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RESEARCH ARTICLE

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Is it all in the baseline? Trajectories of chair stand performance over 4 years and their association with grey matter structure in older adults

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Abstract

Understanding individual variability in response to physical activity is key to developing more effective and personalised interventions for healthy ageing. Here, we aimed to unpack individual differences by using longitudinal data from a randomised-controlled trial of a 12-month muscle strengthening intervention in older adults. Physical function of the lower extremities was collected from 247 participants (66.3 ± 2.5 years) at four time-points. At baseline and at year 4, participants underwent 3 T MRI brain scans. K-means longitudinal clustering was used to identify patterns of change in chair stand performance over 4 years, and voxel-based morphometry was applied to map structural grey matter volume at baseline and year 4. Results identified three groups showing trajectories of poor (33.6%), mid (40.1%), and high (26.3%) performance. Baseline physical function, sex, and depressive symptoms significantly differed between trajectory groups. High performers showed greater grey matter volume in the motor cerebellum compared to the poor performers. After accounting for baseline chair stand performance, participants were re-assigned to one of four trajectory-based groups: moderate improvers (38.9%), maintainers (38.5%), improvers (13%), and decliners (9.7%). Clusters of significant grey matter differences were observed between improvers and decliners in the right supplementary motor area. Trajectory-based group assignments were unrelated to the intervention arms of the

study. In conclusion, patterns of change in chair stand performance were associated with greater grey matter volumes in cerebellar and cortical motor regions. Our findings emphasise that how you start matters, as baseline chair stand performance was associated with cerebellar volume 4 years later.

KEYWORDS
ageing, longitudinal analysis, physical activity, physical function, VBM

1 | INTRODUCTION

Age-related decline in physical function has widespread implications for older adults, ranging from an increased risk of falls to reduced quality of life (Ambrose et al., 2013; Ferrucci et al., 2016). These adverse outcomes extend to brain health. For example, cross-sectional studies have indicated that poor performance on mobility measures correlates with reduced white matter microstructural integrity and grey matter volume in older adults (Demnitz et al., 2017; Rosario et al., 2016).

Mobility outcomes can effectively and inexpensively be improved through physical activity interventions (Pahor et al., 2014; Stathi et al., 2022). While the benefits of physical activity interventions on mobility are well-established, randomised-controlled trials (RCTs) have found their effects on brain structures to be inconsistent (Batouli & Saba, 2017; Gogniat et al., 2021). This inconsistency is largely due to the large amount of unexplained individual variability in response to physical activity (Jonasson et al., 2016; Maass et al., 2015). For example, studies have shown that sex, education, and baseline activity levels may play a role in moderating the benefits of physical activity on the brain (Barha et al., 2019; Erickson et al., 2014; Sink et al., 2015). Identifying the origin of the existing, and notable, individual differences affecting physical activity interventions is key to designing more effective and targeted interventions for brain structure and function. Without a clear depiction of the factors that matter, it will remain difficult to make mechanistic inferences based on the outcomes from interventional RCTs employing physical activity.

Here, we aimed to identify individual differences that may influence patterns of change in physical function and the relationship between these patterns of change and structural brain measures. For this, we used longitudinal data from a physical activity intervention. The LIve active Successful Ageing (LISA) study conducted a RCT of a 12-month strength training intervention aimed at improving muscle mass and physical function in older adults ($n = 451$; aged 62–70). Resistance training was shown to increase muscle strength after 12 months, but no group effects were observed in the preregistered outcome of brain structure—hippocampal volume (Gylling, Eriksen, et al., 2020). Unique to the LISA study, participants continued to be followed-up up to 3 years after the intervention. Accordingly, a data-driven approach was used to categorise individuals into trajectory groups corresponding to declining, maintaining, or improving physical function, regardless of intervention group assignment. For this, the physical function measure showing most change over 4 years was selected: the chair stand test, a commonly used measure which is indicative of functional independence and mobility in older adults (Zhang et al., 2013). Using the LISA dataset, this study tested whether (1) baseline differences in demographic characteristics, mental health, and personality traits were associated with change in physical function and (2) whether patterns of change in physical function were associated with measures of brain structure 4 years later. We hypothesised that participants showing a trajectory of improved or maintained physical function would show greater grey matter volume in comparison to groups showing a decreased trajectory of physical function over 4 years.

2 | METHODS

2.1 | Study sample

Participants were community-dwelling older adults from the LISA study, an RCT of a 12-month muscle strength and resistance training intervention (Eriksen et al., 2016). The LISA study originally randomised 451 participants, aged between 62–70 years, into one of three groups: habitual activity (control), home-based moderate intensity training, or supervised heavy resistance training. Exclusion criteria included performing more than 1 h/week of strenuous exercise, current diagnosis of a severe medical disease (e.g., active cancer), a musculoskeletal disease that could inhibit training or medication use that could influence the effect of training (e.g., androgens). In the present analysis, we further excluded participants who reported a diagnosis of a neurological disorder, had no T1-weighted MRI brain scan at year 4, missing chair stand data, or displayed significant artefacts on their MRI scan (Appendix 1).

