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ORIGINAL ARTICLE

Frailty and functional brain connectivity (FBC) in older adults with mild cognitive impairment (MCI): baseline results from the SYNERGIC Trial

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Abstract Functional brain connectivity (FBC), or areas that are anatomically separate but temporally synchronized in their activation, represent a sensitive biomarker for monitoring dementia progression. It is unclear whether frailty is associated with FBC in those at higher risk of progression to dementia (e.g., mild cognitive impairment -MCI-) and if sex plays a role. We used baseline data from the SYNERGIC trial, including participants with MCI that received brain MRI. In this cross-sectional analyses ($n=100$), we measured frailty using a deficit accumulation frailty index. Using the CONN toolbox, we assessed FBC of networks and regions of interest across the entire connectome. We used Pearson's correlation to investigate the relationship between FBC and frailty index in the full sample and by sex. We also divided the full sample and each sex into tertiles based upon their frailty index score and then assessed between-tertile differences in FBC. The full sample (cluster: size=291 $p\text{-}FDR<0.05$) and males (cluster: size=993 and 451 $p\text{-}FDR<0.01$) demonstrated that increasing (stronger) connectivity between the right hippocampus and clusters in the temporal gyrus was positively correlated with increasing

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(worse) frailty. Males also demonstrated between-tertile differences in right hippocampus connectivity to clusters in the lateral occipital cortex (cluster: size = 289 *p-FDR* < 0.05). Regardless of frailty status, females demonstrated stronger within-network connectivity of the Default-Mode ($p = 0.024$). Our results suggest that increasing (worse) frailty was associated with increasing (stronger) connectivity between regions not typically linked, which may reflect a compensation tactic by the plastic brain. Furthermore, the relationship between the two variables appears to differ by sex. Our results may help elucidate why specific individuals progress to a dementia syndrome. NCT02808676. https://www.clinicaltrials.gov/ct2/show/NCT02808676

Keywords fMRI · Functional brain connectivity · Mild cognitive impairment · Frailty · Older adults · Cross-sectional

Abbreviations

FBC	Functional brain connectivity
FI	Frailty index
MCI	Mild cognitive impairment
ROI	Region of interest
S-V	Seed-to-voxel
SYN	SYNchronizing Exercises, Remedies in GaIt and Cognition
T0	Pre-intervention
T6	Post-intervention
T12	Follow-up

Introduction

Mild cognitive impairment (MCI) represents a prodromal stage between expected age-related cognitive decline and dementia, but more than half of those classified remain stable or recovered [1–4]. Identifying which individuals will eventually progress to a dementia syndrome, including Alzheimer's disease, is an important research goal [5]. Frailty is common in older adults with Alzheimer's disease [6], and it moderates the relationship between Alzheimer's disease pathology and clinical symptoms; individuals with low levels of Alzheimer's pathology but a high degree of frailty appear to be at greater risk for dementia than those with low levels of Alzheimer's pathology and a low degree of frailty [7]. Similar observations have been made regarding the relationship between biomarkers and dementia, and genetic risk and its clinical disease expression [8]. Ultimately, frailty may partially explain the progression or lack thereof to Alzheimer's disease and related dementias amongst individuals with MCI [9].

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Conceptually, frailty is a graded state of age-related decreasing physiological reserve that gives rise to vulnerability to adverse health outcomes or stressors [10], such as the novel COVID-19 virus [11]. Frailty is a distinct [12] multidimensional [13] entity, often including deficits in cognitive [14] and physical function [15], as well as social and affective domains [16]. Like cognitive decline, frailty is dynamic [17] as people can transition between varying states [18, 19]. Changes in frailty status may occur concurrently with dementia-related changes in neural substrates, as frailty has been shown to predict dementia [20]. Recently, there has been a call for an investigation into the common etiology of frailty and dementia [21].

Researchers have shown frailty to be negatively associated with global brain volume [22], as well as the microstructure of gray and white matter [23]. The relationship between frailty and brain function has garnered less attention. Functional brain connectivity (FBC) refers to brain areas that are spatially separated but temporally synchronized in their activation [24]. FBC is believed to enable efficient information processing and the completion of complex functions [25]. FBC can be measured using functional magnetic resonance imaging and is considered a sensitive biomarker in those at risk of progression to dementia as changes precede structural atrophy and occur years before clinical manifestation [26]. We know of only two studies that have examined FBC and frailty status, using magnetoencephalography [27] and functional magnetic resonance imaging [28]. Both studies classified their cognitively healthy sample using the Cardiovascular Health Study–Frailty Phenotype, which focuses largely on physical frailty domains [29] and restricted their investigation of FBC to motor areas [27, 28]. We found no studies that examined the relationship between frailty and FBC in individuals with cognitive impairment or how a more multidimensional measure of frailty status, such as the frailty index (FI) [30], is associated with FBC in motor areas and beyond.

This cross-sectional study investigated the relationship between frailty status, assessed using the FI, and FBC in individuals clinically classified with MCI. We hypothesized that frailty would be associated with FBC in individuals with MCI. Males and females demonstrate differences in cerebral function [31] and blood flow [32]. Additionally, males are at a greater risk of developing MCI [33], but frailty is more common in females [34]. Therefore, we also conducted a sub-analysis based on the hypothesis that males and females would differ in their association between frailty and FBC.

