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Linking objective measures of physical activity and capability with brain structure in healthy community dwelling older adults

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ABSTRACT

Maintaining high levels of daily activity and physical capability have been proposed as important constituents to promote healthy brain and cognitive aging. Studies investigating the associations between brain health and physical activity in late life have, however, mainly been based on self-reported data or measures designed for clinical populations. In the current study, we examined cross-sectional associations between physical activity, recorded by an ankle-positioned accelerometer for seven days, physical capability (grip strength, postural control, and walking speed), and neuroimaging based surrogate markers of brain health in 122 healthy older adults aged 65–88 years. We used a multimodal brain imaging approach offering complementary structural MRI based indicators of brain health: global white matter fractional anisotropy (FA) and mean diffusivity (MD) based on diffusion tensor imaging, and subcortical and global brain age based on brain morphology inferred from T1-weighted MRI data. In addition, based on the results from the main analysis, follow-up regression analysis was performed to test for association between the volume of key subcortical regions of interest (hippocampus, caudate, thalamus and cerebellum) and daily steps, and a follow-up voxelwise analysis to test for associations between walking speed and FA across the white matter Tract-Based Spatial Statistics (TBSS) skeleton. The analyses revealed a significant association between global FA and walking speed, indicating higher white matter integrity in people with higher pace. Voxelwise analysis supported widespread significant associations. We also found a significant interaction between sex and subcortical brain age on number of daily steps, indicating younger-appearing brains in more physically active women, with no significant associations among men. These results provide insight into the intricate associations between different measures of brain and physical health in old age, and corroborate established public health advice promoting physical activity.

1. Introduction

Magnetic resonance imaging (MRI) studies have revealed substantial age-related changes in the human brain, including cortical and subcortical atrophy, ventricular enlargement, and white matter alterations (Fjell et al., 2009; Garde et al., 2000; Westlye et al., 2010; Ylikoski et al., 1995). While group analysis suggests robust effects, studies have revealed considerable heterogeneity across individuals and brain

Abbreviations: MRI, Magnetic resonance imaging; DTI, Diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; BAG, brain age gap; 10 MWT, Timed 10-Meter Walk Test; BMI, body mass index; ICV, intracranial volume; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement; ROI, regions of interest; M-V steps/day, moderate- to vigorous intensity steps per day.

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structures (Allen et al., 2005; Fjell et al., 2013; Raz et al., 2010; Sexton et al., 2014; Tucker & Stern, 2011). As further understanding of the complexity and biological basis of brain and cognitive aging evolves, more targeted preventive measures and innovative models of geriatric care is expected to be developed as part of public health programs.

Physical health indicators, such as daily activity level, balance, walking speed, and hand-grip strength, are associated with healthy aging (Kuh, 2007; Vermeulen et al., 2011), and represent a putative malleable moderator of brain aging. A number of studies have reported positive associations between these indicators and the volume and integrity of brain white and gray matter structures (Bherer et al., 2013; Erickson et al., 2014), including the subcortical areas hippocampus (Erickson et al., 2014; Hamer et al., 2018) and the cerebellum (Chen et al., 2015; Surgent et al., 2019). However, most previous studies are limited by the use of self-report measures of physical activity, including mainly clinical populations or assessment tools primarily designed for clinical populations (Demnitz et al., 2018), which may not be sensitive to detect relevant individual differences among healthy adults. Among the exceptions, a study of healthy adults aged > 80 years reported an association between high levels of accelerometer-measured daily steps and global fractional anisotropy ([FA], Tian et al., 2015), which is an indicator of overall white matter structure based on diffusion tensor imaging ([DTI], Schmierer et al., 2007). An association has also been found between temporal and parahippocampal white matter FA and accelerometer-measured daily steps in low-active adults aged 60–78 years reporting<150 min of moderate physical activity per week (Burzynska et al., 2014). Sex differences in beneficial effects of physical activity on brain health have also been reported. For example, higher number of accelerometer-measured daily walking steps was related to larger surface area in subregions of the hippocampus in women but not in men (Varma et al., 2016).

Recent advances in MRI analysis and machine learning have shown that complex, multidimensional brain imaging data can be aggregated into a sensitive, unitary estimate of brain aging (Cole & Franke, 2017; Franke et al., 2010). Estimated high brain age compared to chronological age (brain age gap [BAG]) in older adults has been suggested to indicate incipient neurodegeneration (Franke & Gaser, 2019) and increased risk of dementia (Wang et al., 2019). Brain age prediction and similar data-driven approaches provide innovative imaging based surrogate markers of brain health, with promising potential to translate complex neuroscience data to more comprehendible public health guidelines, thus bridging the gap between public health and science. The World Health Organization describes improved understanding of analytical approaches for healthy aging a priority of action, including development of biomarkers related to healthy aging (World Health Organization, 2015). To our knowledge, only a few prior studies have investigated the link between BAG and physical activity and capabilities (Cole et al., 2018; Steffener et al., 2016), and only one included objective measures like hand-grip strength and walking speed (Cole & Franke, 2017). Overall, the evidence linking objective measures of physical health and indicators of brain health is conflicting or lacking, both with regard to white matter microstructure (Kilgour et al., 2014; Wassenaar et al., 2019) and BAG based on gray matter morphology. In addition, it is not clear to which degree T1-weighted structural MRI measures and DTI-based markers of white matter structure show differential sensitivity to physical health in ageing men and women.

The main purpose of the current study was to examine the association between objective measures of physical activity level and capability, and two complementary structural MRI based indicators of brain health: white matter FA and MD based on DTI and BAG based on brain morphology. We included 122 (62% women) community-dwelling healthy middle-aged and older adults aged 65–88 years. Physical activity was measured using ankle-worn accelerometer across on average 7 days (range 3 to 9) and physical capabilities were operationalized through grip strength, walking speed, and postural control as a measure of balance. Based on recent implementations and the use of an independent training set, we estimated individual brain age using global and subcortical gray matter from T1-weighted MRI (de Lange & Cole, 2020; de Lange et al., 2019; Kaufmann et al., 2019). We used an independent training set comprising MRI data from 2407 healthy individuals for brain age prediction, and applied the cross-validated models in our unseen test set.