The LISA study was registered on clinicaltrials.gov (NCT02123641) and complies with the declaration of Helsinki. Ethical approval was received from the Ethical Committees of the Capital Region of Denmark (No. H-3-2014-017) and the Danish Data Protection Agency. Primary and secondary outcomes of the study, at years 1 and 2, have been reported elsewhere (Gylling, Bloch-Ibenfeldt, et al., 2020; Gylling, Eriksen, et al., 2020). Briefly, after 1 year, significant group by time effects were observed in muscle measures, such as knee extensor strength and muscle mass and size, and functional measures, such as chair stands. The primary outcome (leg extensor power) and daily step count did not show significant changes.

2.2 | MRI acquisition and pre-processing

Whole-brain MRI scans were acquired at the Danish Research Centre for Magnetic Resonance on a 3 T TX Philips Achieva Scanner MRI scanner (Philips Healthcare, Best, The Netherlands) using a 32-channel head coil. 3D T1-weighted images were acquired over 244 slices with isotropic voxels of 0.85 mm^3 (TR = 9.3, TE = 2.7 ms, 288 × 288 matrix, and flip angle = 8). Brain MRI scans from baseline and year 4 were used in the current analyses.

MRI data were pre-processed using tools from the FMRIB Software Library (FSL v6.0.1; [Woolrich et al., 2009]). T1-weighted images were pre-processed and brain-extracted using fsl_anat. Voxel-based morphometry (VBM) was then carried out using FSL-VBM (Douaud et al., 2007) an optimised VBM protocol (Good et al., 2001). Briefly, the brain-extracted images were grey matter segmented and then registered to the MNI standard space using non-linear registration (Andersson et al., 2007). Resulting images were averaged to create two study-specific grey matter templates. In correlational analyses, the template included all subjects. For comparisons between trajectory-based groups, a separate template was created to ensure a balanced representation from each group. All native grey matter images were then registered to the appropriate study-specific template and modulated to correct for local expansion or contraction. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with sigma of 3 mm. The smoothed grey matter maps were then used for voxel-wise comparisons of grey matter differences that are sensitive to volume.

For longitudinal VBM analyses, the FSL-VBM processing pipeline was adapted with a few additional steps to avoid registration and interpolation biases (Douaud et al., 2009). SIENA (Smith et al., 2002) was used to calculate the mid-space between the two (baseline and year 4) T1-weighted scans for each subject. Each scan was then registered to this halfway space, and averaged. Using BET, a brain mask of the averaged brain was then created and realigned to each native space for both time-points. In native space, the images were segmented with FAST, and both GM time-points were then registered back to halfway space and averaged. The averaged GM image for each subject was then registered to MNI space. Next, each native GM image was modulated using the Jacobian of the warp field produced during the non-linear transformation. Finally, the images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

2.3 | Physical function

The 30-s chair-stand test was used to assess lower extremity physical function. Participants were seated on a chair without armrest and asked to cross their arms against their chest. Performance on the test was measured as the number of stands completed in 30 s (repetitions).

Given our aim to test for the relationship between patterns of change in physical function and grey matter structures, it was important to select the physical function measure that showed most change over time (4 years). For this, the effect sizes of repeated measures ANOVA of available physical function metrics were compared (Appendix 2). Participants showed the most change in the chair stand test, which was then selected as our metric of physical function.

2.4 | Sample characteristics and covariates

Age, sex, and self-reported years of full-time education were recorded at baseline. To test for individual differences between the trajectory-based groups, measures of personality traits, mental health, and habitual physical activity were used. The depression, somatization and anxiety subscales of the Symptom Checklist-90 (SCL-90) were administered, wherein higher scores indicate a higher symptom load (Derogatis et al., 1973). To mitigate a positive skew in score distributions, results were log-transformed for analysis. The Danish version of the NEO Five-Factor Inventory (NEO-FFI) (Mortensen et al., 2014) was used to measure traits along five personality dimensions: neuroticism, extraversion, openness, agreeableness, and conscientiousness. Habitual physical activity was characterised through both objective (accelerometry; daily step count) and subjective (physical activity scale for the elderly [PASE] questionnaire) measures. Daily step count was collected with an accelerometer worn on the thigh of the dominant leg (activPAL micro, PAL technologies, Glasgow, Scotland) and the average step count over 5 days was used. Physical activity was also assessed using the PASE (Washburn et al., 1993), a 12-item questionnaire aimed at capturing leisure, work- and household-related activity.

2.5 | Statistical analysis

Statistical analyses were performed in RStudio version 1.3.1056 (RStudio Team, 2020), running on R version 4.0.2 (R Core Team, 2020), with the psych (Revelle, 2018), ggplot2 (Wickham & Sievert, 2016), and kml (Genolini et al., 2015) packages.

K-means cluster modelling (kml) was used to identify distinct cluster trajectories of chair stands. Kml is a non-parametric hill-climbing algorithm which does not impose assumptions regarding the shape of the trajectories (Genolini et al., 2015). The kml analysis was specified to allow between two and four clusters (trajectories), each obtained by running 1000 permutations. Three versions of the Calinski and Harabasz criteria, along with considerations of interpretability, were used to select the optimum number of clusters. While the traditional variant of the Calinski and Harabasz criterion indicated that the optimum number of clusters was 2, the Genolini and Kryszczuk variants suggested a four-group solution. In both analyses presented here, we opted away from the more reductive two-group solution. Visual assessment of all cluster solutions indicated that, for the clustering of the raw chair stand trajectories, the four-group solution offered little additional information over the three-group solution, so the three-cluster solution was preferred.

