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COGNITIVE CONTROL NETWORK HOMOGENEITY AND EXECUTIVE FUNCTIONS IN LATE LIFE DEPRESSION

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Abstract

Background: Late-life depression (LLD) is characterized by network abnormalities, especially within the cognitive control network (CCN). We used alternative functional connectivity approaches, regional homogeneity (ReHo) and network homogeneity (NeHo), to investigate LLD functional homogeneity. We examined the association between CCN homogeneity and executive functions (EF).

Methods: Resting-state fMRI data were analyzed for 33 depressed older adults and 43 healthy controls. ReHo was performed as the correlation between each voxel and the 27 neighbor voxels. NeHo was calculated as global brain connectivity restricted to 7 networks. T-maps were generated for group comparisons. We measured cognitive performance and EF with the Dementia Rating Scale (DRS), Trail-Making Test (TMT-A and B), Stroop Color Word Test, and Digit Span Test.

Results: Depressed older adults showed increased ReHo in the bilateral dorsal anterior cingulate cortex (dACC) and the right middle temporal gyrus (rMTG), with no significant findings for NeHo. Hierarchical linear regression models showed higher ReHo in the dACC predicted better performance on the TMT-B ($p < .001$; $R^2 = .49$), Digit Span Backward ($p < .05$; $R^2 = .23$) and Digit Span Total ($p < .05$; $R^2 = .23$). Used as a seed, the dACC cluster of higher ReHo showed lower FC with bilateral precuneus.

Conclusions: Higher ReHo within the dACC and rMTG distinguish depressed older adults from controls. The correlations with EF performance support increased ReHo in the dACC as a meaningful measure of the organization of the CCN and a potential compensatory mechanism.

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Lower FC between the dorsal ACC and the precuneus in LLD suggest clusters of increased ReHo may be functionally segregated.

Keywords

Cognitive Control; MRI; Executive Functions; Depression; Aging; Functional Connectivity

INTRODUCTION

A network dysfunction model may help explain the neurobiological underpinnings of LLD (1). Resting state functional connectivity (rsFC) measures the temporal coherence between single or groups of voxels at rest (2). Region-of-interest (ROI), seed-based rsFC studies often show a lower rsFC in the cognitive control network (CCN) among patients with late-life depression (LLD) compared to healthy controls (3,4).

Executive dysfunction is a clinical expression of disrupted CCN functions. Patients with LLD and executive dysfunction, or depression-executive dysfunction (DED) syndrome, have difficulty inhibiting irrelevant stimuli and engaging in goal-directed behaviors (5). DED syndrome is characterized by disability and poor antidepressant response (6–8). Impairments in executive functions often persist even after remission of depression (9). Thus, understanding specific patterns of abnormal rsFC in LLD may inform novel treatment approaches.

Although ROI seed-based rsFC studies have provided valuable insights into network abnormalities in LLD, there are several limitations to this approach. Seed-based approaches require *a priori* decisions for seed placement. These *a priori* decisions are, by definition, hypothesis-driven, and introduce a potential bias to network analyses. In addition, the placement of seeds of varying sizes and coordinates to interrogate the same network can result in different rsFC patterns. These different patterns contribute to ambiguity when interpreting results both within and across laboratories. Furthermore, seed selection can overlook the complexity of a network because within-network activity often depends on multiple functionally heterogeneous sub-regions (10). Although the model-free independent component analysis (ICA) (11) addresses some of these seed-based limitations, ICA often relies on relatively arbitrary judgments to select meaningful patterns among the automatically generated components (12).

Alternative rsFC analytic techniques can address some of the limitations of both seed-based and ICA approaches by focusing on “homogeneity”. Homogeneity, as measured by resting state fMRI, is conceptualized as the synchronization of all voxels in a well-defined area of the brain. The term homogeneity has been applied to two main resting state fMRI approaches: regional homogeneity (ReHo) (13) and network homogeneity (NeHo) (14).