Based on the putative close link between brain health and physical health, we hypothesized that level of physical activity, hand-grip strength, walking speed, and postural control, would be associated with BAG, both estimated using global and subcortical measures, and global FA and MD. Moreover, based on previous evidence we tested for sex differences in the associations between physical health indicators and brain MRI measures, as well as differences in the sensitivity to the physical health indicators between the brain gray and white matter measures. In the case of significant association between BAG, white matter FA or MD, and physical activity and/or capabilities, we conducted a follow-up univariate analysis to complement the main results.

2. Materials and methods

2.1. Participants

Data collection was performed as an integrated part of the prospective StrokeMRI study aiming at identifying predictors of brain and cognitive health, aging and stroke rehabilitation (Dørum et al., 2016; Dørum et al., 2017; Richard et al., 2018). Briefly, healthy adults were recruited from the Oslo area in Norway through advertisements in local papers and by word of mouth, and screened for eligibility through a standardized phone interview before inclusion. Participants reporting counter-indication for MRI, history of severe psychiatric or neurological conditions, for example epilepsy, brain tumour or head trauma with loss of consciousness for more than two minutes, and/or alcohol/drug abuse, were excluded.

All participants (n = 341, 18–94 years) completed demographic information, standardized questionnaires, including for example mood, personality, and sleep habits, a comprehensive cognitive test battery (Richard et al., 2018), clinical and medical assessments, and multimodal structural and functional MRI. In the current study we included participants aged 65 years or older who additionally completed standardized physical tests and accelerometer assessment.

Among a total of 131 eligible participants, nine were excluded due to poor quality on T1-weighted data (n = 5), not completing the MRI protocol (n = 3), or not completing the tests of physical capability and physical activity (n = 1), reducing the number of participants to n = 122, with an average age of 71.4 years (Standard Deviation [SD] = 4.61, 64–88 years, 62 % women). No participants scored below 24 on the Mini-Mental State Examination (MMS-E) (Folstein et al., 1975). For the current sample, the median interval between MRI and the neuropsychological and physical tests was 11 days (IQR = 14.75 days).

The study was completed in accordance with the Helsinki Declaration and approved by the Regional Committees for Medical and Health Research Ethics for the South-Eastern Norway (REK approvals 2014/694, 2015/1282). All participants provided written informed consent. The participants received compensation for participation in the study.

2.2. Cohort used for training set in brain age prediction

The training sample consisted of data from 2407 healthy individuals aged 18–94 years from six different samples (Supplementary Table 1, Supplementary Fig. 1). The participants had been recruited and screened in line with local procedures (Supplementary Table 2), in general ensuring that the participants did not have any contraindications for MRI, or a previous or current serious neurological or psychiatric condition, drug abuse, or head trauma.

2.3. Measures of physical activity and capability

Four measures of physical activity and capability were considered, including daily step count, postural control, walking speed, and hand-grip strength.

A calibrated StepWatch Activity Monitor (The Modus StepWatchTM3 Activity Monitor) assessed daily physical activity level. The StepWatch was placed above the ankle and calibrated according to the participant's height and weight. The instructions for use included wearing the monitor for seven consecutive days, all waking hours, while conducting regular daily activities. Exceptions included bathing or showering. The StepWatch records number of steps taken per one-minute sampling period from one leg. Results were doubled to capture the number of steps taken by each participant (Doherty et al., 2017). According to regular procedures for calculation of activity level, a day was considered valid if consisting of minimum 600 min recordings (Mâsse et al., 2005). Non-wear time was defined as > 90 consecutive minutes of zero counts. A deviation from this rule was if there was a period of maximum two minutes with more than zero counts within a 90 min period with non-wear. The 30 min before and after this interruption needed to be consistently zero counts. A minimum of three valid days of data per participant were required for the analysis (Jefferis et al., 2014; Mudge et al., 2010). Valid StepWatch data was available from all 122 participants, who in average wore the StepWatch for 859 min per day (SD = 66.4), ranging between 3 and 9 days, with a median of 7 days. For descriptive purposes, average daily steps taken at moderate- to vigorous intensity (≥100 steps/ minutes) were also calculated.

Postural control, registered through measurement of centre of pressure, was assessed using a force plate (BTrackS Balance Tracking System Inc. San Diego, CA, USA, 25 Hz). The protocol for measuring centre of pressure was based on recommendations from Low et al. (2017), with double leg stance and 60 s durations of each trial. The balance board was turned towards and 20 cm away from a wall to prevent the participant from turning his or her head or eyes during testing. The participants were asked not to voluntarily move, to keep their hands on their hips, and to position their feet with shoulder-width separation. The data were filtered with a dual-order low pass Butterworth filter with a cut-off frequency of 4 Hz. The average of three trials with eyes closed were used to calculate the mean velocity in cm per second.

Comfortable gait speed was assessed using Timed 10-Meter Walk Test (10 MWT) (Bohannon et al., 1996; Studenski et al., 2011; Wolf et al., 1999). The middle six metres were timed, excluding the effect of acceleration and deceleration, and converted to meter per second. Dominant hand grip strength, expressed in kilograms (kg), was measured with a Jamar hand dynamometer (Sammons Preston Inc., Bolingbrook, IL) with the use of the second handle position for optimal performance. Standard procedure for hand-grip strength test was followed, with the participants in a seated position and elbow-joint fixed in a 90 degrees flection (Mathiowetz et al., 1984). For both walking speed and hand-grip strength, the average of three trials were considered.

2.4. MRI acquisition, processing and analysis

Participants were scanned with a 3 T General Electric (GE) 750 Discovery MRI scanner using identical sequences and a 32-channel head coil at Oslo University Hospital, Norway. Cushioning was used to minimize head motion.

T1-weighted images were obtained using an inversion recovery-fast spoiled gradient echo (BRAVO) sequence with echo time (TE) = 3.18 ms, repetition time (TR) = 8.16 ms, field of view (FOV) = 256 mm × 256 mm, flip angle (FA) = 12°, and voxel size (VS) = 1x1x1 mm. The images were acquired in sagittal plane, and it took 4.43 min to acquire 188 slices. A detailed description of image acquisition for the training samples is provided in Supplementary Table 3.