Mean and standard deviations are reported for each trajectory-group. ANOVAs were used to test whether the identified trajectory

groups significantly differed in demographic (age, sex, and years of education); physical activity (daily step count and PASE scores); mental health (SCL-90 subscores for symptoms of depression, anxiety, and somatization); and personality measures (NEO-FFI scores of neuroticism, extraversion, openness, agreeableness, and conscientiousness) at baseline. The alpha level for ANOVA main effects was set at .003, to adjust for multiple comparisons using a Bonferroni correction (0.05/15). Homogeneity of variance was verified using the Levene's test, and the Welch's *F* ratio was reported if variances significantly differed. Post hoc pairwise comparisons were conducted using the Tukey HSD test. Significant analyses were then repeated with age, sex, and BMI as covariates. Pearson's chi-squared test was used to compare the number of females and intervention group-assignment between trajectory-groups. Omega squared (ω^2) and Cramer's *V* were reported as effect sizes alongside the *F*- and chi-square statistics, respectively.

For statistical whole-brain analyses of grey matter volume, voxel-wise general linear models were applied using permutation-based non-parametric testing using randomize (5000 permutations). In the VBM analysis of baseline MR scans and baseline chair stands, chair stand performance was entered as a continuous regressor in the design matrix for the general linear model. In the longitudinal VBM, change in chair stands (year 4—baseline) was entered as the continuous regressor. When comparing between trajectory-groups, group membership was entered instead. Age and sex were included as confound regressors in all models. Thresholding was carried out using threshold-free cluster enhancement (Smith & Nichols, 2009), and clusters were assessed for significance at $p < .05$, corrected for multiple comparisons across space. Pearson's correlations were conducted to test the association between grey matter within identified clusters, baseline chair stands and change in chair stands over 4 years across all participants.

3 | RESULTS

3.1 | Baseline cerebellar grey matter volume correlates with baseline performance on the chair stand test

Two hundred and ninety-three participants were included in the cross-sectional analysis of grey matter volume and chair stands at baseline (mean age of 66.46 ± 2.47 years). The sample was predominantly female ($n = 177$, 60.4%) and, on average, had 14.41 ± 2.07 years of full-time education and a BMI of 25.61 ± 3.69. Participants completed a mean of 17.11 ± 4.26 chair stand repetitions, with performance ranging between 5 and 33. Baseline chair stand performance correlated with clusters of grey matter volume in the paramedian cerebellar hemispheres (right I–IV and VI; bilateral V-IIb), therefore encompassing the first (I–VI) and second (VIII) motor territories of the cerebellum, as well as a region associated with attentional/executive processing (VI) (Guell & Schmahmann, 2020). Additional clusters were observed in the left head and body of the caudate nucleus and bilaterally in the anterior and posterior areas of the putamen, after covarying for age and sex (Figure 1; see Appendix 3 for cluster characteristics).

3.2 | Intervention groups were not associated with chair stand performance or grey matter outcomes 4 years later

Out of our baseline sample, the data from 247 participants were included in our longitudinal analyses. Notably, there was an even distribution of participants from the three original intervention groups (high-intensity training group: $n = 81$; moderate-intensity training group: $n = 87$; control group: $n = 79$). Participants in the included sample did not differ from the remaining LISA sample in terms of age, education or proportion of female participants (Appendix 4). At year 4 (i.e., 3 years after the 12-month intervention), there was no effect of intervention groups on chair stand performance (F (2, 228) = 0.834, $p = .436$), nor on change in chair stands over the 4 years (F (2, 228) = 0.993, $p = .372$). Accordingly, 3 years after the end of the 12-month training program, between-group comparisons are unlikely to convey an accurate representation of participant's lower extremity physical function. Similarly, no between-group differences in regional grey matter volume were detected with VBM after adjusting for sex and age. However, across intervention groups, chair stand performance changed significantly over the 4 years (Appendix 2), with large amounts of individual variability in the direction and slope of change.

3.3 | Performance-based trajectory groups are associated with baseline measures

Using kml trajectory group-clustering, participants were divided into three groups based on their patterns of change in chair stands (Figure 2a). Interestingly, assigned intervention group was not associated with trajectories of change in chair stand performance over 4 years (Figure 2b). Hence, even though the intervention successfully improved muscle strength after 12 months of physical activity (Gylling, Bloch-Ibenfeldt, et al., 2020), this did not significantly alter the long-term trajectory of change in physical function, as measured by the chair stand test.

3.3.1 | Baseline differences between performance-based trajectory groups

A third of participants ($n = 83$, 33.6%) showed little change in chair stand performance during the year of the intervention (baseline—year 1), or in the following years (poor performance group). Both the mid-performance ($n = 99$, 40.1%) and the high-performance ($n = 65$, 26.3%) groups showed an average trend of an improvement in chair stands after the year of the intervention (baseline—year 1), which was then maintained in the following years. On average, participants in the

