International Psychogeriatrics: page 1 of 7 © International Psychogeriatric Association 2023
doi:10.1017/S1041610223000066

Neuroimaging features of depression–frailty phenotype in older adults: a pilot study

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ABSTRACT

Objective: Frailty and late-life depression (LLD) often coexist and share several structural brain changes. We aimed to study the joint effect LLD and frailty have on brain structure.

Design: Cross-sectional study

Setting: Academic Health Center

Participants: Thirty-one participants (14 LLD + Frail and 17 Never-depressed + Robust)

Measurement: LLD was diagnosed by a geriatric psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition for single episode or recurrent major depressive disorder without psychotic features. Frailty was assessed using the FRAIL scale (0–5), classifying subjects as robust (0), prefrail (1–2), and frail (3–5). Participants underwent T1-weighted magnetic resonance imaging in which covariance analysis of subcortical volumes and vertex-wise analysis of cortical thickness values were performed to access changes in grey matter. Participants also underwent diffusion tensor imaging in which tract-based spatial statistics was used with voxel-wise statistical analysis on fractional anisotropy and mean diffusion values to assess changes in white matter (WM).

Results: We found a significant difference in mean diffusion values (48,225 voxels; peak voxel: pFWER=0.005, MINI coord. (X,Y,Z) = − 26, − 11,27) between the LLD-Frail group and comparison group. The corresponding effect size (f=0.808) was large.

Conclusion: We showed the LLD + Frailty group is associated with significant microstructural changes within WM tracts compared to Never-depressed + Robust individuals. Our findings indicate the possibility of a heightened neuroinflammatory burden as a potential mechanism underlying the co-occurrence of both conditions and the possibility of a depression–frailty phenotype in older adults.

Key words: Late-life depression, Frailty, Diffusion Tensor Imaging

Introduction

Late-life depression (LLD) and frailty are two common and often co-occurring conditions in the elderly. LLD may include both syndromal major depression and subsyndromal presentations of depression. Frailty is a geriatric syndrome associated with declines in health and function. Clinical and epidemiological studies show a strong association between these conditions, with 38.6% of frail elders having clinically significant depressive symptoms and 40.4% of those with LLD meeting the criteria for prefrailty and frailty (Soysal *et al.*, 2017). This evidence suggests a bidirectional relationship in which LLD may accelerate frailty development and frailty may exacerbate LLD (Mayerl *et al.*, 2020; Oude Voshaar *et al.*, 2021; Brown *et al.*, 2020). However, the mechanisms underlying this interplay remain unclear.

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Although much is known regarding the structural brain changes of LLD or frailty, little is known regarding their joint effects on the brain. Previous studies including individuals with LLD or frailty have shown significant subcortical and cortical grey matter atrophy (Benjamin and Steffens, 2011; Lopez-Sanz *et al.*, 2018), with the atrophy being more pronounced in the hippocampus, amygdala, anterior cingulate, striatum, and the frontal gyri (Benjamin and Steffens, 2011; Wen *et al.*, 2014; Chen *et al.*, 2015; Kant *et al.*, 2018). Studies using diffusion-weighted imaging (DWI) to quantify microstructural damages in the white matter (WM) (Lopez-Sanz *et al.*, 2018; Wen *et al.*, 2014), in particular, fractional anisotropy (FA), and mean diffusivity (MD) measures, also showed that LLD or frailty have been associated with significantly lower FA values (indicating reduced axonal integrity) and higher MD values (indicating more inflammatory changes in the WM tracts) (Lopez-Sanz *et al.*, 2018; Charlton *et al.*, 2014; Chen *et al.*, 2006). The most commonly affected tracts in both LLD and frailty were the corpus callosum, uncinate fasciculus, superior fronto-occipital fasciculus, and anterior limb of the internal capsule (Lopez-Sanz *et al.*, 2018; Tian *et al.*, 2020; Wan *et al.*, 2020; Reppermund *et al.*, 2014).

Frailty and LLD share several imaging abnormalities suggesting the presence of a depression–frailty phenotype. However, no previous study has evaluated the effect of frailty and LLD on structural and microstructural brain abnormalities. Therefore, this study aimed to investigate the effect of the association between LLD and frailty on brain structure. Based on prior studies, we hypothesized that the presence of LLD with frailty would be associated with WM changes in the frontal and temporal regions.

