCC seed and a region in the left frontal pole (Figure 1A, Table 3). In models controlling for age, sex, and medical morbidity, depressed subjects continued to exhibit lower PCC-frontal pole connectivity (Wald χ^2_1 = 22.33, p < .001) (Figure 1B), but PCC-frontal pole connectivity was not significantly associated with depression severity (Wald χ^2_1 = 0.87, p = .352) (Figure 1C).

In seed-to-voxel analyses in the depressed cohort (n = 79), we did not observe any DMN or SN regions where functional connectivity was associated with MADRS score. In the CCN, MADRS score was positively associated with functional

Table 2. Cognitive Test Performance by Diagnostic Group and Relationship to Depression Severity

	Group Comparison				Relationship With Depression Severity	
	Depressed (n = 62)	Nondepressed (n = 21)	Wald χ^2_1	p Value	Wald χ^2_1	p Value
Episodic Memory						
Word list memory recall	7.5 ± 1.9	8.1 ± 1.7	5.32	.021	0.01	.926
Paragraph Recall Test	25.5 ± 7.8	32.5 ± 5.8	21.81	<.001	0.14	.706
Constructional Praxis Test	8.8 ± 2.4	9.3 ± 2.1	3.37	.066	0.78	.378
BVRT	6.8 ± 1.7	7.2 ± 1.4	3.07	.080	0.07	.788
Executive Function						
SDMT	42.0 ± 10.2	50.5 ± 8.4	30.79	<.001	0.23	.632
Trail Making Test Part B	96.7 ± 54.2	68.9 ± 21.3	12.18	<.001	0.00	.959
Stroop Color and Word Test	34.1 ± 8.5	43.3 ± 11.2	24.84	<.001	2.19	.139
Working Memory						
Digits Forward Test	8.5 ± 2.4	9.4 ± 1.9	2.48	.115	4.64	.031
Digits Backward Test	7.1 ± 2.2	8.2 ± 2.7	4.84	.028	0.23	.631
Processing Speed						
Stroop Color and Word Test	63.3 ± 13.7	71.2 ± 10.2	14.71	<.001	0.67	.413
Trail Making Test Part A	39.0 ± 32.6	32.1 ± 8.7	1.87	.171	0.02	.890
Language Processing						
Stroop Color and Word Test	90.1 ± 15.4	98.0 ± 12.7	6.24	.013	0.07	.790
Shipley Vocabulary Test	32.6 ± 5.0	35.6 ± 2.4	8.75	.003	0.04	.839

Values are mean ± SD. Group comparison analyses describe regression models with each cognitive test performance as the dependent variable and independent variables of age, sex, medical morbidity, education, and diagnostic group. This allowed us to test whether cognitive performance differed by group. Relationship with depression severity analyses examined regression models in the depressed group alone, with cognitive test performance as the dependent variable and independent variables of age, sex, medical morbidity, education, and Montgomery–Åsberg Depression Rating Scale. This allowed us to test whether cognitive performance was a surrogate marker for depression severity.

BVRT, Benton Visual Retention Test; SDMT, Symbol Digit Modalities Test.