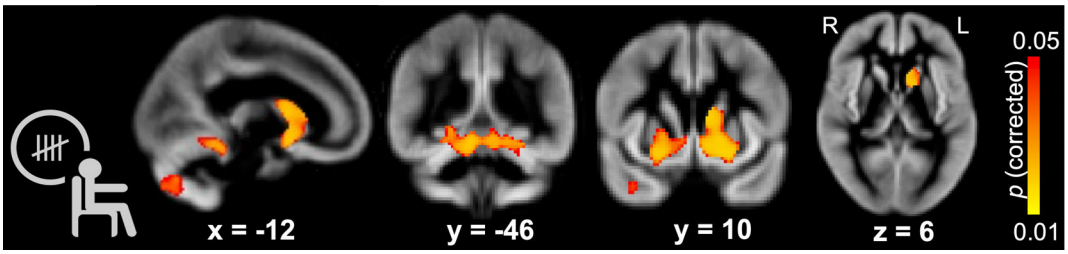

FIGURE 1 At baseline, participants who completed more repetitions of chair stands in the 30-s test period showed greater grey matter volume in clusters of voxels (red-yellow) within the cerebellum, caudate, and putamen ($n = 293$). Voxel-based morphometry (VBM) results are overlaid on the study-specific grey matter template ($p < .05$, corrected for multiple comparisons across space, with age and sex as covariates).

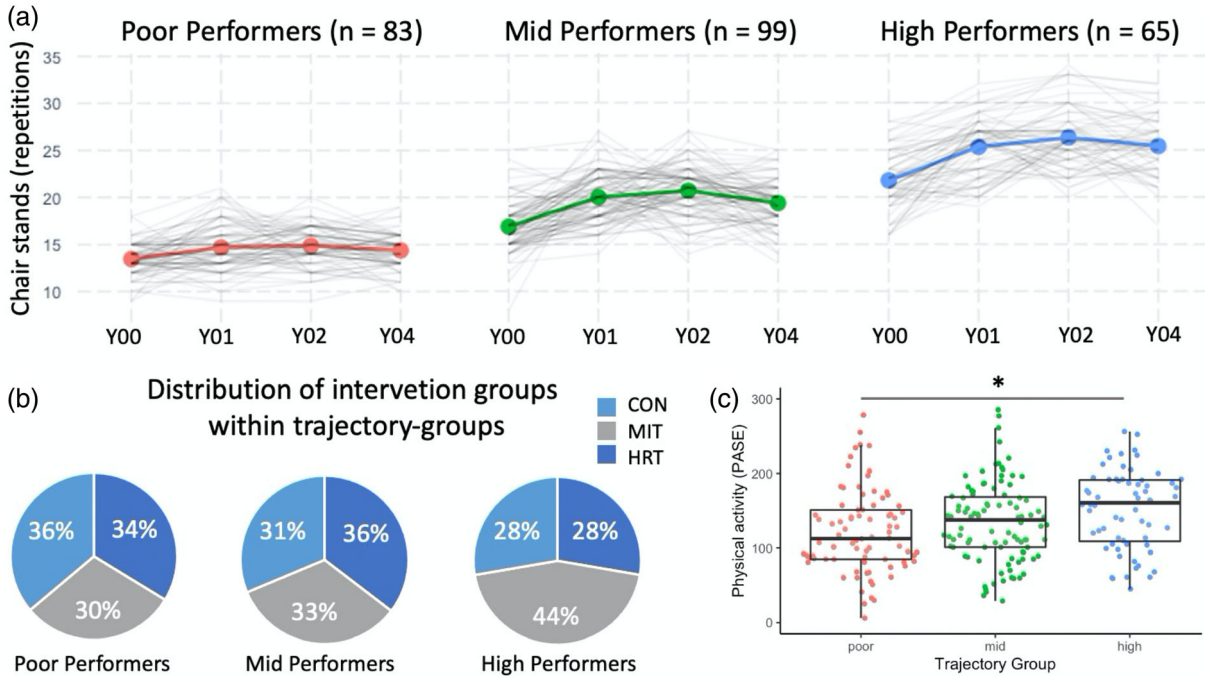

FIGURE 2 Participants were grouped based on their chair stand performance over 4 years, revealing three estimated trajectories of chair stands (a). Solid lines indicate the mean trajectory, while the light grey lines show individual trajectories. While intervention group assignment was not associated with trajectory-grouping (b), baseline self-reported total physical activity did (c). Participants in the 'poor performers' group reported less physical activity than those in the 'high performers' group, but the main effect of physical activity scale for the elderly (PASE) did not survive corrections for multiple comparisons ($p = .007$). Y00, baseline; Y01:Y04, year 1 to year 4; CON, control group; HRT, heavy resistance training group; MIT, moderate intensity group.

poor performance group self-reported less physical activity and had a lower daily step count, a higher BMI and a higher proportion of female participants than high performers at baseline (Table 1; Figure 2c). Differences in the physical activity measures (PASE and daily step count) did not remain significant after corrections for multiple comparisons. Crucially, the three groups had differing chair stand performance already at baseline. Post hoc pairwise comparisons further indicated that all between-group differences in chair stand performance were significant (high > mid > poor performers; Appendix 5). Baseline differences in chair stands remained significant after adjusting for age, sex, and BMI (F (2, 241) = 193.84, $p < .001$). Accordingly, baseline differences in chair stands, number of females and BMI were associated with 4-year trajectory in chair stand performance.