Methods

Sample

We included 31 participants (14 with LLD + Frailty; 17 Never-Depressed + Robust "comparison group") in this analysis. They were recruited from an ongoing cohort that aims to evaluate the impact of LLD on hallmarks of biological aging conducted in the Centre for Addiction and Mental Health, Toronto, Canada.

DEFINITION OF MAJOR DEPRESSION

All study participants were evaluated by a trained geriatric psychiatrist, and the diagnosis of a major depressive episode was based on the *Diagnostic and Statistical Manual of Mental Disorders* 5th ed (DSM–5; American Psychiatric Association, 2013) diagnostic criteria for single episode or recurrent major depressive disorder without psychotic features. The severity of the depressive episode was assessed using the Patient Health Questionnaire (PHQ-9) and Montogomery-Asberg Depression Rating Scale (MADRS) (Levis *et al.*, 2019; Montgomery and Asberg, 1979).

DEFINITION OF FRAILTY

Frailty was assessed using the FRAIL scale, a validated questionnaire that evaluates the five components of the frailty phenotype: fatigue, resistance, ambulation, medical comorbidity, and weight loss (Kojima, 2018). Each item corresponds to a single question, with each scored as 0 (absent) or 1 (present). Possible FRAIL Scale scores range from 0 to 5, classifying subjects as robust (score = 0), prefrail (score = 1–2), or frail (score = 3–5). For this analysis, we combined individuals identified as prefrail (n = 13) and frail (n = 1) in the same group, since prefrailty shares many of the health risks associated with frailty and is a significant risk factor for developing frailty (Kojima, 2018).

COMPARISON GROUP (CG)

Individuals without a past or current history of a major depressive episode and physically robust were included as a CG.

For both groups (LLD + Frailty and Never-Depressed + Robust), the exclusion criteria included a history/current diagnosis of bipolar disorder, schizophrenia, or other major psychiatric disorder; history of dementia or intellectual disability; history of severe head trauma; history of alcohol or substance abuse; history of a major central nervous system disorder or past stroke; current unstable medical condition; a diagnosis of HIV, and chronic use of anti-inflammatory medications. Exclusion criteria for control participants included the use of antidepressants or mood stabilizers for other medical conditions. The CAMH ethics board approved this study, and all participants provided written informed consent after a detailed description of the study.

ADDITIONAL CLINICAL MEASURES

Global cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Nasreddine *et al.*, 2005; Randolph *et al.*, 1998).

MRI acquisition and processing

Subjects were imaged at the Toronto Neuroimaging (ToNI) Facility at the University of Toronto (Toronto, ON, Canada), using a 3T Siemens

https://doi.org/10.1017/S1041610223000066 Published online by Cambridge University Press

Prisma MRI Scanner (Siemens Medical Solutions, Malvern, PA, USA). A 3D T1-weighted neuroanatomical scan was acquired using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence, for cortical and subcortical segmentation (1mm isotropic, TR = 2500.0 ms, TE = 2.9 ms, TI = 1070.0 ms, 178 slices, FOV = 256 × 256 mm^2, 8° flip angle). Structural MRI data were processed using the Freesurfer Software Suite (http://surfer.nmr.mgh.harvard.edu, version 6.0).

Subcortical regional volumes (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens area) were defined according to the Desikan-Killiany atlas (Desikan *et al.*, 2006). These subcortical regional volumes were segmented and processed through the pipelines 'recon-all' command. Specifically, the 'recon-all' image processing involved (1) nonbrain tissue removal; (2) spatial normalization; (3) intensity inhomogeneity correction; (4) tissue-type classification; and (5) parcellation of subcortical regions (Fischl *et al.*, 2004).

Vertex-wise cortical thickness values were obtained through the Freesurfer surface-based processing stream. Specifically, the surface-based processing stream involved (1) processing images through the 'recon-all' command, which has been described above; (2) defining boundaries between white and grey matter and boundaries between grey matter and cerebrospinal fluid; (3) registering individual-level data to a Freesurfer average template, and (4) spatially smoothing images with a Gaussian kernel (FWHM = 10 mm) (Schaer *et al.*, 2008). All volumes and reconstructed surfaces were assessed with FreeSurfer quality assurance tools and by visual inspection to ensure accuracy.