Methods

Design and participants

The SYNchronizing Exercises, Remedies in GaIt and Cognition (SYNERGIC) trial [35] (NCT02808676) was a multi-site, randomized, phase II, fractional factorial, double-blind controlled study evaluating the effect of combined physical exercise separately and synergistically with cognitive training and/or high-dose vitamin D_3 supplementation in older adults (60 to 85 years) with MCI. All SYNERGIC sites were in Canada and included Western University (London, ON; lead site), University of Waterloo (Waterloo, ON), Wilfrid Laurier University (Waterloo, ON), University of Montreal (Montreal, QC), and University of British Columbia (Vancouver, BC). SYNERGIC participants completed three in-person assessments, including baseline or pre-intervention (T0), post-intervention (T6), and follow-up (T12). T0 and T6 occurred immediately before and after a 20-week intervention, while T12 occurred 6 months after T6. Given the cross-sectional nature of the present study, pre-intervention baseline data or T0 is the only time point used in our analyses (Supplemental Material A).

Potential participants were diagnosed with MCI following existing guidelines [36]. The inclusion criteria also required proficiency in English or French (Montreal site), ability to ambulate at least 10 m independently, possessing (corrected) normal vision, in sufficient health according to the Physical Activity Readiness Questionnaire-Plus (PAR-Q+) [37], and ability to comply with trial procedures. The present study's exclusion criteria was identical to the parent trial except for the following additions: (1) did not complete an MRI assessment at baseline; and (2) participants consider their left hand to be dominant. SYN recruited potential participants from the community and clinics serving MCI populations from September 2016 to March 2020; the trial was terminated early due to the COVID-19 pandemic. Subjects' consent was obtained according to the Declaration of Helsinki, and all institutions received approval from their local ethics board.

Frailty

All in-person assessments included collecting demographic information and a battery of tests (Supplemental Material B). Therefore, it permitted a secondary retrospective analysis of participants' frailty status via a FI. The FI is a health state measure that reflects vulnerability to adverse health outcomes or, put more simply, a cumulative deficit model where "the more individuals have wrong with them, the more likely they are to be frail [38]." The FI is calculated as:

$$\mathrm{FI} = \frac{\text{number of health deficits present}}{\text{number of health deficits measured}}$$

A person with 9 of 30 potential deficits has an FI of (9/30) 0.30 and is considered "more frail" than an individual with 4 of 30 potential deficits (4/30 = 0.13). Compared to other tools, the FI is unidimensional and has been suggested to have high predictive value in community settings and for adverse outcomes [39]. All variables in the present study's FI have been previously utilized in other FIs [40, 41] and are listed in Supplemental Material C. The included FI variables were grouped into one of the following nine domains: physical, functional, exhaustion, nutrition, neuropsychiatric, falling, comorbidities, vital signs, and medications. Given the demographic of interest, we excluded measures of cognitive function from our FI as such variables were expected to be impaired; previous research has done the same for cardiovascular outcomes in a cardiac rehabilitation demographic [40]. Notably, the total number of variables included in the FI is inconsequential as long as there are at least 30 [42].

MRIs

MRIs were collected according to version 3.8 of the Canadian Dementia Imaging Protocol [43], but only T1W and resting-state functional magnetic resonance imaging scans were used here. We visually inspected data for overall quality and then organized according to the brain imaging data structure [44], preprocessed via fMRIPrep (version 20.2.0) [45] (Supplemental Material D), skull-stripped using FMRIB Software Library (version 6.0.4) [46] Brain Extraction Tool [47], and then uploaded to the CONN Functional Connectivity Toolbox (version 20.b) [48]. Once in CONN, we denoised and analyzed data using both a region of interest (ROI)-to-ROI (ROI-ROI) and seed-to-voxel (S-V) approach; the rationale to conduct multiple analyses was based upon the study's exploratory nature, and that previous researchers have conducted multiple analyses within the same study [49, 50]. ROIs included the Default-Mode [51], Dorsal Attention [52], Salience [53], Frontoparietal [54], and Sensorimotor [55] networks, while the S-V analysis used both the left and right hippocampus as seeds (Supplemental Material E–F). Finally, we exported significant clusters into both Multi-image Analysis GUI (MANGO; version 4.1) [56] and xjView (version 9.7) [57] to review the overlap of cluster coordinates and consistency in anatomical labeling, respectively.

Notably, CONN's quality assurance plots, including variables related to motion, global signal change, and valid scans, should score ≥ 95% [58]. After completing the original denoising, the quality assurance plots did not achieve the 95% goal. Therefore, we extracted voxel-wise standardization (DVARS) and mean framewise displacement values, which reflect signal change and motion, via MRI Quality Control [59]; similar to fMRIPrep, MRI Quality Control is another application [60] available to datasets organized according to the brain imaging data structure. Subsequently, DVARS and framewise displacement values were imported into the Statistical Package for Social Sciences (SPSS version 27; IBM Canada Ltd. Markham, Ontario) to identify and remove participants classified as extreme (± 3 times the interquartile range) outliers. Quality assurance plots then achieved the recommended 95% goal (Supplemental Material G).

Statistical analyses

Demographic information

Except for sex reported as sample size, we summarized the demographic characteristics using means and standard deviations. To identify trends in whom or potentially why specific individuals chose to forgo MRIs, we also compared the characteristics of participants who completed baseline imaging versus those who did not. In SPSS, an

independent samples *t*-test assessed between-group (i.e., sex and MRI completion status) differences in participant characteristics.

FBC and frailty in ROI-ROI analysis

We applied no cluster or connection threshold to the ROI-ROI analysis as we aimed to ascertain the average connectivity score for every within-network connection for every participant after controlling for the covariates of age, sex, and years of education. We then calculated the average within-network connectivity for each participant by averaging the individual connectivity scores. For example, CONN's Default-Mode network includes four ROIs (medial prefrontal cortex, posterior cingulate cortex, and lateral parietal cortex left and right). We calculated the connectivity of the six possible connections for each participant and then averaged the six connections for a Default-Mode connectivity score. We then imported each participant's average within-network connectivity score into SPSS, where we completed a Pearson correlation with the FI *z*-score. We converted FI to a *z*-score via standardized linear regression residuals to control for the same covariates used in CONN (age, sex, and years of education).