In terms of mental health symptoms, depressive and somatization symptoms differed significantly between groups (Table 1). Tukey's HSD test for multiple comparisons showed poor performers had significantly higher depressive symptoms than the mid- ($p = .005$, 95% C.I. = [0.004, 0.030]) and high- ($p < .001$, 95% C.I. = [−0.039, −0.011]) performers. The same pattern was observed for somatization, as poor performers had higher symptoms than the mid- ($p = .002$, 95% C.I. = [0.005, 0.024]) and high- ($p = .003$, 95% C.I. = [−0.027, −0.005]) performers. After adjusting for age, sex, and BMI, the groups continued to differ in depressive (F (2, 239) = 5.44, $p = .005$) and somatization (F(2, 239) = 4.03, $p = .02$) symptoms, but these did not remain significant after corrections for multiple comparisons. There were no between-group differences in any of the five personality traits.

TABLE 1 Baseline differences between performance-based trajectory groups (mean ± SD).

	High performers	Mid performers	Poor performers	F (or X^2)	p	ω^2 (or Cramer's V)
N	65	99	83			
Age	66.15 ± 2.37	66.28 ± 2.48	66.55 ± 2.58	0.537	.585	0.004
Number of females, %	30, 46.2%	59, 59.6%	64, 77.1%	15.203	<.001	0.25
Years of education	14.58 ± 2.05	14.56 ± 1.96	14.22 ± 2.16	0.779	.46	0.002
Chair stand repetitions	21.75 ± 3.22	16.87 ± 2.69	13.45 ± 1.78	189.35	<.001	0.72
PASE total score	151.6 ± 54.7	135.5 ± 52.4	122.9 ± 55.7	5.039	.007	0.03
Daily step count	10,401 ± 3136	9591 ± 3000	8711 ± 3701	4.675	.01	0.03
BMI	24.45 ± 3.27	25.53 ± 3.17	26.81 ± 4.23	7.31	<.001	0.08
SCL depressive symptoms[a]	0.21 ± 0.25	0.30 ± 0.37	0.48 ± 0.48	9.709	<.001	0.1
SCL anxiety symptoms[a]	0.21 ± 0.32	0.21 ± 0.25	0.29 ± 0.33	1.313	.271	0.003
SCL somatization[a]	0.24 ± 0.26	0.25 ± 0.26	0.40 ± 0.35	7.743	<.001	0.05
Neuroticism	15.56 ± 6.2	16.17 ± 7.56	18.18 ± 7.55	2.704	.069	0.01
Extraversion	30.38 ± 6.14	29.62 ± 6.65	29.05 ± 6.19	0.803	.449	0.002
Openness	30.09 ± 5.45	29.47 ± 5.09	29.82 ± 6.26	0.243	.785	0.006
Agreeableness	34.41 ± 4.69	34.65 ± 5.03	33.51 ± 5.32	1.184	.308	0.002
Conscientiousness	33.55 ± 5.85	34.05 ± 6.13	33.2 ± 5.83	0.485	.616	0.004

Abbreviation: SCL, Symptom Checklist.

[a]SCL values were transformed in the ANOVA calculations due to positive skews in their distribution. To facilitate interpretation of scores, the descriptive values presented here are the raw values prior to transformation.

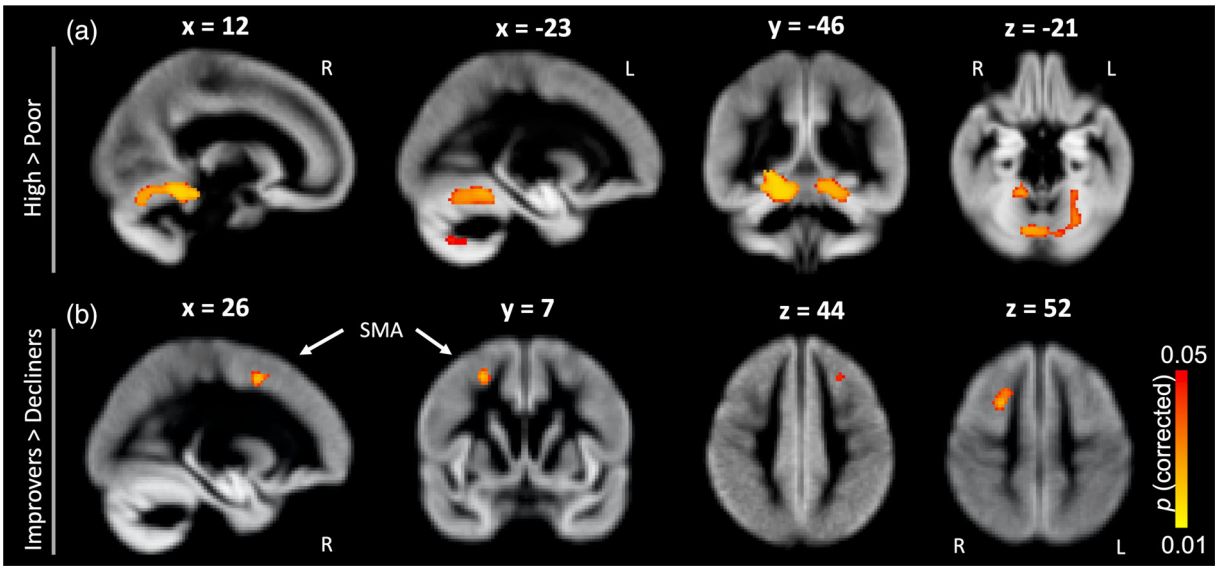

FIGURE 3 Regional grey matter between-group differences at year 4 and their association with motor trajectories: (a) In the motor cerebellum, a greater grey matter volume was found in the high versus poor chair-stand trajectory-groups (raw chair stands). (b) The right supplementary motor area and the dorsolateral prefrontal cortex showed clusters of greater grey matter volume in 'improvers' versus 'decliners' (baseline-normalised chair stands). Clusters (red-yellow) are overlaid on the study-specific grey matter template (p < .05, corrected for multiple comparisons across space, with age and sex as covariates).