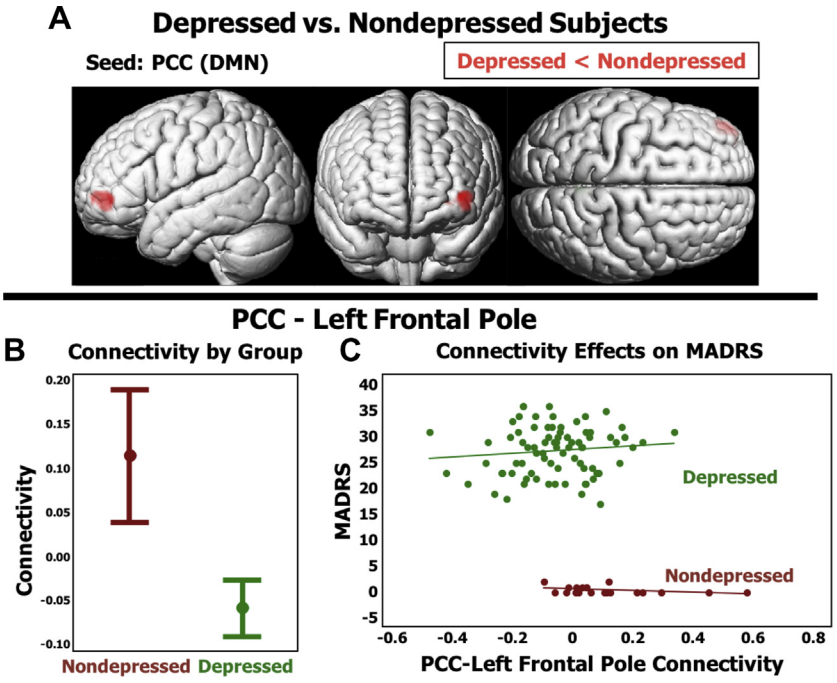

Figure 1. Default mode network (DMN) functional connectivity differences in depressed elderly adults. **(A)** Resting-state functional connectivity pattern with lower connectivity in depressed subjects compared with nondepressed subjects using the posterior cingulate cortex (PCC) seed for the DMN. **(B)** Comparison of 95% confidence intervals of beta values between depressed and nondepressed diagnostic groups. **(C)** The x-axis shows the functional connectivity beta value and the y-axis shows Montgomery–Åsberg Depression Rating Scale (MADRS) score.

connectivity between the left dlPFC and two regions: the bilateral dACC and bilateral supplementary motor cortex (SMC) (Figure 2A, Table 3). In models controlling for age, sex, and medical morbidity, extracted functional connectivity measures between the left dlPFC and both regions continued to be significantly associated with depression severity (dACC [Wald $\chi^2_1 = 20.14$, $p < .001$], SMC [Wald $\chi^2_1 = 23.04$, $p < .001$]) (Figure 2C, E). When examining both depressed and nondepressed subjects, there was no longer a significant association between connectivity and depression severity. Hypothesizing that this may reflect a lack of diagnostic group differences between these regions, we found no statistically significant differences in pairwise connectivity measures between diagnostic groups (dACC [Wald $\chi^2_1 = 3.35$, $p = .067$], SMC [Wald $\chi^2_1 = 0.28$, $p = .596$]) (Figure 2B, D).

Finally, we examined whether the subsample of participants on an antidepressant medication at time of scanning ($n = 9$) influenced these findings. We reran the statistical models described above without those participants, and the results did not appreciably change. Subsequent analyses included all study participants.

Effects of WMH on Connectivity Measures

For the three identified functionally connected pairs (PCC-left frontal pole, dlPFC-dACC, dlPFC-SMC), we examined whether total cerebral or frontal lobe WMH volumes were related to extracted individual-level connectivity values (beta value). One subject was an outlier, with total brain WMH volume of 92.8 mL (7.2 SDs above the mean). When eliminated from our models ($n = 99$), there was no significant effect of whole-brain or frontal lobe WMH volume on pairwise connectivity.

Relationships Between Connectivity Measures and Neuropsychiatric Symptoms

In the three identified functionally connected pairs (PCC-left frontal pole, dlPFC-dACC, dlPFC-SMC), for the subset of 56 depressed subjects with available data, we constructed models controlling for age, sex, medical morbidity, and MADRS score while examining the relationship between connectivity and neuropsychiatric symptoms. The only statistically significant relationships were positive associations between dlPFC-SMC connectivity and anhedonia (Snaith–Hamilton Pleasure Scale

Table 3. Identified Functionally Connected Pairs

Seed	MNI Coordinates (X, Y, Z)	Cluster Size	Regions of Significant Clusters	Uncorrected *p* Value
Depressed vs. Nondepressed				
PCC (default mode network)	−42, +48, −02	228	Left frontal pole	.001
MADRS Regression in Depressed Subjects				
Left dlPFC (cognitive control network)	+10, +20, +28	338	Bilateral anterior cingulate, paracingulate gyrus	.001
	+12, +06, +60	296	Bilateral supplementary motor cortex, right superior frontal gyrus	.001

dlPFC, dorsolateral prefrontal cortex; MNI, Montreal Neurological Institute; PCC, posterior cingulate cortex.