FBC and frailty in S-V analysis

Unlike ROI-ROI, we imported raw FI values into CONN to test the existence of significant associations between connectivity and FI after controlling for the same covariates (age, sex, and years of education). As such, we utilized standard S-V thresholds (cluster threshold, $p < 0.05$ cluster-size *p*-FDR corrected; voxel threshold, $p < 0.001$ *p*-uncorrected) [61]. We did not follow the same procedure for the ROI-ROI analysis due to (1) no interest in a particular connection with the seed and (2) the likely overwhelming number of results produced from eliminating cluster and voxel thresholds.

Sex

The above analyses were repeated in males and females separately, keeping age and years of education as covariates.

Tertiles

We divided our entire sample and each sex into FI tertiles (cut-points = 0.16 and 0.23). Tertiles permit the grouping and, thus, comparison of FBC across a more narrow frailty spectrum (i.e., low, medium, and high). Previous work in frailty and brain health also utilized a tertiles strategy [21]. Average FBC was compared between the three tertiles after controlling for sex, age, and self-reported years of education; sex was removed as a covariate when conducting tertile analyses in males and females. Tertile characteristics were compared in SPSS using a one-way analysis of variance (ANOVA) to determine if any differences other than the mean FI value existed.

Data availability

The data supporting this study's findings are available from the corresponding authors upon reasonable request.

Results

Demographic information SYN randomized 183 participants. One hundred twenty completed a baseline MRI, but we removed 20 from the present study's analysis due to left-handedness, $n = 8$; MRI artifacts, $n = 2$; incomplete dataset, $n = 5$; and identified as an outlier based upon DVARS and/or framewise displacement values, $n = 5$ (Fig. 1). Therefore, the final analysis included 100 participants (females, $n = 48$). Individuals that completed an MRI were significantly older than those who did not (Supplemental Material H; $p = 0.047$). The baseline characteristics of the participants included in the present study's analysis ($n = 100$) generally reflected those of the original ($n = 120$) sample (Supplemental Material I). However, and as expected for sex comparisons within this demographic, height ($p < 0.001$), weight ($p < 0.001$), and years of education ($p = 0.047$) differed (Table 1). The average FI score for the full sample ($n = 100$) was 0.19. Females were frailer than males, but not significantly so. However, females demonstrated statistically higher or stronger within-network connectivity of the Default-Mode network ($p = 0.024$). The full sample also showed a significant difference in body