3.3.2 | Differences in grey matter volume at year 4 between performance-based trajectory groups

In whole-brain voxel-wise analysis, high performers showed larger grey matter volume at year 4 relative to poor performers in clusters within bilateral motor regions in the cerebellum, after adjusting for age and sex (Figure 3a). However, since the groups already differed in chair stand performance at baseline and the observed clusters overlapped with those observed in cross-sectional analyses, we suspected that these clusters were reflecting baseline differences. This was

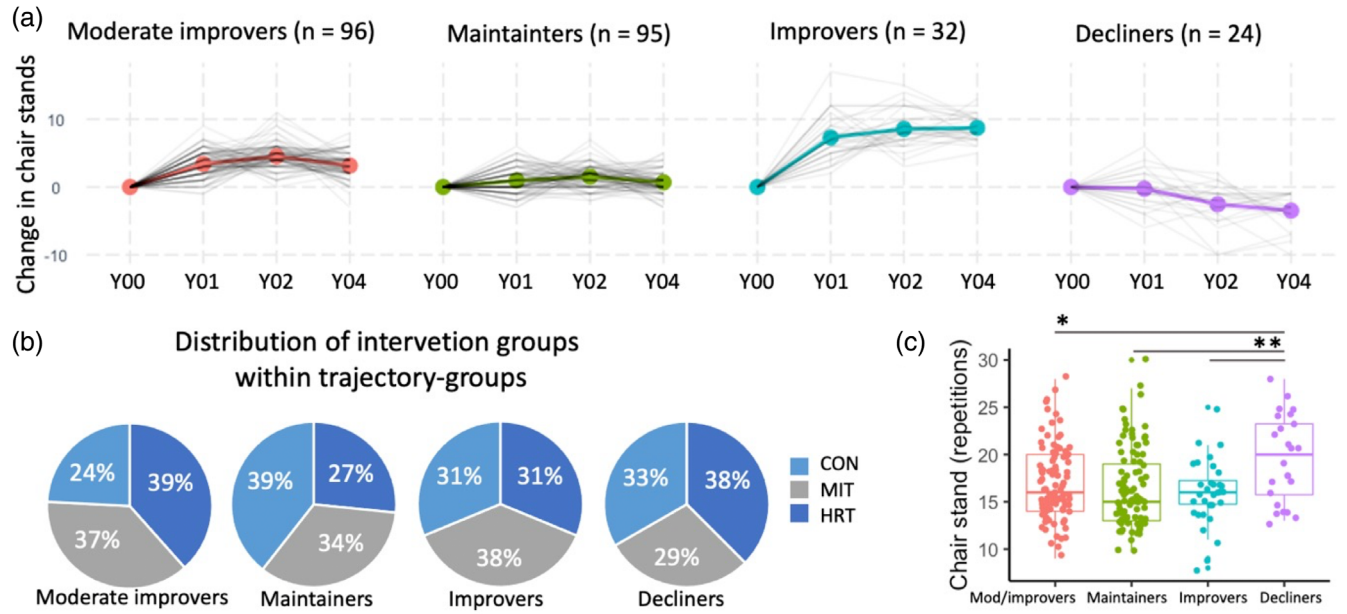

FIGURE 4 After subtracting baseline chair stand values, participants were grouped based on change in chair stand performance over 4 years, revealing (a) four estimated trajectories of chair stands. Solid lines indicate the mean trajectory, while the light grey lines show individual trajectories. Although intervention group assignment was not associated with trajectory-grouping (b), baseline chair stand performance was (c). Participants in the 'decliners' trajectory group completed more chair stands at baseline than participants in the other trajectory-groups (*$p < .05$; **$p < .01$; Appendix 6). Y00, baseline; Y01:Y04, year 1 to year 4; CON, control group; HRT, heavy resistance training group; MIT, moderate intensity group

TABLE 2 Baseline differences between trajectory-based groups (mean ± SD)