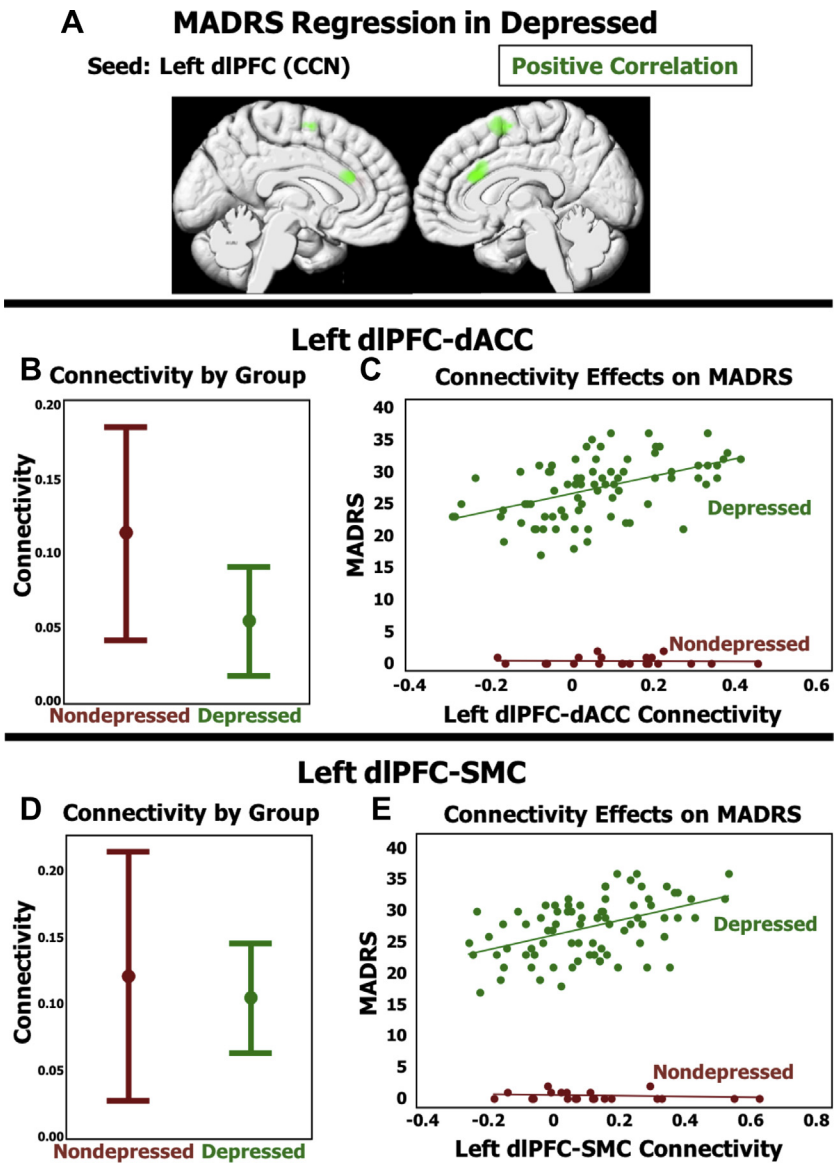

Figure 2. Cognitive control network (CCN) functional connectivity differences associated with depression severity in depressed elderly adults. **(A)** Resting-state functional connectivity pattern associated with higher Montgomery–Åsberg Depression Rating Scale (MADRS) score in depressed subjects using the left dorsolateral prefrontal cortex (dlPFC) seed for the CCN. **(B, D)** Comparison of 95% confidence interval of beta values between depressed and nondepressed diagnostic groups. **(C, E)** The x-axis shows the functional connectivity beta value and the y-axis shows the MADRS score. dACC, dorsal anterior cingulate cortex; SMC, supplementary motor cortex.

total score [Wald $\chi^2_1 = 7.02$, $p = .008$]) (Figure 3A) and fatigue (Fatigue Severity Scale score [Wald $\chi^2_1 = 6.31$, $p = .012$]) (Figure 3B). There were no significant connectivity-symptom associations for measures of worry, apathy, or rumination.