ReHo (13) is a measure of the temporal synchronization of BOLD time series between every voxel and its nearest neighbors. ReHo provides a measure of local connectivity and has the advantage of probing a well-defined anatomical area by assessing the synchronization of spatially adjacent voxels. ReHo allows the definition of boundaries between functionally heterogeneous within-network sub-regions and the detection of within-network hubs of

functional abnormality (15). A meta-analysis of ReHo in adults with MDD suggests widespread abnormalities involving primarily areas of the default-mode network (DMN) (e.g., increased ReHo in the medial prefrontal cortex) (16). Reports of ReHo in LLD show abnormalities involving the CCN and the DMN, but demonstrate inconsistent directionality across samples and do not show a relationship of ReHo to executive functions among actively depressed older adults (17–20). ReHo can locate highly homogeneous clusters within the brain and serve as a data-driven method to identify seeds for rsFC studies (21). Further, ReHo correlates with measures of functional segregation such as clustering coefficient and local efficiency (22) and is thought to have a substantially similar biological meaning, where higher ReHo (within-region highly synchronous activity) could indicate decreased communication with remote brain regions.

NeHo (14) is a voxelwise measure of the correlation of a voxel with all other voxels within a network, thus allowing an unbiased examination of within-network connectivity. NeHo can be investigated with a graph-theory based approach called restricted Global Brain Connectivity (rGBC) (23). rGBC provides a measure of the connectivity between each voxel and every other voxel in a predefined restricted space (i.e., a network mask). As such, rGBC allows the evaluation of the averaged within-network connectivity of an entire network. In adults with MDD, NeHo analyses suggest homogeneity abnormalities in prefrontal regions of the CCN and in the DMN (24,25).

Employing connectivity measures less reliant on *a priori* assumptions about network organization is particularly important in understanding network abnormalities in the aging brain, because brain long-range connectivity is particularly vulnerable to aging (26), and so are intra-network and inter-networks connectivity (27).

The primary objectives of this article are to examine 1) group differences in rsFC homogeneity measures in LLD and nonpsychiatric comparison participants and 2) the association between functional homogeneity and executive performance in LLD. We hypothesized that 1) the group differences in ReHo and NeHo will involve the CCN and 2) CCN homogeneity will be associated with executive performance. Secondly, we investigate broader network organizational levels by using clusters of CCN abnormal functional homogeneity (ReHo, NeHo) as data-driven seeds for exploratory whole-brain FC analysis.

MATERIALS AND METHODS

Participants

This study included 33 participants with LLD and 43 elderly non-psychiatric comparison participants (age range 60 – 85 years). The depressed group consisted of participants who met DSM-IV criteria for MDD without psychotic features, with a score of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS) (28) and a score of 26 or greater on the Mini Mental State Examination (MMSE) (29). Participants were recruited through print and radio advertisements along with referrals from outpatient mental health providers. Healthy controls had no history or presence of any psychiatric disorder. All participants signed informed consent as approved by local Institutional Review Boards.

Participants were excluded for the presence of any of the following: 1) high suicide risk; 2) any Axis I psychiatric disorder other than MDD or Generalized Anxiety Disorder (GAD); 3) history of psychiatric disorders other than MDD or GAD; 4) mild cognitive impairment (MCI) or dementia; 5) acute or severe medical illness; 6) any neurological brain disease; 7) history of electroconvulsive therapy; 8) ongoing treatment with drugs associated with depression, i.e. steroids, alpha-methyl-dopa, clonidine, reserpine, tamoxifen, or cimetidine; 6) metal implants or other contraindications to MRI.

Assessment

In participants with LLD, a diagnosis of major depression was made by Structured Clinical Interview for DSM Disorders (SCID) criteria. Further, depression severity was assessed with the HDRS prior to study entry. Two clinician investigators specialized in geriatric psychiatry reached consensus on the diagnosis of major depression and ruled out the possibility of MCI based on review of neuropsychological tests and overall function. If MCI was suspected, a comprehensive neuropsychological battery was administered. Depressed participants and controls were administered a baseline neuropsychological battery. Overall cognitive function was assessed with the MMSE (29) and the Dementia Rating Scale (DRS) (30). Processing speed and executive function were assessed with the Trail Making Test, Parts A and B (TMT-A and TMT-B) (31), the Stroop Color Word Test (32) and the Digit Span Test forward, backward and total score (33). Vascular risk was extracted from the Charlson Comorbidity Index (namely, 'hypertension', 'smoking status', and 'diabetes' items) (34).