DTI data were obtained using an echo planar imaging (EPI) sequence with 60 unique directions, b-value of 1000 s/mm^2, TE = 83.1 ms, TR = 8150 ms, FA = 90 degrees, FOV = 128 × 128 mm, 2 mm isotropic voxels, and 5b = 0 volumes. Scan time was 8:58 min. 7b = 0 volumes with reversed phase-encoding direction were also obtained.

FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu, Fischl, 2012) was used for automated surface-based morphometry and subcortical segmentation of the T1-weighted images, providing measures of cortical thickness, area, and volume, as well as the volumes of all subcortical structures. Technical details of the procedures are described in prior publications (Dale et al., 1999; Fischl et al., 2002). A visual quality-check of reconstructions and subsequent correction, if required, was performed for the StrokeMRI data. The training samples, consisting of data from multiple sites, were all quality checked using FreeSurfer's Euler number as a proxy (Rosen et al., 2018). In a follow-up analysis including regional analyses, the following subcortical regions were selected due to their involvement in cognitive aging, neurodegenerative disorders and physical activity: hippocampus, thalamus, cerebellum and caudate (Acosta-Cabronero & Nestor, 2014; Chen et al., 2015; Erickson et al., 2014; Fjell et al., 2009; Hamer et al., 2018; Surgent et al., 2019). We calculated the mean volume across the two hemispheres.

DTI data were processed using Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (https://fsl.fmrib.ox.ac.uk/fsl). Using topup (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup) and eddy (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy), we corrected for motion, eddy currents, and geometrical distortions (based on the b = 0 volumes collected with a reversed phase-encoding direction) in an integrated stream (Andersson & Sotiropoulos, 2016) which also includes identification and replacement of outlier slices (Andersson et al., 2016). The resulting corrected datasets were used to estimate FA and MD using *dtifit* in FSL.

Further processing was performed using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). Here, a skeletonized map was generated by thinning the mean FA map across participants. The mean FA skeleton was thresholded at FA > 0.2 and then projected onto the normalized FA maps. The same transformation was applied for MD, resulting in voxelwise FA and MD skeletons for each participant. Using these maps, representing the core of major white matter pathways, we computed mean global FA and MD for each individual. The TBSS skeletons were also submitted to voxelwise analysis (see 2.6. Statistical analysis).

2.5. Brain age prediction

In line with a recent implementation (Kaufmann et al., 2019), age prediction models were trained using *XGBoost* (extreme gradient boosting) in R (Chen & Guestrin, 2016) based on cortical volume, thickness, and area (Glasser et al., 2016), as well as subcortical volumes (Fischl et al., 2002) as features, totalling 1118 features for each individual (Kaufmann et al., 2019). We trained the models separately for each sex, ensuring that possible sex-related differences in brain aging did not influence the results. In addition, all models were controlled for total intracranial volume (ICV). Parameters were tuned in a nested cross-validation that estimated the optimal number of model training iterations (settings: nround = 1500, early stopping rounds = 20). The learning rate was set to eta = 0.01 while all other parameters were left as default. To comply with the notion of heterogeneous brain aging we trained two different brain age models, one for the full brain, including all features, and one for all subcortical features combined, including the cerebellum (Kaufmann et al., 2019). The models were validated with 10-fold cross validation. Finally, the two models were applied to calculate brain age for each individual in the unseen test sample (n = 122).

To account for a well-known bias in age prediction we used a described procedure (de Lange & Cole, 2020). First, we calculated the difference between estimated brain age and chronological age. Next, we estimated the association between BAG and age using linear models including age and sex in the models. The beta representing this bias was then subtracted from the estimated age, yielding a corrected brain age for each individual. Chronological age was subtracted from this

corrected brain age, and the resulting BAG was used to test for associations with measures of physical activity and capability.

2.6. Statistical analysis

Statistical analyses were performed using R, version 3.6.2 (R Core Team, 2019). Data from the StepWatches were analysed with an in-house script, calculating mean (SD) daily activity. Descriptive data are presented as mean (SD) or median (IQR), as appropriate. Due to the use of multidimensional measures of physical activity and capability, and to examine to which degree the measures reflect differentiable components, bivariate associations between measures were examined using Kendall's tau. The same test of correlation was also used to test for various associations between physical activity, physical capability, sample characteristics, age, and body mass index (BMI). Sex differences in the physical measures were examined using Wilcoxon Rank Sum Test or two-sample *t* test, as appropriate. To test for interactions between age and sex on the physical measures, Bayes Factor was computed as implemented in the *BayesFactor* package in R (Richard & Rouder, 2018) and used to compare models with and without the interaction term. To validate the estimation of brain age in the training set, a 10-fold cross validation was used for men and women separately. Further, correlation between estimated and chronological age for the test-set was assessed divided by sex, and finally the association between the BAGs, global FA and MD and age were assessed.

Multiple linear regression analyses were performed using the function *lm* in R to test for associations between physical activity and physical capability and BAGs and white matter integrity. For each MRI variable (global and subcortical BAG, global MD and global FA) each of the physical activity and capability variables (daily number steps, grip strength, 10 MWT, and postural control) were included as dependent variables in different linear models, with the MRI measure and age and sex as independent variables. Regression diagnosis for influential cases on the models were performed using Cook's distance. The results indicated that no cases were overly influential on the results. To explore the association between physical activity and capability and structural brain health further, we ran the regression analysis adding an interaction term between each MRI variable and sex, testing for interaction effect between sex and structural brain health on the physical measures. To ease the interpretation, significant effect sizes including daily number of steps were presented in units of 1000 steps per day (Varma et al., 2015). Based on the results from the main analysis, follow-up regression analysis was performed replacing the global measures with key subcortical regions of interest (ROI), controlling for the covariates listed above, in addition to ICV. In addition, a follow-up voxelwise analysis was performed using TBSS to test for associations between walking speed and FA across the white matter skeleton. Here, we used randomise (Winkler et al., 2014) in FSL to conduct permutation-based testing (5000 iterations) and threshold-free cluster enhancement ([TFCE], Smith & Nichols, 2009), revealing statistical maps fully corrected for multiple comparisons across space. Age and sex were included in all models. Using Fisher z-transformation of the standardized coefficient from the different models, we tested if BAG and global DTI measures showed differential associations with the physical health indicators (daily steps, walking speed, hand-grip strength, and postural control).