Relationships Between Connectivity Measures and Cognitive Performance

For subjects with neuropsychological data (62 depressed, 21 nondepressed), we examined relationships between pairwise connectivity and cognitive performance. To test for potential group differences in connectivity-performance relationships, we included a group-connectivity interaction term that was removed if not statistically significant.

PCC-left frontal pole connectivity exhibited a statistically significant interaction term only for word list memory recall (Table 4, Figure 4A). However, in post hoc analysis, neither group on its own exhibited a significant functional connectivity-performance relationship. There were no statistically significant primary effects.

Left dlPFC-dACC connectivity exhibited multiple statistically significant group-by-connectivity interaction relationships with cognitive performance (Table 4, Figure 4B–E). Post hoc analyses in the nondepressed group demonstrated that greater dlPFC-dACC connectivity was associated with significantly better performance on the Symbol Digit Modalities Test, Paragraph Recall Test, and Digits Forward Test. In the depressed group, greater dlPFC-dACC connectivity was associated with significantly poorer performance on word list memory recall and the Paragraph Recall Test. For all tests, with increasing dlPFC-dACC connectivity, the depressed group performed progressively worse than the nondepressed group (Table 4, Figure 4B–E). dlPFC-dACC connectivity exhibited a

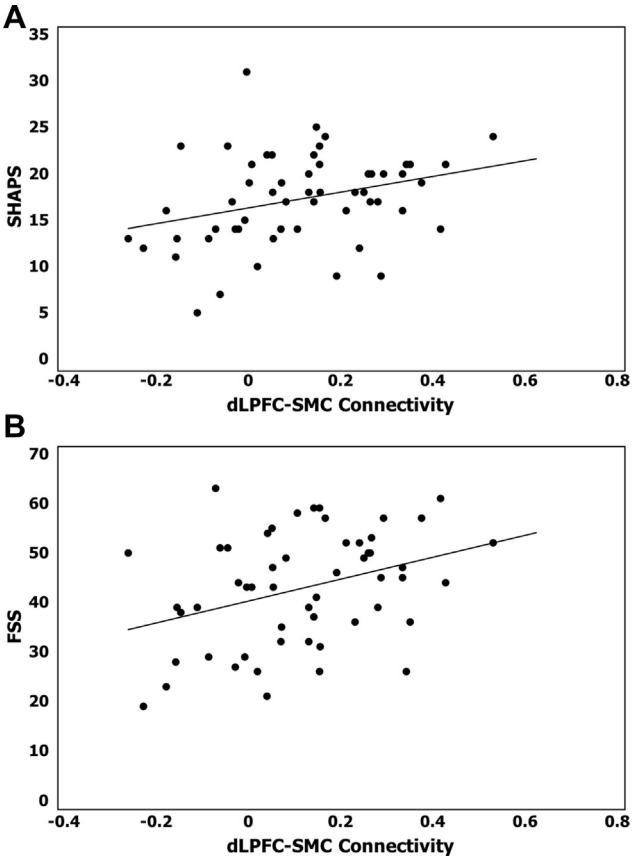

Figure 3. Functional connectivity relationship with neuropsychiatric symptoms. The x-axis shows the functional connectivity beta value for the left dorsolateral prefrontal cortex (dlPFC)-supplementary motor cortex (SMC) and the y-axis shows the severity of the specified neuropsychiatric symptom for scores on the **(A)** Snaith–Hamilton Pleasure Scale (SHAPS) and **(B)** Fatigue Severity Scale (FSS). Higher scores on both scales indicate greater symptom severity.

primary effect only for Stroop test performance, with positive relationships observed for color naming (Wald $\chi^2_1 = 4.29$, $p = .038$) and word naming (Wald $\chi^2_1 = 7.79$, $p = .005$) conditions, with a trend for the interference condition (Wald $\chi^2_1 = 3.50$, $p = .0615$).