	Improvers	Decliners	Mod improvers	Maintainers	F (or X^2)	p	ω^2 (or Cramer's V)
N	32	24	96	95			
Age	65.72 ± 2.23	66.41 ± 2.68	66.09 ± 2.45	66.78 ± 2.50	2.028	.111	0.01
Number of females, %	21, 65.6%	13, 54.2%	58, 60.4%	61, 64.2%	1.102	.777	0.07
Years of education	14.75 ± 2.2	14.02 ± 1.72	14.38 ± 2.12	14.53 ± 2.01	0.663	.575	0.004
Chair stand repetitions	16.03 ± 3.42	19.63 ± 4.56	17.04 ± 3.96	16.36 ± 4.14	4.281	.006	0.04
PASE total score	138.40 ± 56.22	143.51 ± 59.20	138.52 ± 54.12	129.5 ± 54.65	0.661	.577	0.004
Daily step count	9272 ± 2655	10,431 ± 3679	9479 ± 3341	9443 ± 3453	0.596	.618	0.005
BMI	25.64 ± 3.43	26.91 ± 3.86	25.16 ± 3.23	25.89 ± 4.11	1.63	.183	0.008
SCL depressive symptoms	0.22 ± 0.23	0.37 ± 0.52	0.33 ± 0.39	0.38 ± 0.42	1.235	.298	0.003
SCL anxiety symptoms	0.19 ± 0.26	0.23 ± 0.3	0.26 ± 0.39	0.24 ± 0.29	0.280	.840	0.009
SCL somatization	0.27 ± 0.34	0.30 ± 0.29	0.29 ± 0.29	0.27 ± 0.34	0.295	.829	0.009
Neuroticism	14.71 ± 7.19	17.71 ± 7.92	16.97 ± 6.54	16.76 ± 7.83	0.972	.407	0.004
Extraversion	32.13 ± 6.43	29.58 ± 6.81	28.73 ± 6.36	29.71 ± 6.09	2.325	.076	0.02
Openness	32.23 ± 5.73	29.17 ± 4.75	28.89 ± 5.38	29.97 ± 5.75	2.977	.032	0.02
Agreeableness	34.87 ± 5.41	35.54 ± 5.01	34.06 ± 4.99	33.76 ± 4.98	0.993	.397	<0.001
Conscientiousness	33.84 ± 6.80	34.75 ± 5.91	33.65 ± 5.47	33.28 ± 6.18	0.396	.756	0.007

confirmed by additional post hoc analyses which included baseline chair stand performance as a covariate. In this case, no significant grey matter clusters were observed. Both analyses indicate that the difference between groups in cerebellar grey matter was driven by baseline differences in chair stand performance.

3.4 | Trajectory-based groups: Focusing on change in chair stand repetitions

Given the observed effect of baseline chair stands, we re-ran the trajectory analysis using baseline-normalised scores to focus on change

TABLE 3 Overview of clusters showing significant grey matter differences at year 4 between improvers and decliners.

Anatomical description	Cluster size (voxels)	MNI coordinates of peak (*x*, *y*, *z*)	Correlation with baseline chair stands (*r*, *p*)	Correlation with change in chair stands (*r*, *p*)
Right supplementary motor area/along superior frontal sulcus	95	27, 8, 51	−.099, .122	.173, .008
Right supplementary motor area	26	6, −6, 66	−.019, .764	.244, <.001
Left dorsolateral prefrontal cortex	13	−26, 26, 44	−.117, .067	.267, <.001

in performance. This resulted in four group-based trajectories: moderate improvers ($N = 96$, 38.9%); maintainers ($N = 95$, 38.5%); improvers ($N = 32$, 13%); and decliners ($N = 24$, 9.7%). The improving trajectory showed a marked increase in chair stand performance during the intervention year (baseline to year 1), which was then maintained over the following years. In contrast, the declining trajectory group tended to maintain its performance in the first year and showed decline in the subsequent assessments (Figure 4a).

Baseline demographic characteristics, personality, and mental health symptoms did not differ between trajectory groups (Table 2). Chair stands performance significantly differed between groups and this difference remained significant after adjusting for age, sex, and BMI (F (3, 240) = 4.85, $p = .003$). Post hoc pairwise comparisons indicated that this difference was driven by the contrast between the decliners and the other groups, wherein, on average, the 'decliners' completed more chair stands at baseline (Figure 4c; Appendix 6). Improvers scored higher on items of 'openness' in the NEO-FFI than 'decliners', although this difference was no longer significant after adjusting for multiple comparisons. Assigned intervention group was not associated with trajectory-based groups of change in chair stands ($X^2(6, 247) = 6.73$, $p = .35$; Figure 4b).

3.4.1 | Differences in grey matter at year 4 between trajectory groups

VBM analyses revealed clusters with greater grey matter volume in participants from the improvers group compared to the decliners group in the right supplementary motor areas, extending into the frontal eye field, and the left dorsolateral prefrontal cortex, after adjusting for age and sex (Figure 3b). Change in chair stand performance (Y04-Y01) was associated with grey matter volume in the identified clusters, while baseline chair stands were not (Table 3). Similarly, the contrast between improvers and maintainers revealed clusters of greater regional grey matter volume in the bilateral pre-motor and supplementary motor areas (Appendix 7). These clusters remained significantly different after including baseline chair stands as a covariate. In all clusters, grey matter volume positively correlated with change in chair stands, but not with baseline chair stands. Of note, these differences in grey matter volume were expressed in spatially distinct areas from the subcortical regions showing a cross-sectional relationship with chair stand performance.

To explore potential change–change associations across the grey matter template, a longitudinal VBM analysis tested for associations between change in grey matter (Y04-Y01) and change in chair stands (Y04-Y01). No significant voxels were detected.

4 | DISCUSSION

This exploratory study aimed to delineate individual patterns of change in lower limb motor function in older adults, and how these functional changes relate to regional grey matter volume. Using chair stand performance measures over 4 years, our data-driven analyses identified groups showing trajectories of improving, declining, and maintaining physical function. Interestingly, these trajectory-based groups were not associated to intervention arm, suggesting that participating in a one-year long training programme was not the best indicator of change in physical function in the long term. Our findings suggest that, in the years following the intervention, baseline variables were more indicative of patterns of change in lower limb motor function than the intervention itself.