MRI Data Acquisition

MRI scans were acquired on a 3T Siemens TiM Trio (Erlangen, Germany) equipped with a 32-channel head coil at the Center for Biomedical Imaging and Neuromodulation (C-BIN) of the Nathan Kline Institute for Psychiatric Research. For patients who were under antidepressant treatment, one-week washout was done before MRI data acquisition. Anatomical imaging included a dual echo T1-weighted MPRAGE for coregistration with functional data (TR = 2500ms, TE = 3.5ms, slice thickness = 1mm, TI = 1200ms, 256 axial slices, matrix = 256 × 256, 1mm isovoxel, FOV = 256mm). Resting state images were acquired using a single-shot, T2-weighted echo planar BOLD contrast image, which allowed whole brain coverage (TR = 2500ms, TE = 30ms, flip angle = 80°, slice thickness = 3mm, 38 axial slices, matrix = 72 × 72, 3mm isovoxel, FOV = 216mm, IPAT = 2). Acquisition time was 6 minutes, 15 seconds (150 volumes). Patients were instructed to stay awake with eyes closed. Wakefulness during the scan was verified at the end of the resting state sequence by the MR technician.

Image preprocessing

The preprocessing of resting state data was performed using Data Processing Assistant for Resting-State fMRI (DPARSF) 4.3 Advanced Edition (35), a software plug-in within DPABI_V3.0_171210 (<http://rfmri.org/dpabi>), which is based on SPM (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>).

The first 5 volumes of the BOLD sequence were discarded to reduce relaxation effects. The remaining images were then corrected for slice timing and head motion. T1 images were

skull-stripped, co-registered to functional images, segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) based on SPM priors. Global signal regression (GSR) was not applied because it can bias effects on local and long-range correlations (36). In lieu of GSR, CompCor was used to reduce the effect of physiological noise (37). Nuisance regression was applied using WM, CSF, and Friston 24 motion parameters as covariates. The images were segmented and spatially normalized using DARTEL (38), resampled to 3mm isovoxels, and smoothed with a Gaussian kernel of 4 mm full-width half-maximum (FWHM). In the ReHo data analysis (13) only, smoothing was not performed during preprocessing but just after ReHo calculation. Lastly, the resulting fMRI data were filtered ($0.01 < f < 0.1$ Hz) to reduce low-frequency drift and high-frequency physiological noise.

To minimize physiologic sources of head displacement, we adopted the following exclusion strategies 1) Participants with VanDijk Framewise Displacement (FD) (mean relative root-mean-square) (39) greater than 2SD above the mean were excluded (40), as well as those with absolute mean FD > 0.2 mm. 2). Participants with single frame maximum head motion of more than 2.5 mm of displacement in any direction (x, y or z) or 2.5 degrees of angular motion were also excluded. While this is a somewhat lenient motion correction approach, these parameters were selected because a more conservative approach may not have been appropriate for our older sample with difficulties in executive function.

Regional Homogeneity data analysis

Regional homogeneity was performed with DPARSF (35). Individual ReHo maps were generated based on the Kendall's coefficient of concordance, which is computed as the correlation between the time series of each voxel and those of its nearest neighbors (13) in a voxel-wise manner. Concordance was computed on 27 voxels (the node voxel plus the 26 neighboring voxels), which is suggested as the more appropriate cluster size in order to cover all directions in 3D space (15). ReHo maps were then standardized using Fisher's r-to-z transformation.

Network Homogeneity: Restricted Global Brain Connectivity data analysis

DPARSF was used to calculate the time series for each subject. To calculate the correlation between each voxel time series and all the other voxels within brain networks, the resulting preprocessed 4D NIfTI files were then used as inputs in Analysis of Functional NeuroImages (AFNI) software (41) using 3dTcorrMap. We used the masking option to restrict the analysis to seven networks liberal masks (42): Visual Network (VN), SomatoMotor Network (SMN), Dorsal Attention Network (DAN), Ventral Attention Network (VAN), Limbic Network (LN), Frontoparietal Network (FPN), and Default-Mode Network (DMN). To examine regional effects that might reflect local hubs of abnormal within-network connectivity, a group-comparison map was created for each of the seven networks.

Secondary analysis: Homogeneity-seeded Functional Connectivity

Clusters of significant CCN abnormal functional homogeneity (ReHo or NeHo) from previous steps were first saved as binary masks and then entered as seeds in seed-based

functional connectivity analysis. FC maps were calculated from preprocessed data on a voxel-wise manner and Fisher r-to-z transformed (zFC) were calculated. For the seed-to-voxel functional connectivity analysis, we used a voxel p-value threshold of $p < 0.01$ and cluster threshold of $p < 0.05$.