Finally, dlPFC-SMC connectivity exhibited significant group differences for Paragraph Recall Test, Digits Forward Test, and Digits Backward Test performance (Table 4, Figure 4F–H). Post hoc analyses in the nondepressed group associated greater dlPFC-SMC connectivity with better Paragraph Recall Test and Digits Backward Test performance, but did not observe significant associations in the depressed group. Thus, with greater dlPFC-SMC connectivity, depressed participants performed relatively more poorly (Table 4, Figure 4F–H). There were no significant primary effects for other cognitive tests.

DISCUSSION

Our primary finding is that LLD is characterized by decreased connectivity between the PCC in the DMN and the frontal pole, a CCN region. Contrary to our initial hypothesis, no significant group differences in connectivity were found for the CCN or SN seeds. However, in the LLD group, increased CCN connectivity was associated with greater depression severity, greater anhedonia and fatigue, and poorer performance on tests of episodic memory, executive function, and working memory. Thus, despite no significant group differences and a comparable range of regional connectivity (Figure 2), connectivity among the left dlPFC, dACC, and SMC is associated with depressive symptomatology and poorer cognitive performance.

Decreased PCC-Frontal Pole Connectivity Differentiated LLD Adults From Nondepressed Older Adults

LLD subjects exhibited lower positive functional connectivity (loss of positive correlation and reversal to anticorrelation) between the PCC and left frontal pole, indicating lower connectivity between these regions (42). Past work similarly reported

Table 4. Group-by-Functional Connectivity Interactions Related to Cognitive Test Performance

Functional Connectivity Pair	Cognitive Test	Group × Functional Connectivity Interaction		Post Hoc Analysis: Correlation × Diagnostic Group			
				Nondepressed		Depressed	
		Wald χ^2_1	p Value	Wald χ^2_1	p Value	Wald χ^2_1	p Value
PCC-Left Frontal Pole	Word list memory recall	4.19	.041	3.07	.080	1.07	.301
Left dlPFC-dACC	SDMT	7.18	.007	18.35	<.001	0.45	.501
	Word list memory recall	5.89	.015	0.20	.656	14.26	<.001
	Paragraph Recall Test	10.82	.001	9.14	.003	6.20	.013
	Digits Forward Test	5.35	.021	5.62	.018	0.19	.6627
Left dlPFC-SMC	Paragraph Recall Test	4.65	.031	4.01	.045	2.25	.134
	Digits Forward Test	4.29	.038	1.29	.256	3.14	.076
	Digits Backward Test	5.83	.016	8.92	.003	0.79	.374

Regression models with cognitive test performance as the dependent variable and independent variables of age, sex, medical morbidity, and education, plus a diagnostic group-by-connectivity interaction term. This allowed us to test whether the relationship between connectivity and cognitive performance differed by group. Cognitive tests with significant group-by-functional connectivity interactions are reported above. If not listed, there was no significant group-by-functional connectivity interaction relationship. In post hoc analyses, regression models were run separately for each diagnostic group, with cognitive performance as the dependent variable and independent variables of age, sex, medical morbidity, education, and connectivity.

dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; PCC, posterior cingulate cortex; SDMT, Symbol Digit Modalities Test; SMC, supplementary motor cortex.