VBM analyses of individual structural MRI images showed that participants with better physical function trajectories had greater grey matter densities than their counterparts. Trajectory-based groups showed differences in grey matter structures within motor regions. Crucially, the clusters fell within distinct motor regions when the trajectories were computed using raw or baseline-normalized chair stand values. In cross-sectional analyses and performance-based trajectory groups driven by baseline differences, better chair stand performance was associated with grey matter volume in the cerebellum. The findings from the cross-sectional analyses partially replicate our findings of a similar cerebellar-chair stand correlation in a separate cohort of older adults (Demnitz et al., 2017). However, not all have replicated this association. A similar study of the neural correlates of mobility measures in older adults found no significant association between the chair stand test and cerebellar volume (DiSalvio et al., 2020). This could plausibly be due to their smaller sample size ($n = 70$), although it is worth noting that DiSalvio et al. (2020) observed grey matter volume associations with other mobility measures in the parahippocampus, postcentral gyrus, superior temporal gyrus, supramarginal gyrus, and the inferior parietal lobe. Other measures of functional mobility, such as gait speed and balance, have also been found to correlate with grey matter volume in the cerebellum and putamen of older adults (Rosano et al., 2007; for review, see Holtzer et al., 2014). Further, volumetric studies have indicated that reduced grey matter volume in the cerebellum is indicative of fear of falling (Tuerk et al., 2016) and frailty (Chen et al., 2015)—both of which have also been associated

with performance on the chair stand test (Deshpande et al., 2008; Kim & Won, 2022). Taken together, these studies lend reliability to the findings that older adults with better lower extremity physical function, as measured by the chair stand test, present with greater regional grey matter volume, particularly in the cerebellum.

In trajectory-groups targeted at change (using baseline-corrected values), grey matter differences between the improvers and decliners were found within the supplementary and pre-motor regions. The supplementary motor area, reputed for its 'event-planning' role in the temporal organization of movements (Cona & Semenza, 2017), has previously shown grey matter changes in association with motor skill improvement (Hamzei et al., 2012; Taubert et al., 2010). Accordingly, it is plausible that the cross-sectional associations may reflect a more cumulative and lifelong effect of better physical function, while the grey matter differences in the supplementary and pre-motor regions are more sensitive to the change in physical function observed over 4 years.

Several sources of individual differences have been put forth as moderators of the relationship between physical function and volumetric brain measures. Here, we tested plausible candidates such as age, sex, years of education, personality traits, and symptoms of mental distress. Age and education did not differ between trajectory-based groups. However, baseline BMI, reduced physical activity (both self-reported and daily steps), fewer chair stands, symptoms of depression and somatization and being female were characteristic of the poor performing trajectory-group. Whereas the association with sex and BMI may be reflective of expected differences in body composition and are therefore arguably less surprising, our results showed that symptoms of mental distress and daily physical activity can also contribute valuable information. When trajectories accounted for baseline in chair stands, a less explored factor, personality differences, yielded interesting results. Participants in the 'improvers' group scored higher on measures of openness. Despite not surviving corrections for multiple comparisons, we would cautiously suggest that personality traits should be further investigated as potential moderators of a participant's willingness to engage with an intervention program.

Some limitations are of note. First, we cannot discard the possibility that the observed relationship between declining physical function and reduced motor cortical grey matter may be attributed to reverse causation. For example, physical activity has been shown to decline up to 9 years before a dementia diagnosis (Sabia et al., 2017). It is therefore plausible that the reduced physical function is an early indicator, as opposed to a contributing risk factor, of neurological troubles ahead. Further, the study focused on a single measure of physical function, the chair stand test. It is likely that other measures would have results in slightly different trajectory-based groups, as the measures showed different levels of change over time. Nonetheless, our reasoning for this choice was threefold: (1) our previous results suggested that the chair stand test correlated with grey matter volumes in older adults (Demnitz et al., 2017), (2) it showed the largest degree of change over 4 years, and (3) it is a reliable measure of lower extremity strength that can predict falls and sarcopenia in older populations (Bohannon, 2011; Pinheiro et al., 2016; Ward et al., 2015). Finally, it is worth noting that the list of variables examined here is far from exhaustive. Other variables to be considered include genetic predispositions, diet, sleep quality and cardiovascular risk factors.

5 | CONCLUSION

As Stillman et al. (2020) put it, identifying the characteristics of people most likely to benefit from increased exercise is a key outstanding question for our field. Addressing this is a necessary and unavoidable step to develop targeted and effective physical activity interventions. Here, we found that how you start matters: baseline values in chair stands were associated with long-term outcomes in physical function and correlated with later grey matter volume in the cerebellum. Still, when subtracting baseline chair stand values, participants showing a trajectory of improved physical function showed greater grey matter volume in other motor regions, the right pre-motor and supplementary motor cortices. Accordingly, RCTs may be underestimating the effects of exercise on brain structure with insufficient attention to existing baseline differences. Cognitive ageing neuroscience has long stressed the importance of considering predictors of trajectories (Nyberg et al., 2020). Here, we have shown that the same approach would be valuable for the study of long-term effects of exercise and the ageing brain.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The LISA dataset is currently not openly available due to restrictions imposed by GDPR and Danish regulations on the protection of personal information (data are not fully anonymised).

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SUPPORTING INFORMATION

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