For transparency, we report both uncorrected and corrected p-values. The significance threshold was set at $p < .05$, and for corrected p-values, we employed a Bonferroni correction method. Bayes Factor was also reported alongside p-values for all models in order to quantify the evidence for the null hypothesis, in line with recent recommendations (Keysers et al., 2020).

3. Results

3.1. Sample characteristics

Table 1 summarizes demographic and clinical characteristics. Average years of education was 15.7 (SD = 3.45), ranging from 8 to 27 years. Median MMSE score was 29 (IQR = 2), ranging from 24 to 30. Mean BMI was 24.9 (SD = 3.38), ranging from 17.2 to 38.1, with no significant sex differences (t = -0.98, $p = .331$).

3.2. Physical capability and physical activity level

Table 1 summarizes the physical capability and activity measures. Mean hand-grip strength was 32.6 kg (SD = 9.92). Men had a significantly greater hand-grip strength (mean 42.5 (SD = 7.64) kg) compared to women (mean 26.3 (SD = 4.72) kg; t = -13.0, $p = < 0.001$). Median postural control was 1.32 (IQR = 0.59) cm/sec. Women (median 1.41 (IQR = 0.53) cm/s) exhibited significant less postural control than men (median 1.87 (IQR = 1.31) cm/s; W = 807; $p = < 0.001$, r = -0.455). Average walking speed was 1.41 (SD = 0.19) m/s, with women (1.44 (SD = 0.18) m/s) having a significantly higher average speed than men (1.35 (0.19) m/s.; t = 2.48, $p = .015$). The participants had an average of 12088.8 (SD = 3666.72) steps per day, with no significant sex differences (t = 1.8, $p = .080$). Still, women exhibited significant (t = 2.9, p = .005) more moderate- to vigorous-intensive steps per day (mean 3030.0, SD = 2154.80, 24.1 % of mean total daily steps), than men (mean 2123.4, SD = 1317.12, 18.7 % of mean total daily steps). Mean wear time of the Step Activity Measure was 14.2 h (SD = 1.14 h), with no significant sex differences (t = 0.97, p = .334).

Bivariate correlation analysis revealed weak relationships between the various physical test performances, age, and BMI (Fig. 1). In addition, Bayes Factor suggested no evidence of interactions between age and sex on walking speed (BF = 0.21, ± 4.34 %), daily steps (BF = 0.40, ± 1.9 %), hand-grip strength (BF = 0.64, ± 2.13 %), or postural control (BF = 0.11, ± 6.82 %).

3.3. Brain age prediction

In the training set, 10-fold cross validation revealed a correlation of r = 0.90 for both men and women ($p < .001$) between estimated brain age from the full brain model and chronological age (men: MAE = 6.82, RMSE = 8.49, women: MAE = 6.64, RMSE = 8.47). The subcortical model yielded a correlation of r = 0.87 for both men and women ($p < .001$, Men: MAE = 7.49, RMSE = 9.62, Women: MAE = 7.45, RMSE = 9.54). As expected (de Lange et al., 2021), due to smaller age-range in the test set, the correlation between estimated and chronological age for the full model for men was r = 0.32 ($p = .002$, MAE = 6.44, RMSE = 7.59) and r = 0.34 ($p < .001$, MAE = 6.93, RMSE = 8.53) for women. The subcortical model yielded a correlation of r = 0.28 ($p = .005$, MAE = 7.90, RMSE = 9.39) for men, and r = 0.26 ($p < .001$, MAE = 6.94, RMSE = 8.54) for women.

Fig. 2 shows the association between the BAGs and the global DTI measures.

3.4. Association between physical activity, physical capability and BAG

Table 2 summarizes the results from the linear models testing for associations between BAG and measures of physical activity and capability. No significant associations were found after correcting for multiple comparisons, with Bayes Factors generally suggesting equivocal to low evidence for the models not including BAGs compared to the models including BAGs.

Models including subcortical BAG by sex interactions revealed a significant main effect of daily steps (β = -0.35, $p = .003$), indicating lower subcortical BAG in people with a higher number of daily steps, and a significant interaction between subcortical BAG and sex (β = 0.34, $p =$

Table 1
Characteristics of the StrokeMRI sample.