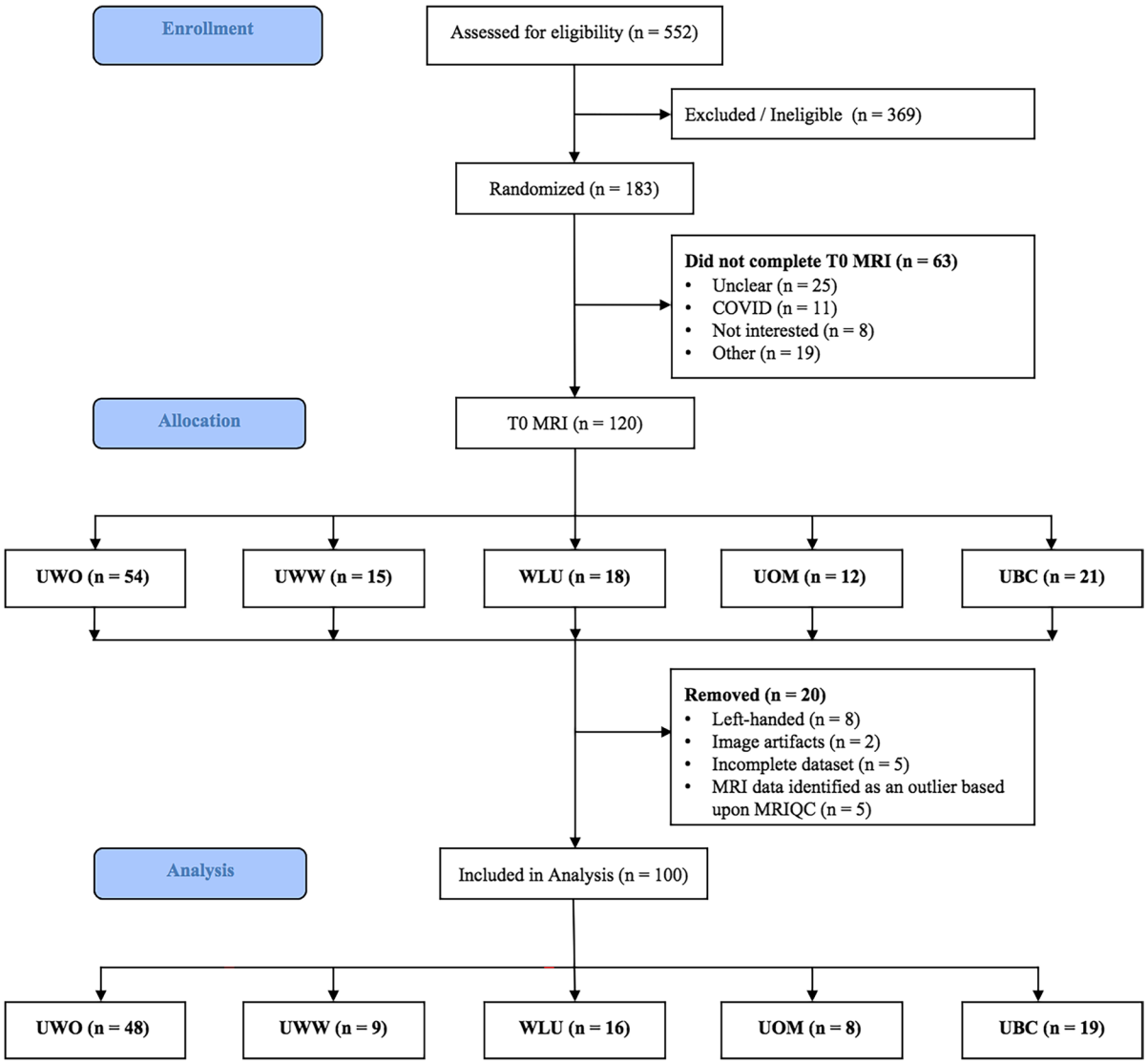

Fig. 1 Study flowchart for participants included in imaging analysis, stratified by study site. UWO, University of Western Ontario; UWW, University of Waterloo; WLU, Wilfrid Laurier University; UOM, University of Montreal; UBC, University of British Columbia

mass index when comparing the low and medium tertiles ($p = 0.023$; Table 2). There were no significant between-tertile differences in baseline characteristics for each sex (Tables 3 and 4).

FBC and frailty in ROI-ROI analysis There were no significant correlations between within-network connectivity (Default-Mode, Sensorimotor, Salience, Dorsal Attention, and Frontoparietal) and FI values for the full sample nor males and females. All effect sizes were considered insignificant or small ($|r| < 0.3$; Table 5 and Supplemental Material J-K).

FBC and frailty in S-V analysis After controlling for covariates, the full sample demonstrated that the FI score was positively correlated with connectivity between the right hippocampus and a cluster located in the left inferior and middle temporal gyrus (Fig. 2/Table 6; cluster:

Table 1 Characteristics of full sample ($n = 100$)

Characteristic	Total ($n = 100$)	Males ($n = 52$)	Females ($n = 48$)	*p-value*
Age	73.79 ± 6.24	74.27 ± 6.19	73.27 ± 6.31	0.426
# of comorbidities	4.73 ± 2.54	4.65 ± 2.57	4.81 ± 2.53	0.757
Years of education	15.10 ± 3.67	15.79 ± 4.08	14.33 ± 3.04	***0.047***
Height (cm)	167.33 ± 10.05	173.81 ± 7.21	160.31 ± 7.70	***< 0.001***
Weight (kg)	74.94 ± 14.89	82.56 ± 13.40	66.69 ± 11.77	***< 0.001***
Body mass index	26.65 ± 4.20	27.29 ± 3.94	25.96 ± 4.41	0.114
MoCA	22.88 ± 3.06[a]	22.94 ± 2.89	22.81 ± 3.27[b]	0.829
Frailty index value	0.19 ± 0.07	0.19 ± 0.07	0.20 ± 0.07	0.594
Default-Mode connectivity	0.5283 ± 0.1712	0.4915 ± 0.1659	0.5682 ± 0.1696	***0.024***
Sensorimotor connectivity	0.5784 ± 0.2462	0.6085 ± 0.2405	0.5458 ± 0.2505	0.205
Salience connectivity	0.3974 ± 0.1490	0.3785 ± 0.1497	0.4179 ± 0.1470	0.188
Dorsal Attention connectivity	0.4458 ± 0.1674	0.4695 ± 0.1836	0.4201 ± 0.1456	0.141
Frontoparietal connectivity	0.4875 ± 0.1730	0.4693 ± 0.1834	0.5072 ± 0.1605	0.275

All values are mean ± standard deviation. Independent samples *t*-test used in analysis of males versus females. *MoCA* Montreal Cognitive Assessment, *#* number, *cm* centimeters, *kg* kilograms; [a]$n = 99$; [b]$n = 47$. Bolded *p*-values indicate statistical significance

Table 2 Characteristics of full sample divided into tertiles based upon frailty index value

Characteristic	Low ($n = 39$)	Medium ($n = 31$)	High ($n = 30$)	*p-value*
Age	72.62 ± 6.39	74.16 ± 7.04	74.93 ± 4.97	0.289
Years of education	14.94 ± 3.02	15.73 ± 4.86	14.63 ± 3.00	0.486
Height (cm)	169.11 ± 10.71	168.68 ± 9.37	163.62 ± 9.11	0.052
Weight (kg)	72.59 ± 14.06	79.03 ± 15.45	73.79 ± 14.97	0.175
Body mass index	25.22 ± 3.39	27.69 ± 4.59	27.44 ± 4.36	***0.023****
MoCA	22.69 ± 3.33	23.19 ± 2.96	22.79 ± 2.87[a]	0.784
Default-Mode connectivity	0.5340 ± 0.1818	0.5418 ± 0.1518	0.5070 ± 0.1796	0.710
Sensorimotor connectivity	0.5580 ± 0.2777	0.6420 ± 0.2232	0.5394 ± 0.2186	0.215
Salience connectivity	0.4034 ± 0.166	0.3957 ± 0.1354	0.3914 ± 0.1436	0.945
Dorsal Attention connectivity	0.4240 ± 0.1970	0.4609 ± 0.1256	0.4585 ± 0.1658	0.587
Frontoparietal connectivity	0.4750 ± 0.1899	0.5081 ± 0.1791	0.4825 ± 0.1450	0.719

All values are mean ± standard deviation. One-way ANOVA used for analysis. *MoCA* Montreal Cognitive Assessment, *#* number, *cm* centimeters, *kg* kilograms; [a]$n = 29$. *, low significantly different than intermediate