Statistical analysis

SPSS Statistics 25 was used to perform two-sample t-tests and chi-squared tests on demographic and clinical variables. DPARSF Statistical Analysis tool was used to perform a two-sample t-test on the groups ReHo maps, the rGBC maps and zFC maps with sex, education, and mean framewise displacement as covariates. Sex was regressed based on the evidence of its influence on ReHo values at rest (43). To further control for the effect of motion artifacts, mean framewise displacement values were also used as covariate. Finally, education was regressed due to the significant difference between the two groups. Age was not included as a covariate because the two samples are well matched on that variable (Table 1). Multiple comparison correction was carried out using Gaussian Random Field (GRF) with smoothness estimated on statistical image directly. Given the recent debate on spatial clustering (44,45) we adopted the following threshold for both the ReHo and NeHo analyses: voxel p value < 0.005 , cluster p value < 0.05 , one-tail. We used one-tailed t tests in all comparisons, because we had a priori hypotheses that ReHo would be higher in the cognitive control and default mode networks, as per the review by Iwabuchi and colleagues (16). Similarly, we hypothesized that for ReHo-seeded functional connectivity, higher ReHo would be associated with lower functional connectivity. To examine the association between ReHo or NeHo abnormalities and cognitive performance variables, Fisher's r-to-z transformed connectivity values were extracted at the subject-level from each significantly different cluster and input into SPSS for further analysis. Correlations between significant clusters' connectivity values and those cognitive variables that showed to be significantly different between groups were calculated, as well as with age, education, depression severity and vascular risk. Cognitive variables that were found to be significantly correlated with ReHo or NeHo were included in listwise Hierarchical Linear Regression Models as outcome variables. Each regression model included two steps, the first accounting for the effect of covariates, the second for the independent effect of ReHo or NeHo.

Exploratory Analysis: We used SPSS Statistics 25 to conduct two additional exploratory analyses. First, we examined sex as a moderator in the association of ReHo and cognitive performance. The Hierarchical Regression Models described above were run with an additional third step that entered a ReHo x Sex interaction term to identify the moderating effect of sex differences in accounting for the relationship between ReHo and cognitive variables. We also examined the association between ReHo and cognitive variables that did not differ between groups at baseline. ReHo values were extracted at the subject-level and correlated with cognitive scores using Spearman's rank-order correlation approach.

RESULTS

Participants

Demographic, clinical and cognitive characteristics of the sample are summarized in Table 1. Compared to controls ($N = 43$), the depressed group ($N = 33$) had fewer years of education, greater HDRS total score and poorer performance on DRS Total, DRS Memory, TMT-A, TMT-B, Stroop Word, Stroop Color, Stroop Color-Word, Digit Span Backward, and Digit Span Total (all $p < 0.05$). We also report that vascular risk and framewise displacement did not significantly differ between groups.

Regional Homogeneity in Depressed vs. Controls

A significant group difference between depressed older adults and controls in ReHo was detected in the dorsal Anterior Cingulate Cortex (dACC) bilaterally, a region on the edge of paracingulate and medial frontal gyrus, and the right Middle Temporal Gyrus (MTG), with depressed patients having greater ReHo relative to healthy controls. Results are summarized in Table 2. Figure 1 shows the depressed vs. control group map comparison.

Association between ReHo and Executive Function

To investigate the relationship between increased ReHo in the two clusters (ACC and rMTG) and executive functions, Spearman correlations were performed within the two groups. Within depressed older adults, ACC ReHo significantly correlated with TMT-B ($\rho = -0.552$, $p = 0.001$), Digit Span Backward ($\rho = 0.459$, $p < 0.01$), Digit Span Total score ($\rho = 0.468$, $p < 0.01$), and education ($\rho = 0.509$, $p < 0.01$) (all FDR $q < 0.05$); the only correlation with rMTG ReHo that survived FDR correction was with education ($\rho = 0.464$, $p < 0.01$). Within healthy controls, no correlation survived FDR correction. Scatterplots of the relation between ACC ReHo and executive measures are displayed in Figure 2.