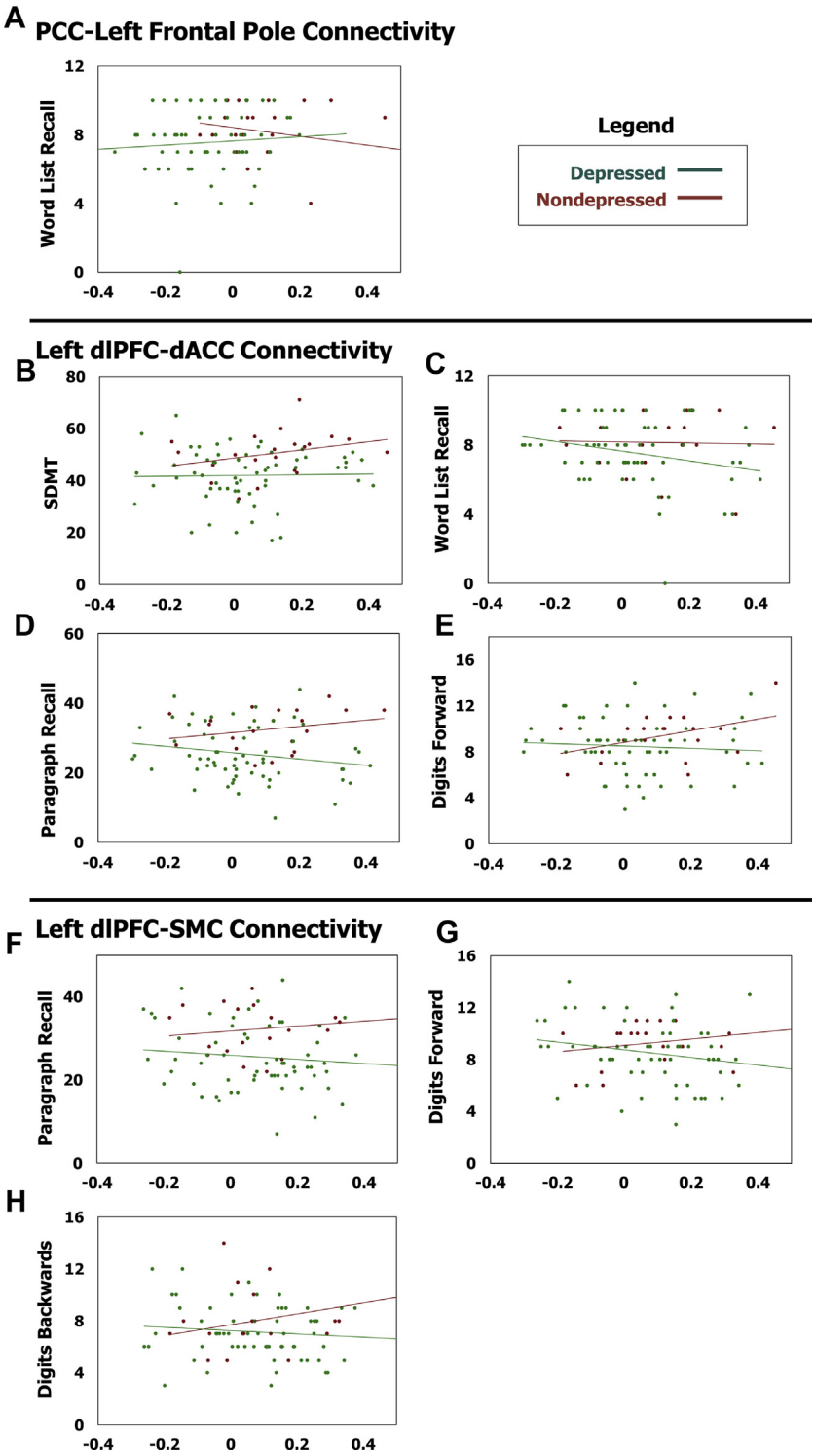

Figure 4. Functional connectivity relationship with cognitive test performance. The x-axis shows the functional connectivity beta values for the specified functionally connected pair and the y-axis shows the performance on the specified cognitive test for posterior cingulate cortex (PCC)-left frontal pole connectivity on **(A)** word list memory recall; for left dorsolateral prefrontal cortex (dlPFC)-dorsal anterior cingulate cortex (dACC) connectivity on **(B)** the Symbol Digit Modalities Test (SDMT), **(C)** word list memory recall, **(D)** the Paragraph Recall Test, and **(E)** the Digits Forward Test; and for left dlPFC-supplementary motor cortex (SMC) connectivity on **(F)** the Paragraph Recall Test, **(G)** Digits Forward Test, and **(H)** Digits Backward Test.

decreased PCC connectivity patterns in LLD (40,41), although others reported different patterns (11,43). These inconsistent findings may be partly explained by methodological differences across studies or population heterogeneity. Additionally, these studies often had smaller sample sizes and different entry criteria, which may contribute to discrepant findings. Importantly, although others have associated DMN connectivity with neuropsychiatric symptoms (11), the observed group difference

in DMN connectivity was largely unrelated to our examined neuropsychiatric or neuropsychological measures. Thus, as hypothesized by others (44), decreased DMN connectivity may be a biomarker of depression vulnerability that does not drive symptoms during an episode.