Table 3 Characteristics of female sample divided into tertiles based upon frailty index value

Characteristic	Low ($n = 18$)	Medium ($n = 12$)	High ($n = 18$)	*p-value*
Age	71.44 ± 5.88	74.17 ± 9.05	74.5 ± 4.09	0.302
Years of education	14.81 ± 3.11	14.79 ± 3.58	13.56 ± 2.55	0.397
Height (cm)	160.99 ± 8.56	162.67 ± 8.56	158.06 ± 5.8	0.25
Weight (kg)	63.53 ± 11.22	70.52 ± 15.14	67.31 ± 9.36	0.275
Body mass index	24.43 ± 3.43	26.67 ± 5.67	27.02 ± 4.15	0.174
MoCA	22.61 ± 3.57	22.92 ± 3.85	22.94 ± 2.63[a]	0.95
Default-Mode connectivity	0.6134 ± 0.1411	0.5520 ± 0.1588	0.5338 ± 0.1993	0.353
Sensorimotor connectivity	0.5586 ± 0.3090	0.5399 ± 0.2661	0.5370 ± 0.1788	0.968
Salience connectivity	0.4093 ± 0.1435	0.4122 ± 0.1720	0.4303 ± 0.1405	0.905
Dorsal Attention connectivity	0.3988 ± 0.1619	0.4338 ± 0.0919	0.4323 ± 0.1617	0.741
Frontoparietal connectivity	0.4892 ± 0.1843	0.5322 ± 0.1879	0.5086 ± 0.1167	0.778

All values are mean ± standard deviation. One-way ANOVA used for analysis. *MoCA* Montreal Cognitive Assessment; *#* number, *cm* centimeters, *kg* kilograms; [a]$n = 17$. No *p*-values reached statistical significance

Table 4 Characteristics of male sample divided into tertiles based upon frailty index value

Characteristic	Low ($n=21$)	Medium ($n=19$)	High ($n=12$)	*p-value*
Age	73.62 ± 6.76	74.16 ± 5.70	75.58 ± 6.20	0.686
Years of education	15.05 ± 3.01	16.32 ± 5.54	16.25 ± 2.99	0.569
Height (cm)	176.07 ± 6.73	172.47 ± 7.91	171.98 ± 6.31	0.176
Weight (kg)	80.35 ± 11.47	84.40 ± 13.38	83.52 ± 16.84	0.618
Body mass index	25.91 ± 3.28	28.33 ± 3.79	28.08 ± 4.77	0.11
MoCA	22.76 ± 3.19	23.37 ± 2.34	22.58 ± 3.29	0.72
Default-Mode connectivity	0.4659 ± 0.188	0.5353 ± 0.1513	0.4668 ± 0.144	0.359
Sensorimotor connectivity	0.5574 ± 0.2556	0.7065 ± 0.1686	0.5429 ± 0.2768	0.080
Salience connectivity	0.3984 ± 0.1865	0.3853 ± 0.1104	0.3331 ± 0.1328	0.478
Dorsal Attention connectivity	0.4457 ± 0.2244	0.4780 ± 0.1426	0.4977 ± 0.1713	0.721
Frontoparietal connectivity	0.4628 ± 0.1982	0.4929 ± 0.1768	0.4433 ± 0.1778	0.755

All values are mean ± standard deviation. One-way ANOVA used for analysis. *MoCA* Montreal Cognitive Assessment, *#* number, *cm* centimeters, *kg* kilograms. No *p*-values reached statistical significance

Table 5 Pearson correlation between frailty index values and functional brain connectivity (region of interest to region of interest analysis) in the full sample of participants, as well as males and females

Group	Variables included in correlation analysis		Correlation score (*r*)	Significance (2-tailed; *p*)
All subjects ($n=100$)	Frailty index	Default-Mode connectivity	−0.098	0.334
		Sensorimotor connectivity	0.040	0.692
		Salience connectivity	−0.014	0.892
		Dorsal Attention connectivity	0.178	0.076
		Frontoparietal connectivity	−0.035	0.727
Females ($n=48$)	Frailty index	Default-Mode connectivity	−0.210	0.153
		Sensorimotor connectivity	0.000	0.998
		Salience connectivity	0.129	0.382
		Dorsal Attention connectivity	0.155	0.294
		Frontoparietal connectivity	0.029	0.845
Males ($n=52$)	Frailty index	Default-Mode connectivity	0.007	0.963
		Sensorimotor connectivity	0.076	0.590
		Salience connectivity	−0.146	0.302
		Dorsal Attention connectivity	0.200	0.156
		Frontoparietal connectivity	−0.095	0.504

No *p*-values reached statistical significance

size = 291 *p-FDR* < 0.05). Females showed no significant association between FI and FBC within this analysis. Conversely, males demonstrated that their FI score was positively correlated with connectivity between the right hippocampus and clusters from bilateral regions of the inferior and middle temporal gyrus (Fig. 3/Table 6; cluster: size = 993 and 451 *p-FDR* < 0.01) even after controlling for covariates; one cluster demonstrated overlap with the cluster from the full sample (Supplemental Material L). The significant associations within the full sample and males mean that higher (worse) FI values were associated with greater FBC.

Only males demonstrated a significant between-tertile difference in connectivity between the right hippocampus and a cluster located in the lateral occipital cortex. Specifically, low demonstrated less connectivity than the medium tertile but more than the high tertile (Fig. 4/Table 6; cluster: size = 289 *p-FDR* < 0.05). Notably, the significant difference for low versus medium was at a more liberal ($p < 0.05$) voxel threshold. Anatomical labeling of all significant connections according to both CONN and xjView are available in Supplemental Material M.