Based on these correlations, three regression models were utilized. We respectively entered TMT-B, Digit Span Backward and Digit Span total score as outcome variables in each model (Table 3). In Model 1 (TMT-B as outcome), we first entered age, education and HDRS total score as covariate. Age and education because they correlated with TMT-B (respectively, age: $\rho = 0.365$, $p < 0.05$; education: $\rho = -0.433$, $p < 0.05$) and HDRS total score in order to detect the effect of ReHo on executive functions independent of depression severity. In a second step, we added ACC ReHo to the model in order to examine its contribution to the explained variance above and beyond covariates. In Models 2 and 3 (Digit Span as outcome), we first entered only HDRS as covariate because age and education did not significantly correlate with Digit Span performance. Among patients, in Model 1, ReHo significantly predicted TMT-B scores ($R^2 = 0.08$, $p = 0.047$) above and beyond covariates; this final model predicted almost half of the variance in TMT-B scores ($R^2 = 0.49$; $F = 6.61$, $p < 0.001$). In Model 2 (outcome Digit Span Backward) and Model 3 (outcome Digit Span total score) ACC ReHo significantly predicted scores on cognitive outcomes (Model 2: $R^2 = 0.23$, $F = 4.35$, $p = 0.022$; Model 3: $R^2 = 0.23$, $F = 4.40$, $p = 0.021$) above and beyond HDRS (Model 2: $R^2 = 0.20$, $p = 0.011$; Model 3: $R^2 = 0.18$, $p = 0.014$). None of these models were significant in the healthy comparisons group.

ReHo Exploratory Analyses: We performed exploratory analyses to examine the potential moderator effects of sex differences on the association between ReHo and measures of executive function, and to also examine the relationship between ReHo and performance on tasks that did not show group differences at baseline between depressed participants and healthy controls.

We performed exploratory regression models with sex as a moderator. These models included the variables and covariates reported above and in Table 3. In Model 1 (TMT-B as outcome), age, education, and HDRS total were entered as covariates in the first step, ACC ReHo was entered as a predictor in the next step, and an ACC ReHo x Sex interaction term was entered in the next step to explore the moderating effect. In Model 1, the addition of the ACC ReHo x Sex moderator was not significant ($R^2=-0.11$, $p=0.12$). In Models 2 and 3 (Digit Span Backwards and Total as outcomes, respectively), HDRS total was entered as a covariate in the first step, ACC ReHo was entered as a predictor in the next step, and an ACC ReHo x Sex interaction term was entered in the next step to explore the moderating effect. In Model 2, the addition of the ACC ReHo x Sex moderator was also not significant ($R^2=-0.004$, $p=0.70$). In Model 3, the addition of the ACC ReHo x Sex moderator was also not significant ($R^2=-0.03$, $p=0.34$). These exploratory results suggest that sex differences did not account for a significant amount of the variance in explaining the observed relationship between ACC ReHo and executive function.

We also examined the relationship of ACC and MTG ReHo to the measures of the cognitive battery that did not show significant group differences at baseline (i.e., the following subscales of the DRS: Attention, Initiation/Perseveration (I/P), Construction, and Conceptualization). There were no significant correlations between ACC or MTG ReHo and DRS subscale scores in the LLD group or the healthy controls.

Network Homogeneity in Depressed vs. Controls

NeHo, as measured by restricted GBC, did not significantly differ between depressed participants and controls in any of the seven networks analyzed. Among the network group comparison maps, no regional effect survived GRF correction in any of the seven networks of rGBC. Therefore, NeHo values were not extracted and correlations with cognitive performance were not performed.

Secondary analysis: ReHo-seeded Functional Connectivity

We used the ACC cluster of increased ReHo as a data-driven seed to explore seed-based zFC maps in both groups. Group-comparison were performed through independent two-sample t test and revealed a region of decreased connectivity involving the bilateral precuneus. Given the exploratory nature of this secondary analysis, here we applied a less conservative threshold of voxel p value <0.01 , cluster p value <0.05 (Figure 3). Within depressed older adults, zFC values extracted from this area correlated with DRS total score ($\rho=-0.367$, $p<0.05$) and education ($\rho=-0.353$, $p<0.05$) although neither survived FDR correction.