	All	Women	Men	r with age (p) [all]	r with age (p) [women]	r with age (p) [men]
N	122	75	47			
Age	71.35 (4.61)	70.17 (3.75)	73.24 (5.23)			
Education, years	15.71 (3. 45)	15.55 (3.15)	15.98 (3.91)	0.07 (0.302)	0.00 (0.963)	0.09 (0.388)
MMS-E (median, IQR)	29 (2)	29 (2)	29 (1.5)	−0.08 (0.224)	−0.05 (0.534)	−0.25 (0.028) *
BMI, kg/m^2	24.94 (3.38)	24.72 (3.69)	25.30 (2.82)	−0.02 (0.733)	−0.05 (0.522)	−0.06 (0.557)
Wear time SAM, minutes	853.50 (68.27)	858.35 (65.36)	845.60 (72.80)	−0.10 (0.104)	−0.08 (0.325)	−0.09 (0.394)
Total steps/day	12088.76 (3666.72)	12549.58 (3696.94)	11337.43 (3527.98)	−0.13 (0.041)*	−0.08 (0.301)	−0.09 (0.384)
M-V steps/day[a]	2685.34 (1925.91)	3030.02 (2154.80)	2123.35 (1317.12)	−0.06 (0.361)	−0.05 (0.564)	0.05 (0.650)
Hand-grip strength, kg	32.63 (9.92)	26.35 (4.72)	42.51 (7.64)	0.10 (0.116)	−0.06 (0.425)	−0.12(0.226)
Postural control, cm/sec (median, IQR)	1.49 (0.85)	1.32 (0.59)	1.87 (1.31)	0.08 (0.189)	0.00 (0.993)	−0.07 (0.521)
Walking speed, m/s	1.41 (0.19)	1.44 (0.18)	1.36 (0.19)	−0.12 (0.048) *	−0.10 (0.188)	−0.10 (0.336)
Global FA	0.47 (0.02)	0.46 (0.02)	0.47 (0.02)	−0.17 (0.006)*	−0.23 (0.003)*	−0.07 (0.474)
Global MD[b]	742.32 (25.35)	742.25 (23.18)	742.43 (28.74)	0.20 (0.001)*	0.29 (<0.001)*	0.08 (0.409)
Subcortical ROI[c] (volume)						
Hippocampus	3701.14 (413.94)	3689.68 (379.48)	3719.43 (467.43)	−0.20 (0.001)*	−0.15 (0.056)	−0.34 (<0.001)*
Caudate	3523.60 (544.02)	3396.94 (471.05)	3725.72 (594.68)	0.05 (0.450)	−0.05 (0.504)	−0.01 (0.956)
Thalamus	6981.53 (713.32)	6725.11 (585.77)	7390.70 (712.88)	0.02 (0.715)	−0.10 (0.200)	−0.06 (0.545)
Cerebellum: Cortex	49962.30 (4967.85)	48318.86 (4421.05)	52584.82 (4695.12)	0.03 (0.555)	−0.01 (0.876)	−0.14 (0.153)
Cerebellum:White matter	13793.95 (2155.49)	13133.02 (1710.75)	14848.64 (2380.01)	−0.02 (0.748)	−0.11 (0.185)	−0.16 (0.119)

Note. If not specified, data is reported as mean (SD), r = Kendall tau correlation coefficient, IQR = inter-quartile range, BMI = body mass index, SAM = Step Activity Measure, M-V steps/day = Moderate- to vigorous intensity steps per day, FA = fractional anisotropy, MD = mean diffusivity, ROI = Regions of interest
*Significant associations with p < .05.
[a] ≥ 100 steps/minute.
[b] MD = mm^2/s × 10^{-6}. MD was multiplied with 10^6 to increase precision in the reporting.
[c] The volumetric unit = mm^3.

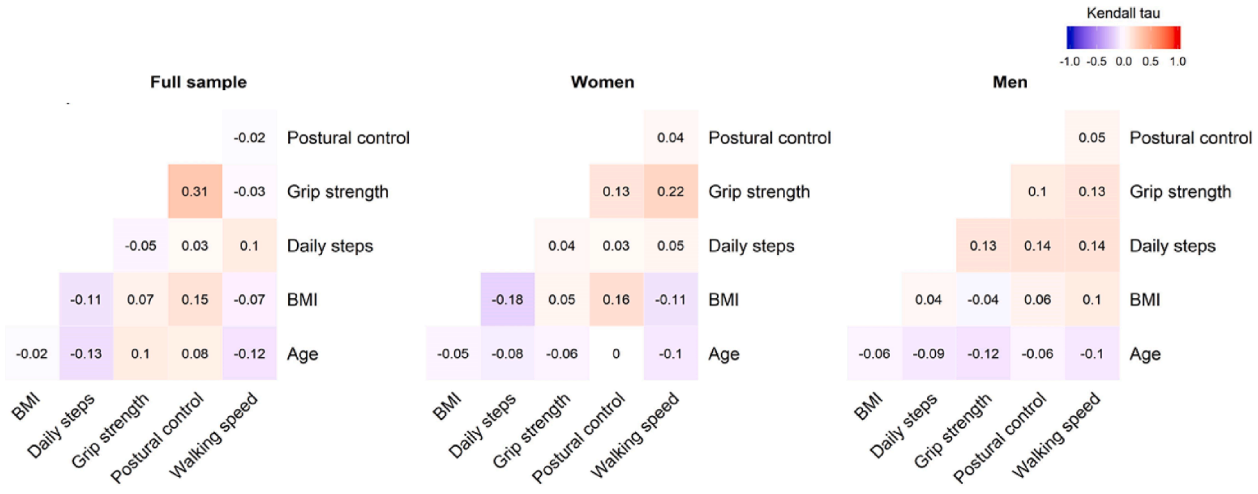

Fig. 1. Correlations (Kendall tau) between the physical measurements. Heatmaps showing the associations between the measures of physical capability and activity for the full sample (N = 122), among women (N = 75) and among men (N = 47). BMI = body mass index.

.003), with Bayes Factor suggesting strong evidence for the model including the interaction term (BF = 16.51, ± 1.63%) (Supplementary Table 4). Follow-up analyses stratified by sex revealed a significant association between subcortical BAG and number of steps among women, where a decrease of 1000 steps per day was significantly associated with a 7.03 increase in BAG (β = -0.34, p = .003). The association was not significant for men (β = 0.20, p = .172) (Fig. 3). For the remaining models, including the interaction term did not change the results, with Bayes Factor in general suggesting equivocal to low evidence for the models not including interaction effects.

Follow-up analysis, based on the main results of association between subcortical BAG and daily number of steps in women, revealed no significant associations between subcortical volumes and daily number of steps (Supplementary Table 5), including any interaction with sex (Supplementary Table 6), with Bayes Factor generally suggesting equivocal to low evidence for no associations between the ROIs and daily step, and likewise for the models including interaction term.

3.5. Association between physical activity, physical capability and DTI measures

Supplementary Fig. 2 shows the association between age and DTI measures. Global FA (r_τ = -0.17, p < .006, BF = 7.85, ± 0%) and MD (r_τ = 0.20, p < .001, BF = 29.45, ± 0%) were significantly associate with age.