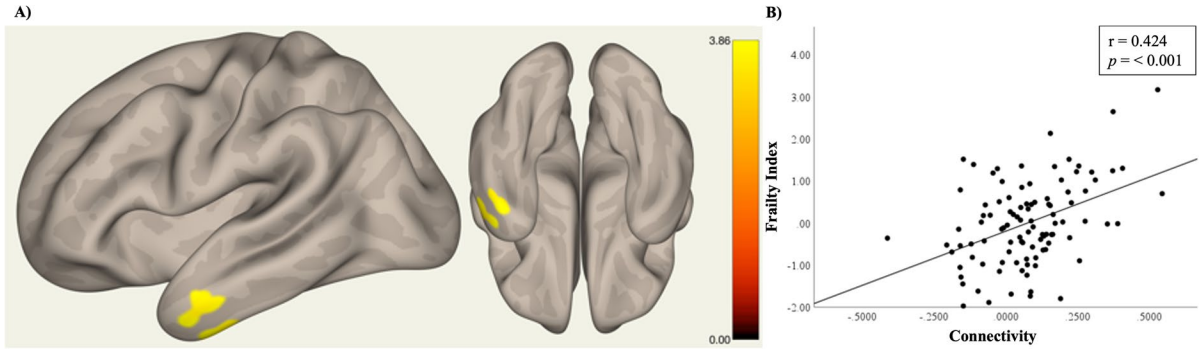

Fig. 2 Functional brain connectivity (FBC) in relation to frailty index (FI) score, in the full sample ($n = 100$; 48 female). **A** Depicts how increasing (higher) frailty is associated with increasing connectivity between the right hippocampus and the cluster shown (see Table 6 for more details about cluster). Left and inferior view for brain images. **B** Degree of FBC (between the right hippocampus and the cluster shown) by the degree of frailty. FBC is a Fisher-transformed correlation coefficient. FI was converted to a *z*-score via standardized residuals of linear regression to control for same covariates used in FBC analyses

Discussion

In this cross-sectional study of older adults with MCI, we examined the relationship between frailty status, assessed using the FI, and FBC throughout the brain. In support of our hypothesis, we found significant associations between FI scores and FBC in the full sample. Also supporting our hypothesis, we found significant sex-specific differences in the relationship between FI and FBC.

The ROI-ROI analysis included five networks (Default-Mode, Sensorimotor, Salience, Dorsal Attention, and Frontoparietal) with a total of 42 different connections. The main finding from the ROI-ROI analysis was that females possess greater connectivity within the Default-Mode network, regardless of frailty status and despite all participants being classified with an identical cognitive status (i.e., MCI). Notably, no ROI-ROI networks demonstrated a significant association between connectivity and FI values in the full sample or by sex. The S-V analysis used the right and left hippocampus as a seed, but only the right demonstrated connections significantly associated with FI values. When analyzing the full sample and males continuously, the right hippocampus increased connectivity to the left and bilateral regions of the inferior and middle temporal gyrus. Such results suggest that males are likely driving the significant connection to the left inferior/middle temporal gyrus in the full sample.

The connectivity coefficients that were significantly associated with FI demonstrated a positive correlation; this means that higher or worse FI values were associated with greater or increasing FBC. The significant connections appear between regions not typically linked or belonging to a single network. Admittedly, this is difficult to confirm given the broad (temporal lobe) anatomically labeling applied to the cluster as per the imaging programs utilized (i.e., CONN and xjView). We speculate that this connection may reflect compensation or an attempt by the plastic brain to maintain homeostasis by increasing connectivity via alternative circuits or regions not typically connected. Such adjustments reflect the "scaffolding" theory [62] and have been previously demonstrated with the Default-Mode [63]. Further support for this compensatory behavior is reflected in the lack of significant negative associations between FI scores and within-network connectivity. Such compensatory behavior, however, does not appear to exist in perpetuity according to our male tertile results.

The male low tertile possessed less connectivity than the medium tertile but more than the high tertile. Such findings conflict with the correlation observed in our continuous data and may suggest that individuals from the low and medium tertiles are driving the significant positive correlations between FI and FBC. More importantly, these findings indicate that as the individual becomes more frail or moves into the high tertile, the brain is incapable of maintaining

Table 6 All connections from functional brain connectivity (seed to voxel analysis) that were significantly correlated with frailty index score after controlling for covariates

Demographic	Seed	Direction of connectivity	Cluster						
			x, *y*, *z*	Size	Size *p*-FDR	Peak *p*-unc	Anatomical area	%	Voxels
Full ($n=100$)	Right hippocampus	↑	−48 + 2 − 44	291	***0.029812***	***0.000107***	Inferior temporal gyrus, anterior division left	44	127
							Temporal pole left	13	37
							Middle temporal gyrus, anterior division left	11	31
							Not-labeled	33	96
Male ($n=52$)	Right hippocampus	↑	−44 + 4 − 46	993	***0.000021***	***0.000004***	Inferior temporal gyrus, anterior division left	26	262
							Inferior temporal gyrus, posterior division left	18	174
							Temporal pole left	11	105
							Middle temporal gyrus, anterior division left	9	91
							Middle temporal gyrus, posterior division left	2	15
							Temporal fusiform cortex, anterior division left	0	2
							Temporal fusiform cortex, posterior division left	0	1
							Not-labeled	35	343
		↑	66 − 28 − 26	451	***0.00351***	***< 0.000001***	Inferior temporal gyrus, posterior division right	49	219
							Middle temporal gyrus, posterior division right	20	88
							Inferior temporal gyrus, temporooccipital part right	0	2
							Not-labeled	31	142
Male tertiles ($n=52$) *Intermediate > low and high*	Right hippocampus	↑	−26 − 70 + 16	289	***0.015491***	***0.000006***	Lateral occipital cortex, inferior division left	6	18
							Lateral occipital cortex, superior division left	2	5
							Not-labeled	92	266

Bolded *p*-values indicate statistical significance

the new compensatory connection. Such a trajectory may mean that the high tertile is at the greatest risk of progression to Alzheimer's disease, despite receiving an identical cognitive classification (i.e., MCI) as the medium and low tertiles. Stated differently, if cognitive status does indeed reflect brain function, then we would expect our tertiles to have insignificant differences in FBC, but this is not the case, and increasing or worse frailty appears to play a role. Future research, inclusive of associations with behavioral or clinical implications (i.e., cognitive test scores), as well as a larger sample size with a more diverse frailty spectrum, should test such theories.