DISCUSSION

The principal finding of this study is that relative to healthy elderly controls, elderly depressed participants display increased functional regional homogeneity in the CCN. Specifically, local homogeneity of the dorsal ACC, as measured by ReHo, was higher in depressed participants relative to controls. Further, increased ReHo in the ACC predicted better cognitive control performance as measured by brief clinical measures of working memory and task switching. Another non-CCN region, the right MTG, displayed increased functional regional homogeneity, but did not predict performance on objective clinical measures of cognitive control. Our results expand upon prior reports of aberrant spontaneous activation at rest in the CCN of individuals with LLD (3,4,46). However, the application of ReHo in this study improves upon some of the limitations inherent to previously used seed-based approaches.

Within depressed older adults, higher ReHo of the dACC was primarily associated with better cognitive flexibility and working memory, as revealed by the significant contribution of dACC ReHo to explained variance in performance on TMT-B and Digit Span. Increased ReHo in the rMTG did not relate to measures of cognitive control. The relationship between dACC ReHo and stronger cognitive control performance in depressed older adults indicates that ReHo may be a meaningful neurobiological measure of the organization of the CCN at rest. Because LLD patients show increased ReHo values in the dACC, which in turn relates to better executive functions, we propose that a higher ReHo in the ACC may be a compensatory mechanism necessary to support select executive functions in LLD.

Although there have been some reports of abnormal ReHo regions within the CCN in depressed older adults (17–19,47) these findings have not been consistently linked to the clinical expression of poor cognitive control. One preliminary study (20), conducted in a small sample of patients in remission, revealed a negative relation between ReHo of other CCN regions (superior frontal gyrus) and TMT-B performance.

Our findings support the association between executive functions in depression and CCN connectivity (46,48). Within the CCN, we observed increased ReHo in the dorsal ACC. This sub-region acts in concert with other components of the CCN and in healthy individuals is associated with increased engagement of other cognitive control regions (e.g., posterior parietal cortices, lateral prefrontal cortex) (10,49,50). Across a number of psychiatric conditions, grey matter volume reduction of the dorsal ACC relates to executive dysfunction (49). Dorsal ACC activation during cognitive control tasks may predict subsequent cognitive decline in LLD (51), and is associated with conflict monitoring during Stroop tasks (52). Further, dorsal ACC volume predicts treatment response in LLD (53), consistent with the idea that the dorsal ACC may be an integral node of the CCN that plays a role in illness course.

ReHo correlates with measures of “functional segregation” like local efficiency and clustering coefficients (22). Therefore, increased ReHo may have similar biological significance reflecting a restriction of information transfer to spatially close areas, at the expense of broader connections with more distant brain regions. Regions of increased ReHo

may be functionally segregated from distant hubs and respond to lesser information transfer by synchronizing their activity. Within the aging brain, long-range connections with distant hubs, rather than short-range, are preferentially impaired (26, 27). Of note, we did not observe significant relationships between ReHo and executive functions in the elderly non-depressed adults. It is possible that the functional segregation higher ReHo may represent in depressed older adults, which is reflected as weaker executive performance, may be below a “threshold” in healthy older adults that does not contribute to detectable difficulties on measures of executive functions.

Converging evidence shows reduced functional connectivity between ACC and spatially distal brain regions in LLD (46,48). We found that ReHo-seeded ACC has decreased connectivity with posterior regions of the bilateral precuneus. The specific region of the precuneus to which we observed decreased functional connectivity is a posterior component of the frontoparietal network. The precuneus is believed to act in concert with more anterior aspects of the frontoparietal network to support cognitive control processes and this dorsal ACC/precuneus disruption may reflect aging-related disruption of long-range connections of the frontoparietal network (54–56). Further, this disruption in connectivity to the precuneus converges with the putative role of the precuneus in higher-order cognitive functions relevant to depression, such as self-referential thinking and first-person perspective taking (57), as well as sustained attention, cognitive flexibility, and task-switching (58). ReHo may play a compensatory role through the segregation of information processing at the local level, in accordance with prior reports indicating the strength of ACC-seeded inter-network connectivity relates to the expression of depression (59).