DWI acquisition and processing

DWI data were acquired via a multishell high angular resolution diffusion image (b-values = [500, 1000, 2000, and 3000 s/mm^2], b0s = 3, 1.7mm isotropic, TR = 4200.0 ms, TE = 89 ms, 103 slices, FOV = 1260 × 1260 mm^2, 90° flip angle). Quality control compared several metrics (namely absolute motion, relative motion, percent outliers, average signal-to-noise ratio, and mean framewise displacement) against a threshold of plus or minus two standard deviations beyond the mean for each metric. A single participant from the depressed–frail group was removed from the analysis after surpassing this threshold in three of the five metrics.

DWI data were preprocessed to remove eddy current-induced distortions and fit a diffusion tensor via the FMRIB Software Library (https://fsl.fmrib.ox.ac.,uk version 5.0.10). Tract-based spatial statistics (TBSS) was then used to perform a voxel-wise statistical analysis comparing the two participant groups on measures of FA and MD. Image processing for TBSS included the erosion of individual subject FA images; aligning all preprocessed FA images to a 1×1×1 standard space (FMRIB58_FA) using nonlinear regression; merging all standard-space FA images into an averaged FA skeleton; thresholding and binarizing of the aforementioned skeleton; and creating a mask of voxels to which all subsequent processing was restricted (Smith *et al.*, 2004). These steps resulted in two 4D images for each subject: one image representing subjects' normalized FA and MD data, respectively.

Statistical analysis

Between-groups differences of subcortical volume were tested with separate univariate analyses of covariance including sex, age, and estimated total intracranial volume (eTIV) as covariates, and corresponding effect sizes were computed using Cohen's f. Significance was determined using p-values that were corrected for testing across multiple regions (n = 14) using the false discovery rate < 0.05. All analyses were performed in R.

The FreeSurfer command tool, *mri_glmfit-sim*, was used to analyze between-group differences in cortical thickness at each vertex on the cortical surface. Specifically, *mri_glmfit-sim* was used to perform cluster-wise correction for multiple comparisons by running a permutation simulation with 10,000 iterations. The initial vertex-wise threshold and the subsequent cluster-forming threshold were set to $p < 0.05$. P-values were adjusted for testing in two hemispheres. The corresponding general linear model included sex and age as covariates.

The FSL software suit command tool, *randomize*, was used to test between-group differences in FA and MD at each voxel along the sample-specific mean FA skeleton, representing the centers of the major WM tracts common to all subjects in the sample. Separate permutation simulations, run with 10,000 iterations and threshold-free cluster enhancement, were used to identify regions of significant between-groups differences in FA and MD. Significance was determined using family-wise error-corrected (FWER) p-values that were further adjusted for testing across multiple phenotypes: pFWER = 0.025. All analyses were done controlling for sex and age. When a significant between-groups difference was detected, cluster means and labels were extracted using *fslmeants* and *autoaq*, respectively, the latter with the JHU ICBM-DTI-81 White-Matter Labels atlas. Post-hoc analyses, including effect size computation (Cohen's f), were performed in R.

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Table 1. Sample characteristics

	DEPRESSED AND FRAIL (N=14)	NEVER-DEPRESSED AND ROBUST (N=17)	T	X^2	P-VALUE
Age (mean ± s.d.)	68.07 ± 6.91	68.82 ± 7.08	0.29		0.77
Sex (male:female)	2:12	10:7		6.38	0.01
Years of Education	13.40 ± 2.32	15.76 ± 1.16	3.15		0.001
FRAIL SCALE (mean ± s.d)	1.42 ± 0.62	0 ± 0	− 9.14		<0.001
MoCA (mean ± s.d.)	25.00 ± 3.54	26.23 ± 1.62	1.24		0.22
PHQ-9 (mean ± s.d.)	13.21 ± 4.60	0.88 ± 1.21	− 10.28		<0.001
MADRS (mean ± s.d.)	18.78 ± 5.26	1 ± 1.41	− 12.54		<0.001
RBANS (mean ± s.d.)	97.53 ± 14.38	101.32 ± 14.42	0.67		0.50

Abbreviations: t = Independent Sampled t-test; X^2 = Chi squared test; MoCA = Montreal Cognitive Assessment; PHQ-9 = Patient Health Questionnaire-9; MADRS = Montgomery-Asberg Depression Rating Scale; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

Results

Participant demographics and clinical characteristics are shown in Table 1. The scores for the FRAIL scale, PHQ-9, MADRS, sex frequency, and years of education were significantly different between groups. The two groups did not differ in age, MoCA, and RBANS score. We found no significant between-groups differences in regional subcortical volumes (Table 2) and vertex-wise cortical thickness when comparing the LLD + Frail and Never-depressed + Robust groups.