Our findings both support and refute previous research. Only two studies have examined the relationship between FBC and frailty status [27, 28]. Both used the Cardiovascular Health Study–Frailty Phenotype [29], only included cognitively *normal* older

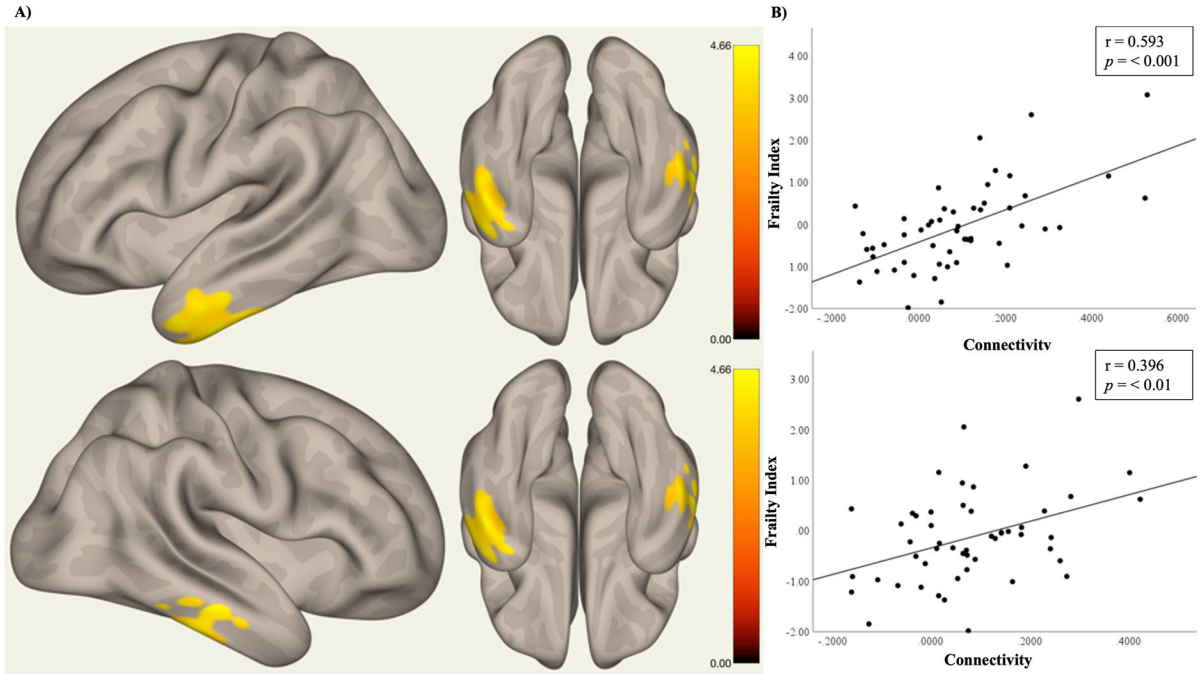

Fig. 3 Functional brain connectivity (FBC) in relation to frailty index (FI) score, in the male sample ($n=52$, top and $n=51$, bottom). **A** Depicts how increasing (higher) frailty is associated with increasing connectivity between the right hippocampus and the clusters shown (see Table 6 for more details about cluster). Left, right, and inferior view for brain images. **B** Degree of FBC (between the right hippocampus and the clusters shown) by the degree of frailty. FBC is a Fisher-transformed correlation coefficient. FI was converted to a *z*-score via standardized residuals of linear regression to control for same covariates used in FBC analyses