In contrast with the examination of potential widespread, across-network ReHo abnormalities, our approach to Network Homogeneity (rGBC) allowed us to examine group differences in the average connectivity of seven independent networks. Contrary to our hypotheses, the comparison of rGBC in depressed older adults versus controls did not show significantly different clusters of across-voxel connectivity in any of the seven networks analyzed. This result suggests that averaging the correlation between voxels of vast brain regions may mask subtle effects detectable at a more local level. Although conducting a functional homogeneity analysis at the network-level avoids the bias of seed-selection and placement process, in this case the application of *a priori* network templates may have contributed to the lack of significant group differences. The use of data-driven network masks, in place of *a priori* network templates, could facilitate further studies in identifying foci of abnormal NeHo in the aging brain.

Our findings should be interpreted within the context of its limitations. First, the cross-sectional nature of the study does not allow to infer causality. We applied a somewhat lenient motion correction threshold; this was done to avoid possible sample bias, because more cognitively impaired subjects tend to move more in the scanner (60); to mitigate motion effect we accounted for motion both at the preprocessing and the group-level analysis. An additional methodological limitation is the length of the resting-state scan (6 minutes, 15 seconds), which is of a relatively short duration by current standards. Work by Zuo and colleagues (61) supports the stationarity of ReHo over time, showing high intra-scan reliability across multiple scan sessions with resting-state scans of a shorter duration (5

minutes). However, data quality may be improved with longer scan sequences and improved multi-band acquisition parameters (62). In future studies, it will be important to replicate these current results in scans of longer length to address concerns of stationarity. The analyses were limited to the use of a 3DReHo technique instead of 2DReHo, which investigates the brain surface (rather than brain volume) and may be more specific to the organization of the cortical mantle; however, we adopted 3DReHo at 27 voxels (instead of 9 voxels) to cover all directions in 3D space (15). Additionally, TMT-B is not a “pure” measure of set shifting and may include a processing speed component. Finally, our subjects were instructed to stay awake with eyes closed, a condition uncontrolled for arousal level; however, wakefulness status was verified for each participant at the end of the session.

Conclusions and Future Directions

We observed that local functional homogeneity abnormalities in the ACC, within the CCN, and in the middle temporal gyrus distinguished depressed older adults and healthy controls. In contrast, averaging the functional connectivity at the entire network level did not distinguish between the depressed patients and healthy controls on any of the seven networks analyzed. Increased ReHo within the CCN predicted better cognitive flexibility and working memory in LLD, and the ReHo-seeded ACC cluster showed decreased connectivity to posterior regions of the DMN. Increased ReHo within the CCN of depressed older adults may represent a segregation mechanism that attempts to preserve executive performance. These findings provide a preliminary characterization of the brain’s functional topography in LLD and expand upon the existing model of CCN abnormalities in LLD.

These findings can be used to inform novel targets for interventions in individuals suffering from depression with executive dysfunction who do not respond to typical antidepressant treatments. Such findings can be used to inform neurostimulation approaches, including transcranial magnetic stimulation and cognitive interventions that attempt to rescue dysfunctional circuitry. Further, future investigation of LLD should focus on interactions between local and remote levels of connectivity.

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Figure 1. Clusters of significant ReHo increase in depressed older adults compared to healthy controls.

Clusters GRF corrected voxel $p < 0.005$, cluster $p < 0.05$.

ACC=anterior cingulate cortex; ReHo=Regional Homogeneity; R-MTG=right middle temporal gyrus.

Figure 2. Scatterplots of the relations between dorsal anterior cingulate ReHo values and executive performance in depressed older adults and healthy controls

Fig2A 3D View of dorsal ACC cluster of increased ReHo in patients compared to controls (BrainNet Viewer) (63)

Fig 2B Upper right & bottom: scatterplots of the relation between ACC ReHo r-to-z values to executive performance.

ACC=anterior cingulate cortex; ReHo=Regional Homogeneity; TMT-B=Trail Making Test B.

Figure 3. Clusters of significant decreased ReHo-seeded Functional Connectivity depressed older adults compared to healthy controls.

3d View (BrainNet Viewer) (63) of precuneus clusters GRF corrected voxel $p < 0.01$, cluster $p < 0.05$.

Table 1.