Increased CCN Connectivity Is Associated With Depression Severity, Anhedonia, Fatigue, and Poorer Cognitive Performance

Despite no significant group differences, CCN connectivity was associated with neuropsychiatric symptom severity. Additionally, the relationship between CCN connectivity and cognitive performance differed between groups (Table 4, Figure 4). Thus, although functional connectivity among the dlPFC, dACC, and SMC is comparable between depressed and nondepressed subjects (Figure 2), connectivity measures between these regions have clinical implications during depressive episodes. This supports that circuit influences on clinical or cognitive symptoms are not limited to circuits exhibiting differences between diagnostic groups.

Past work implicates these regions in LLD. The dACC is involved in conflict monitoring, processing of cognitively demanding information, response selection, and inhibition (45). Both structural and functional dACC abnormalities predict antidepressant response in LLD (11,46). Our results are concordant with an independent component analysis study in LLD that associated connectivity between the left CCN and dACC with depression severity (4). The SMC is related to implicit motor learning capacity and motor planning. However, the SMC exhibits reduced volume in melancholic depression (47). This structural association is concordant with our finding that increased left dlPFC-SMC connectivity was associated with increased anhedonia and fatigue, characteristics of melancholic depression.

The explanation is less clear for the different relationships between CCN connectivity and cognitive performance. The CCN broadly and the dACC specifically facilitate cognitive control by directing attentional resources to relevant stimuli (48). We propose that negativity bias in directing attention, a characteristic of depression, may subvert this process. In depression, we hypothesize that increased CCN connectivity in the context of negativity bias may result in greater attention being directed toward negatively valenced stimuli. This persistent negative focus could contribute to worsening depression severity with resultant worsening cognitive performance. Importantly, this hypothesis cannot be tested in our current study, as we neither assessed negativity bias nor included emotional valence tests assessing attention. It should also be noted that the negativity bias observed in depression may be related to circuit changes outside the CCN, although some CCN regions are implicated as contributing to negativity bias (49). Future studies could test this theory by incorporating measures of negativity bias as well as assessments of emotional and nonemotional attention performance.

WMH Burden Is Not Associated With Network Differences

An important negative finding was that the observed connectivity findings were not associated with WMH burden. This is in contrast to previous studies reporting an association between WMH volume and connectivity in these networks (40,41); however, these studies studied older participants than in our analysis. It is possible that WMH severity affects network connectivity broadly, even if not related to connectivity among the regions we examined.

Limitations

There are several important limitations to our analyses. First, we combined data across three studies, but not all studies gathered the same neuropsychiatric and cognitive data, resulting in some analyses examining a subsample. This may have reduced power to detect relationships among connectivity, neuropsychiatric symptoms, and cognitive performance. Moreover, these analyses of neuropsychiatric symptoms and cognitive performance involved multiple comparisons, so results should be viewed as exploratory and require confirmation. Second, the sample sizes for the diagnostic groups were unequal, which limits the power of our group comparisons and may have reduced our ability to detect group differences. Third, our analyses are limited to the networks chosen for analysis and the three subsequently identified functionally connected pairs (PCC-left frontal pole, dlPFC-dACC, dlPFC-SMC). These are likely not the only circuits that differ in LLD or are related to depression severity, neuropsychiatric symptoms, or cognitive performance. In fact, the cognitive domains we analyzed involve additional networks beyond the scope of this report.

Conclusions

This study is among the largest to examine functional connectivity differences in LLD. Our findings support past work reporting that LLD is characterized by differences in DMN connectivity, and also suggest that this may be a vulnerability marker unrelated to clinical presentation. In contrast, the study supports that CCN connectivity plays a role in LLD symptomology during depressive episodes, even if connectivity measures are comparable to those seen in nondepressed elders. Thus, we cannot assume that clinical or cognitive symptoms are related only to circuits exhibiting clear group differences. Further work is needed to conduct dimensional analyses of both neuropsychiatric symptoms and cognitive performance in LLD and how brain aging may contribute to network alterations and influence progression of these symptoms.

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