In the analysis of DWI data, one participant (Never-depressed + Robust group) had head motion that interfered with the DWI analysis. Therefore, the total sample for this analysis comprised 30 participants (LLD + Frail (n = 14) and Never-depressed + Robust (n = 16)). We detected a significant between-group difference (LLD + Frail > Never-depressed + Robust) in MD measures, adjusted for sex and age, in one cluster (48,225 voxels; peak voxel: pFWER = 0.005, MNI coord. (X, Y, Z) = − 26, − 11, 27) (Figure 1). The corresponding effect size was large (Cohen's f = 0.808). The spatial extent of this cluster was large, covering nearly 38% of the mean FA skeleton, representing the centers of the major WM tracts, the corpus callosum, anterior and superior corona radiata, internal and external capsule, and superior longitudinal fasciculus (Figure 1). On the other hand, we identified no significant between-group differences in voxel-wise FA when comparing LLD + Frail and Never-depressed + Robust groups. Including years of education as an additional covariate reduced the overall spatial extent of the effect, but preserved its MD specificity and direction, as well as its localization over the same major WM tracts (Supplementary Table 1 and Supplementary Figure 1).

Table 2. Difference in Subcortical Volumes Among LLD-Frail and CG

REGION	LLD-FRAIL VS. CG			
CV = SEX, AGE, ETIV	STATISTIC	P.VALUE	P.FDR	COHENS.F
Thalamus, L	0.224	0.640	0.878	0.093
Thalamus, R	0.578	0.454	0.878	0.149
Caudate, L	0.501	0.485	0.878	0.139
Caudate, R	1.478	0.235	0.878	0.238
Putamen, L	3.147	0.088	0.878	0.348
Putamen, R	1.675	0.207	0.878	0.254
Pallidum, L	0.074	0.788	0.878	0.053
Pallidum, R	0.429	0.518	0.878	0.128
Hippocampus, L	0.024	0.878	0.878	0.030
Hippocampus, R	0.957	0.337	0.878	0.192
Amygdala, L	0.053	0.819	0.878	0.045
Amygdala, R	0.637	0.432	0.878	0.157
Accumbens area, L	0.130	0.722	0.878	0.071
Accumbens area, R	0.031	0.862	0.878	0.034

There were no significant differences observed when comparing subcortical volumes between LLD-Frail and CG individuals. Abbreviations: CV = covariates; eTIV = estimated total intracranial volume; FDR = false discovery rate; CG = Never-depressed + Robust; LLD-Frail = depressed, frail.

Discussion

In this study, we showed a significantly higher MD values in LLD + Frail compared to Never-depressed + Robust individuals. The difference in MD values between LLD + Frail and Never-depressed + Robust individuals had a large effect size and extended to many WM tracts that support inter-hemispheric communication, emotional, and cognitive processing. MD is a DTI metric that

https://doi.org/10.1017/S1041610223000066 Published online by Cambridge University Press

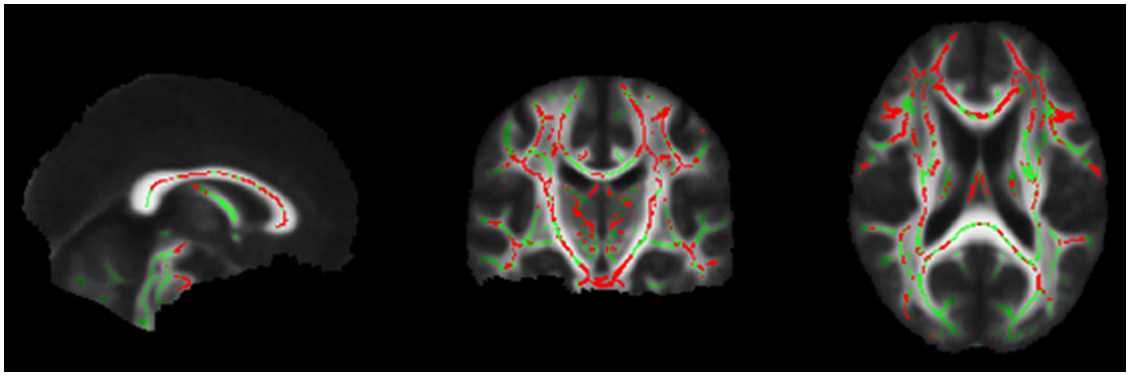

Figure 1. Regions of significant between-groups difference in MD (red: LLD-Frail > CG), overlaid onto the mean FA skeleton (green). A single cluster representing several WM tracts, the corpus callosum, anterior and superior corona radiata, internal and external capsule, and superior longitudinal fasciculus had a significant between-group difference (LLD + Frail > Never-depressed + Robust) in MD measures. Abbreviations: *FA = fractional anisotropy; FWER = family-wise error rate; CG = Never-depressed + Robust; LLD-Frail = depressed, frail; MD = mean diffusivity*.