Comparison between depressed older adults and healthy controls on demographic, clinical and cognitive variables

Variable	LLD (N=33)	HC (N=43)	T test	Sig.
	Mean (SD)	Mean (SD)		
Age	72.2 (6.6)	73.4 (6.5)	0.75	ns
Female (%)	21 (63.6)	25 (58.1)	0.24 χ^2	ns
Education, years	14.4 (2.7)	17.0 (2.0)	4.65	<.001
HDRS total score	22.7 (4.3)	1.1 (1.1)	-27.9	<.001
DRS Total (n=75)	138.8 (4.2)	140.8 (3.1)	2.3	<.05
DRS Attention	36.0 (1.2)	36.3 (1.4)	1.0	ns
DRS I/P (n=75)	36.2 (1.5)	36.7 (0.7)	1.6	ns
DRS Construction	5.8 (0.6)	5.9 (0.4)	1.0	ns
DRS Conceptualization	37.3 (1.7)	37.5 (2.9)	0.2	ns
DRS Memory	23.3 (2.4)	24.5 (0.7)	2.8	<.01
TMT-A (n=74)	62.5 (51.0)	38.6 (14.2)	-2.6	<.05
TMT-B (n=74)	137.4 (74.7)	86.3 (33.4)	-3.6	<.001
Stroop Word	85.4 (16.6)	98.5 (16.7)	3.4	<.01
Stroop Color	55.2 (11.8)	64.3 (11.6)	3.4	<.01
Stroop CW	31.0 (8.3)	35.0 (9.2)	2.0	<.05
Digit Span Forward (n=75)	7.1 (2.3)	8.2 (2.4)	2.0	=.052
Digit Span Backward (n=74)	5.9 (2.2)	6.9 (1.8)	2.2	<.05
Digit Span Total (n=74)	13.0 (3.8)	15.1 (3.5)	2.6	<.05
Vascular Risk (n=73)	1.0 (1.1)	0.6 (0.8)	-1.5	ns
Mean FD	0.071 (0.03)	0.068 (0.03)	-0.43	ns

χ^2 = Chi-Square test; CW=ColoWord; DRS=Mattis Dementia Rating Scale; FD=Frame-wise Displacement, measured as VanDijk's mean *relative root-mean-square*; HC = Healthy Controls; HDRS=Hamilton Depression Rating Scale; I/P=initiation/perseveration; LLD=Late-Life Depression; TMT=Trail-Making Test.

Table 2.

Clusters of abnormal Regional Homogeneity and ReHo-seeded Functional Connectivity (depressed older adults versus healthy controls).

Clusters	R/L	Cluster Size	Peak MNI Coordinates (x, y, z)	Peak Effect Size
Increased ReHo				
Anterior Cingulate Cortex	Bilateral	80	-6, 39, 36	4.14 ^a
Middle Temporal Gyrus	Right	96	57, -21, -6	4.76 ^a
ACC ReHo-seeded FC				
Precuneus	Bilateral	208	-12, -51, 69	-3.56 ^b

^a voxel $p < 0.005$, GRF corrected cluster $p < 0.05$.

^b voxel $p < 0.01$, GRF corrected cluster $p < 0.05$.

ACC=Anterior Cingulate Cortex; MNI=Montreal Neurological Institute

Table 3.

Final regression models

Model 1: TMT-B as outcome variable							
	R ²	R ²	B	SE	β	t	p (Sign. F change)
Age	--	--	3.15	1.61	0.28	1.96	0.061
Education	--	--	-9.27	4.36	-0.34	-2.12	0.043
HDRS total score	--	--	-2.64	2.40	-0.15	-1.10	0.282
<i>ACC ReHo</i>	0.49	0.08	-72.45	34.82	-0.34	-2.08	0.047
<i>F=6.61, p<0.001</i>							
Model 2: Digit Span Backward as outcome variable							
	R ²	R ²	B	SE	β	t	p (Sign. F change)
HDRS total score	--	--	-0.07	0.08	-0.14	-0.88	0.383
<i>ACC ReHo</i>	0.23	0.20	2.72	1.00	0.44	2.71	0.011
<i>F=4.35, p=0.022</i>							
Model 3: Digit Span Total score as outcome variable							
	R ²	R ²	B	SE	β	t	p (Sign. F change)
HDRS total score	--	--	-0.16	0.14	-0.19	-1.16	0.255
<i>ACC ReHo</i>	0.23	0.18	4.57	1.75	0.43	2.60	0.014
<i>F=4.40, p=0.021</i>							

ACC = Anterior Cingulate Cortex; HDRS=Hamilton depression rating scale; ReHo=Regional Homogeneity; TMT=trial making test.