Table 3 summarizes the results from the linear models testing for

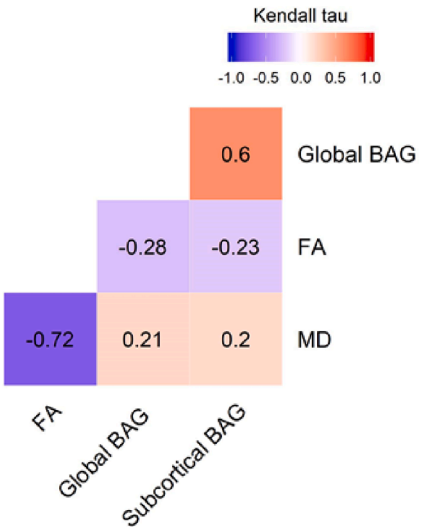

Fig. 2. Correlation matrix of the brain imaging measures (Kendall tau) indicating their shared variance. BAG = brain age gap, FA = fractional anisotropy, MD = mean diffusivity.

associations between the DTI measures and the various measures of physical activity and capability. After correction for multiple comparisons, linear models revealed a significant positive association between global FA and walking speed (β = 0.25, p = .006, BF = 7.5, ± 2.72%), with the model including FA being preferred by Bayes Factor. The results are indicating higher average pace with higher FA. Follow-up voxelwise analysis showed widespread significant positive associations between white matter FA and walking speed, such that participants that walked faster also exhibited higher FA (Fig. 4), accounting for age and sex. For walking speed, Bayes Factor also suggested moderate evidence for the model including global MD compared to the model including only age and sex, indicating higher walking speed with lower MD. This association did not remain significant after correction for multiple comparisons (β = -0.24, p = .01, BF = 5.05 ± 2.73%). No other significant associations were found, with Bayes Factors generally suggesting equivocal to low evidence for the models not including DTI-measures compared to the models including DTI-measures, and with similar results when adding the interactions with sex (Supplementary Table 7).

3.6. Differences in sensitivity between the various imaging results

Fisher z-transformation indicated differences in the associations between walking speed and FA compared to global BAG (t = 3.35, p = .001), subcortical BAG (t = 3.48, p = .001), and MD (t = 3.8, p < .001). No other robust differences were found in the associations between physical activity or physical capability between the different imaging modalities (Supplementary Table 8).

4. Discussion

The purpose of the current study was to examine the association between objective measures of physical activity level and capability, and two complementary structural MRI based indicators of brain health in healthy older adults. The study focuses on identifying lifestyle-factors with potential dissimilar protecting effect against grey and white matter changes in the aging brain. Our study indicates a positive association between total daily steps and a younger appearing brain based on the subcortical model in women, but not in men, with Bayesian analyses strongly supporting an association. Moreover, our results indicate that a higher walking speed is associated with higher global FA, with Bayesian analysis suggesting moderate evidence for the association, and voxelwise analysis showing widespread significant positive associations.

4.1. Daily activity level and brain health

Based on the assumption that physical activity promotes brain health in non-demented older adults, we hypothesized that people with higher levels of physical activity would show evidence of less apparent brain aging than their less physically active peers. In line with this, our analyses revealed a significant linear association between subcortical BAG and daily steps for women, where a decrease of 1000 steps per day was associated with 7.03 years increase in BAG, after regressing out the effect of age. While cross-sectional findings should be interpreted with

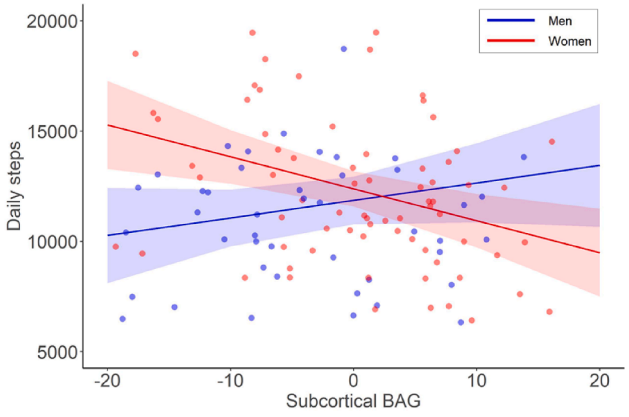

Fig. 3. Associations between daily steps and subcortical brain age gap (BAG) among men and women.

Table 2
Results of linear models examining the association between physical activity and capability and brain age.

	Daily steps			Walking speed			Hand-grip strength			Postural control		
	β	p	BF (error %)	β	p	BF (error %)	β	p	BF (error %)	β	p	BF (error %)
Age	−0.19	0.041*	–	−0.15	0.103	–	−0.13	0.021	–	−0.08	0.360	–
Sex [Male]	−0.11	0.254	–	−0.19	0.039*	–	0.82	<0.001**	–	0.44	<0.001**	–
Global BAG	−0.07	0.468	0.33 ± 1.84	−0.17	0.053	1.42 ± 2.7	−0.12	0.033*	2.20 ± 2.95	−0.13	0.120	0.85 ± 1.82
R^2	0.08			0.10			0.66			0.23		
F	2.68 (p = 0.05)			4.34 (p = 0.006)**			76.90 (p < 0.001)**			10.38 (p <0.001)**		
Age	−0.2	0.037*	–	−0.15	0.101	–	−0.13	0.024*	–	−0.08	0.361	–
Sex [Male]	−0.12	0.195	–	−0.2	0.030*	–	0.83	<0.001**	–	0.44	<0.001**	–
Subcortical BAG	−0.13	0.141	0.34 ± 1.83	−0.19	0.033*	2.05 ± 2.06	−0.08	0.156	0.72 ± 2.62	−0.12	0.161	0.71 ± 1.41%
R^2	0.15			0.11			0.66			0.21		
F	3.27 (p = 0.024)*			4.64 (p = 0.004)**			74.41 (p < 0.001)**			10.19 (p < 0.001)**		

Note: β = standardized coefficients. Bayes Factor (BF) was estimated using *BayesFactor* package in R, and represent the evidence of the full model against null model. Null model: dependent variable ~ age + sex. BAG = brain age gap.
*Significant associations with p < .05
**Significant associations after Bonferroni correction.

Table 3
Results of linear models examining the association between physical activity and capability and DTI measures.