measures the average water diffusion in a voxel, representing WM microstructure and is viewed as an indirect measure of inflammatory activity, with higher values indicating lower regional cellular density and higher local inflammatory activities (O'Donnell and Westin, 2011). Our findings suggest that individuals with LLD and frailty have a significant loss of WM integrity compared to Never-depressed + Robust subjects and are consistent with previous studies showing LLD and frailty to be independently associated with abnormal WM integrity and higher neuroinflammation (Lopez-Sanz *et al.*, 2018; Wen *et al.*, 2014; Chen *et al.*, 2006).

The mechanisms underlying the abnormal WM microstructure in LLD and frailty remain unclear. However, since MD is sensitive to cytotoxic edema and WM primary contains glial cells, we hypothesize that inflammation and low-grade cytotoxic edema within glial cells may potentiate LLD and frailty (Ampo *et al.*, 2022; Diniz *et al.*, 2022; Aizenstein *et al.*, 2016). Our results indicate that LLD + Frailty is associated with a higher neuroinflammatory burden in tracts related to interhemispheric communication, emotional, and cognitive processing. This is in line with a recent study showing that subjects with LLD + Frailty have more systemic inflammatory and mitochondrial dysfunction burden when compared with Never-depressed + Robust individuals (Ampo *et al.*, 2022). Therefore, we hypothesize that a higher inflammatory burden in the central nervous system and the periphery can be a shared mechanism of depression and frailty in older adults and its associated loss of WM tract integrity.

The present study did not show a significant difference in subcortical volume or cortical thickness between frail LLD participants and controls. Grey matter atrophy and ventricular enlargement have consistently been observed in LLD and frail individuals (Chen *et al.*, 2006; Benjamin and Steffens, 2011; Lopez-Sanz *et al.*, 2018). Our findings may suggest a lack of statistical power due to a small sample size analyzed. On the other hand, these results may also be because the majority of the participants included in this analysis had a milder presentation of the frailty syndrome and might not have yet developed significant gray matter and subcortical structural changes.

The results of this study should be viewed in light of several additional limitations. First, the sample size is relatively small, raising the risk of type II error. Second, our analysis did not include additional CGs (LLD + Robust and Never-depressed + Frail), limiting our ability to infer the extent LLD or frailty contributed to the results. Third, this is a cross-sectional study that limits one's ability to infer casualty. Fourth, the observational nature of imaging will make this study prone to residual cofounding in which a common, unknown factor is responsible for the significant statistical associations. The small sample size may also make it hard to control for specific cofounding variables, introducing bias into our analysis. Finally, the study has limited external validity as the participants were recruited from two nearby study centers, and the depressed subjects mainly consisted of prefrail females. Future studies utilizing larger samples, additional CGs, and a longitudinal design are necessary to confirm our hypothesis and evaluate the prognostic significance of elevated inflammatory burden in these individuals.

In conclusion, we showed that the LLD + Frailty is associated with significant microstructural abnormalities within WM tracts compared to Never-depressed + Robust individuals. Our findings indicate that heightened neuroinflammatory burden can be a shared mechanism underlying both conditions and suggests the possible existence of a depression–frailty phenotype in older adults.

https://doi.org/10.1017/S1041610223000066 Published online by Cambridge University Press

Conflict of interest

The authors do not have any conflict of interest to report.

Source of funding

This work was funded by NIMH grant R01MH 115953.

Description of authors' roles

E. Shuster: Study design, statistical analyses, and drafting of the manuscript.

A. Miles: Neuroimaging analyses, statistical analyses, and drafting of the manuscript.

L. Heyland: Neuroimaging analyses, statistical analyses,

N. Calarco: Neuroimaging analyses, statistical analyses,

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A.Voineskos: Study design, intellectual input, and drafting of the manuscript.

D.Steffens: Intellectual input, and drafting of the manuscript.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610223000066

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