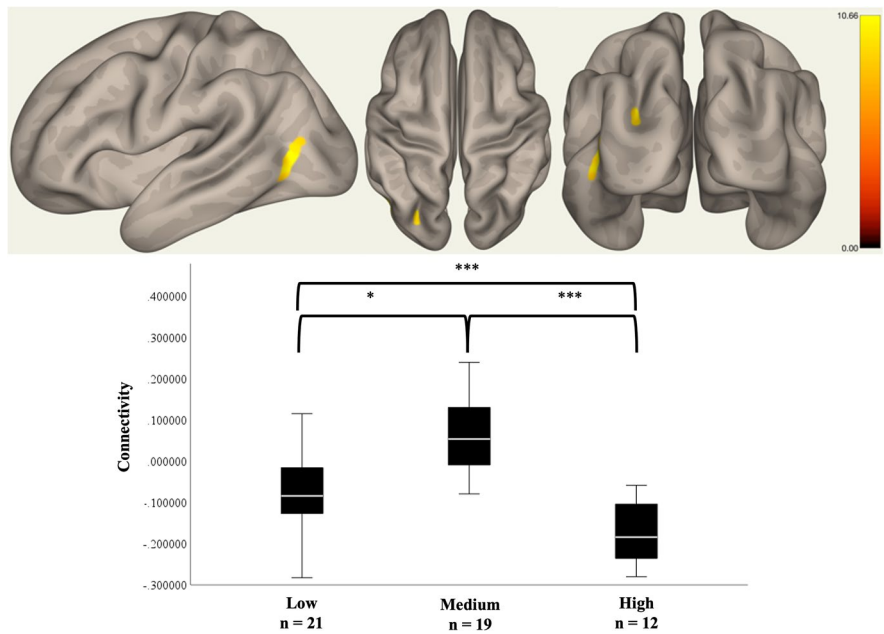

Fig. 4 Functional brain connectivity (FBC) in each male tertile ($n=52$); tertiles were created from FI scores. Tertiles were compared using a one-way analysis of variance (ANOVA). FBC (between the right hippocampus and the cluster shown) demonstrated a significant between-tertile difference. FBC is a Fisher-transformed correlation coefficient. Left, superior, and posterior for brain images. ***, standard cluster and connections thresholds; *, connection threshold at a more liberal voxel threshold of p-value = 0.05

adults, and restricted their analysis to motor regions. Only Lammers and colleagues used functional magnetic resonance imaging and performed scans with eyes closed [28]. They found a significant negative relationship between frailty and the Supplementary Motor Area but not the pre-SMA [28]. Conversely, we found no significant associations between the Sensorimotor Network and FI nor any of our other predefined networks. The discrepancy between studies may reflect methodological differences as we utilized an FI that included variables from various domains, focused on clinically impaired older adults, and performed functional magnetic resonance imaging scans with eyes open; visual status is an essential consideration for neural function [64]. Network-specific associations to an identical health outcome are further supported by previous work examining the relationship between FBC and gait parameters [65]. Evidently, more research is needed on FBC and its relationship with frailty.

Our results suggest that sex is essential in understanding the association between frailty and FBC. Lammer and colleagues did not conduct a separate analysis by sex, but other researchers have demonstrated sex-specific differences in brain function [31] and brain blood flow [32]. Furthermore, sex-specific differences in frailty are well established as females become frail earlier and at any given age are more frail than their male counterparts but manage to live longer; such a phenomenon is known as "the male–female health survival paradox" [34, 66] and is an active area of research [67]. Females' greater within-network Default-Mode connectivity and lack of what we identified as compensatory connectivity may reflect better brain function and further support females' resilience or their ability to handle neurodegeneration. Sex hormones likely play a role, but a 2017 review highlighted two biological theories for the frailty-sex discrepancy: (1) males possess less physiological reserve so, at the same FI score, they are at a greater risk of mortality; and (2) females tend to accumulate less severe deficits or deficits associated with lower risk of mortality, highlighting an issue with collecting the number, but not the nature of the deficits [68]. Notably, sex differences may have convoluted the full sample and, thus, be responsible for the lack of more meaningful findings in the present study. Ultimately, more research is needed on the relationships between FBC, frailty, and sex.

In addition to the suggestions already put forth, future studies should consider frailty scores and sex when conducting FBC analyses in clinical groups as it may impact findings. Similar to research in frailty and exercise interventions [18, 19], future research should analyze frailty status using the Frailty Phenotype and FI to determine if they produce divergent findings. Furthermore, such analyses should be simultaneously conducted in cognitively healthy and impaired older adults to help elucidate how dementia-related neurodegeneration alters the FBC-frailty relationship. Along the dementia spectrum, researchers may even want to consider the stage or classification of MCI (i.e., amnestic vs. non-amnestic [69, 70], early vs. late [71], and single vs. multi-domain [72, 73]) as this is potentially another factor impacting findings. Researchers should not restrict their analysis to a single region as some networks are more susceptible to neurodegeneration, which subsequently affects within and between-network connectivity [74]. Moreover, the "neural context" hypothesis suggests that the functional relevance of a brain area depends on the status of other connected areas [75]. Therefore, alterations in one region do not necessarily have the same implications as alterations in another. Only by examining the entire connectome will we better understand global and local alterations and their potential downstream consequences on behavioral outcomes. Tracking the longitudinal relationship between FBC and frailty will provide the greatest insight into many of the suggestions offered above while also creating an opportunity for early intervention.

We conducted the first study to cross-sectionally analyze the relationship between FBC and frailty status using the FI in individuals with MCI, but it is not without limitations. We classified most but not all of our participants with amnestic MCI. Therefore, different sub-types may be convoluting our findings. As is typical with FBC, the present study merely reflects two analyses available to researchers. Our previous systematic reviews [76, 77] and other works [78] have demonstrated that researchers can take different methodological approaches to answer the same question. Our sample may be considered less frail than other work in frailty and brain health as our maximum value was the equivalent of another study's upper tertile cut-point [21]; this is reflective of Neyman bias [79] or when more sick individuals are erroneously excluded. Similarly, our sex tertile results should be

interpreted cautiously, given their small sample size (< 20). No cognitively healthy comparator makes drawing interpretations for biological or *normal* aging difficult. Finally, cross-sectional studies inherently create several limitations, including the inability to make causal inferences and the "snapshot" nature.

The present study examined the cross-sectional association between FBC throughout the brain, and frailty status, as per a FI. Individuals with worse frailty scores demonstrated increased connectivity of the right hippocampus to broadly labeled clusters within the temporal gyrus. We believe such changes reflect compensation by the brain to maintain homeostasis via an increase in between-network connectivity or regions that are not typically linked. Outcomes differed by sex as only males demonstrated significant correlations between frailty and FBC, but females showed greater within-network Default-Mode connectivity than males regardless of frailty status. Overall, our findings add to the growing literature on how frailty impacts males' and females' (brain function) differently and suggest why only some individuals may progress to a dementia syndrome.

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Declarations

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