	Daily steps			Walking speed			Hand-grip strength			Postural control		
	β	*P*	BF (error %)	β	*p*	BF (error %)	β	*p*	BF (error %)	β	*p*	BF (error %)
Age	−0.17	0.080	–	−0.08	0.373	–	−0.11	0.067	–	−0.11	0.218	–
Sex [Male]	−0.11	0.244	–	−0.19	0.036*	–	0.83	<0.001**	–	0.47	<0.001**	–
FA	0.1	0.270	0.48 ± 1.80	0.25	0.006**	7.70 ± 2.02%	0.08	0.166	0.66 ± 2.81	−0.12	0.176	0.62 ± 1.56
R^2	0.07			0.13			0.66			0.20		
F	2.93 (p = 0.037)			5.73 (p= <0.001)			74.53 (p=<0.001)			10.13 (p=<0.001)		
Age	−0.16	0.094	–	−0.08	0.427	–	−0.12	0.046*	–	−0.12	0.178	–
Sex [Male]	−0.11	0.235	–	−0.2	0.034*	–	0.84	<0.001**	–	0.47	<0.001**	–
MD	−0.1	0.266	0.48 ± 1.82	−0.24	0.010*	5.23 ± 2.03	−0.03	0.654	0.31 ± 2.85	0.14	0.117	0.81 ± 1.53
R^2	0.07			0.12			0.65			0.21		
F	2.94 (p = 0.036)			5.40 (p = 0.002)			72.66 (p=<0.001)			10.4 (p = 0.001)		

Note: β = standardized coefficients. Bayes Factor (BF) was estimated using *BayesFactor* package in R, and represent the evidence of the full model against null model. Null model: dependent variable ~ age + sex. FA = fractional anisotropy, MD = mean diffusivity.
*Significant associations with p < .05
**Significant associations after Bonferroni correction.

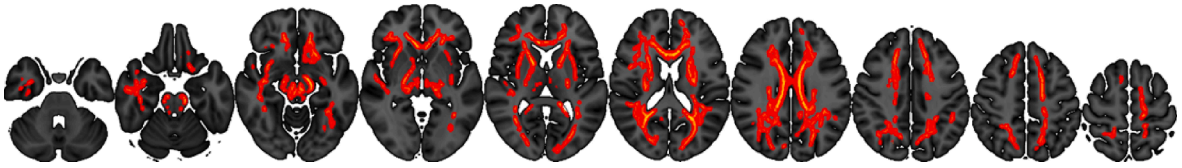

Fig. 4. White matter regions displaying significant associations (corrected p < .05, permutation based, TFCE) between walking speed and fractional anisotropy (FA). Age and sex were included in the models.

caution, these results suggest that higher physical activity is associated with relatively spared brain aging, and demonstrate the importance of integrating lifestyle physical activity among the predictors of a healthier brain in older adults.

In previous studies, cerebellar and hippocampal volumes have been associated with self-reported (Chen et al., 2015; Erickson et al., 2014) and sensor-measured (Hamer et al., 2018; Varma et al., 2016) activity level in older adults. The results of the current study support and extend previous studies by demonstrating that the relationship persists in a sample with highly active older adults when using brain age prediction and a sensor-based measure of activity level. The latter is considered to provide a more valid proxy of activity level than questionnaires, possibly due to older adults getting more daily physical activity from low-intensity activity (Dyrstad et al., 2014), which may be more difficult to recall than hours at the gym or other specific events (Guo et al., 2019). Importantly, the follow-up univariate analysis provided no evidence of an association between subcortical volumes (hippocampus, thalamus, cerebellum and caudate) and daily steps. Additional information beyond volumetric information is combined when estimating the individual brain age, which may explain the lack of univariate associations. Further, the current results substantiate the value of BAG as an individual surrogate biomarker of brain health, as recently suggested (Dunås et al., 2021).

There are several biological mechanisms that could explain the finding of younger appearing brains in women with higher physical activity level. First, both animal- and human models have shown that physical activity and exercise might influence the levels of neurotropic factors as brain-derived neurotrophic factor (BDNF), which are central for preventing deterioration of neurons (Oliff et al., 1998; Ruscheweyh et al., 2011; Voss et al., 2013). Our analysis revealed significant interactions with sex, with the association between subcortical BAG and daily activity level only present in women. One possible explanation for the results can be the suggested upregulations in neurotropic factors associated with a higher intensity of daily steps. Compared to the men in the study, that averaged at 18.7 % with moderate to high-intensity steps (≥100 steps per minute) of the total amount of daily steps, women averaged at 24.1 %. This suggest that the women in this study engaged in more intensive stepping activities. There were no sex-difference in the total number of daily steps. It has also been suggested that sex-hormones as estrogen can modulate BDNF levels in women (Singh et al., 1995). In human models, an interaction between hormone replacement therapy and exercise on age related decline in grey matter volume has been demonstrated (Erickson et al., 2007), indicating increased neuroprotective effect of exercise in combination with enhanced level of sex-hormones for postmenopausal women. Importantly, an animal-study demonstrated that by removal of female sex-hormones, the positive effect of exercise on BDNF level disappeared (Berchtold et al., 2001). In postmenopausal women the level of sex-hormones, including estrogen, is reduced, but not completely disappeared. Further, a link between cumulative sex-hormone exposure and BAG has been demonstrated (de Lange et al., 2020). Even though there is a lack of direct studies on the ability of physical activity level to upregulate BDNF-level in postmenopausal women (Barha et al., 2017b), female sex-hormones might have contributed to the BAG being sensitive to variation in daily activity level. A third biological mechanism supporting the findings of the current study is the suggested association between physical activity and the cardiovascular system (Myers, 2003), with the positive effect of increased cerebral blood flow and angiogenesis on brain health (Bloor, 2005; Voss et al., 2013). In support of this link, a recent study from a partly overlapping sample also found an association between MRI-measured adipose tissue and body composition measures and BAG (Beck et al., 2021). Although the current association between a measure cardiovascular risk factor, obesity (BMI), and activity level was low in both men and women, the level of high intensity steps in women might also have contributed to variations in cardiovascular health and the present results.

The observed interaction with sex is in line with a previous study suggesting an association between sensor-measured total daily walking with larger hippocampal volume, but only in older women (Varma et al., 2015), and with multiple studies analysing the association between various brain health measures and exercise (Barha et al., 2017a; Colcombe & Kramer, 2003; Liu-Ambrose et al., 2018). Knowledge on potential moderators, such as sex, on the relation between BAG and daily activity level might stimulate to the development of more personalized

lifestyle guidance. This is an exciting field for future research with clear clinical relevance.

In contrast to previously reported associations between white matter measures and sensor-measured physical activity (Burzynska et al., 2014; Tian et al., 2015), our analysis revealed no significant associations between physical activity and global BAG or white matter DTI. Sample characteristics such as the average and variance in physical activity may partly explain the discrepancies in results between studies. Our participants had an average of 12,088 steps per day, which is high compared to normative data for adults (mean 2000–9000 steps per day) (Tudor-Locke et al., 2009). Finally, we used total daily steps as a proxy of overall physical activity, and did not include intensity or temporal aspects of daily physical activity in our models, which are likely relevant factors.

4.2. Physical capability and brain health

In the present study we hypothesized that indicators of physical capability such as grip strength, walking speed, and postural control would associate with structural MRI based indicators of brain health in healthy older adults. In contrast to a previous study on participants aged 73 years (Cole & Franke, 2017), we found no significant associations between walking speed and global or subcortical BAG. However, supporting the hypothesis, the results demonstrated a positive association between white matter FA and walking speed, indicating higher average pace with higher FA. These results are in line with a previously reported association between white matter measures and a latent variable for physical fitness created from grip strength, forced respiratory volume, and 6-metre walk time, in participants aged 76 years (Ritchie et al., 2017). The association between white matter FA and walking speed could be of importance because of the possibility that structural brain changes may represent a mediator between physical capability and brain and cognitive function in senescence. By facilitating swift and synchronised information flow, brain white matter microstructure has been demonstrated to provide critical support for cognitive functions (Strömmer et al., 2020). Moreover, maintaining white matter integrity has formerly been identified as an important predictor for successful cognitive aging (Kennedy & Raz, 2009). The current study design does not allow for causal inference, and our results do not necessarily imply that improving walking speed in older age will contribute to a better brain health, or vice versa. Supporting a possible causal association, a recent large-scale study utilizing data from UK Biobank identified 70 independent genetic loci with significant associations with self-reported walking speed. Approximately 10% of the variance in self-reported walking speed was attributed to individual differences in common genetic variants, and significant genetic correlations were reported between self-reported walking speed and cardiometabolic, respiratory and psychiatric traits, educational attainment and mortality. Further, follow-up Mendelian randomization analyses, which allows for causal inference, suggested that increasing walking pace decreases cardiometabolic risk, in line with current public health advice (Timmins et al., 2020). Moreover, a number of studies have reported that walking speed is a strong predictor of mortality (Cooper et al., 2010; Ganna & Ingelsson, 2015) and a relevant index of "vital aging" (Vermeulen et al., 2011). The results of the present study substantiate the possible importance of walking speed as a target in public health interventions, and as a possible index of white matter brain health in older adults.

In addition to walking speed, hand-grip strength and postural control has been suggested as markers of healthy aging due to multiple associations with measures of health (Bohannon, 2019; Vermeulen et al., 2011). Both strength and postural control dependent on mechanical contributions from both the muscles-, skeletal, and joint systems (Granacher et al., 2008), but also visual, vestibular, haptic and proprioceptive information are critical in specific for maintaining postural control (Alcock et al., 2018). Integration of this information has been suggested to be partly related to the structure and function of the brain, and potentially be affected by the aging process in the brain with following reduction of function (Sullivan et al., 2009). In contrast to this and other previous work (Cole et al., 2018), our analyses revealed no significant associations between brain MRI and hand-grip strength in a presumably healthy sample. Former publications including mainly clinical populations have characterized postural control as a "whole brain phenomenon", but also highlighted cerebellum as an important region (Surgent et al., 2019). Our results indicated no significant associations between subcortical or global BAG or DTI measures of brain integrity and postural control. For FA and MD, this was in line with a previous study reporting weak associations in the postural control association with regional FA, and a lack of association with MD (Massa et al., 2019). We are not aware of previous studies testing for associations between subcortical BAG, including the cerebellum, or global BAG and postural control measured with a forced pressure platform. However, in relation to former studies highlighting cerebellum as important structure for postural control, this is also suggested to be a region more implicated in clinical populations than in healthy ones (Surgent et al., 2019), and this might substantiate the findings in the present study. The neurobiological underpinning in the brain of variation in postural control in healthy older adults remains uncertain.

4.3. Methodological considerations

The strengths of our study include objectively measured physical activity, several objective and sensitive tests of physical capability, and the advanced multimodal imaging approach.

Some limitations should also be emphasized. The study sample was relatively homogenous and high functioning in terms of level of education and physical activity, which may have limited the sensitivity. With increasing age, it is conceivable that a more selective and less representative part of the population volunteers for a study including an extensive protocol including both multimodal MRI and physical and neuropsychological tests. Further studies are needed to test the generalisability to other populations. In addition, future studies with larger sample sizes should pursue multivariate or other approaches that will allow for a more detailed delineation of the specific and unique contributions of each of the MRI measures on the different physical activity and capability measures.

The cross-sectional design does not permit inference about brain changes. Longitudinal studies covering a larger part of the lifespan are required to explore the dynamics of the associations, for example to which degree the effects of physical activity vary across the lifespan, and to which degree early intervention may protect against age-related decline years or decades later.

4.4. Conclusions

In conclusion, we have demonstrated that different markers of brain white matter structure and brain aging are associated with objectively measured daily activity and physical capability. The strongest associations were found between subcortical BAG and daily physical activity, but only for women, and between white matter FA and walking speed. Although our design does not allow for causal interpretation, the associations indicate that lifestyle physical activity and walking speed are associated with brain structure in older adults, and may thereby suggest that by maintaining physical activity it may improve brain health in late life. While larger longitudinal studies are needed to explore potential causal and long-term effects of physical activity on brain aging, our results also suggest that combining multimodal measures of brain structure provides complementary information and show dissociable associations with physical activity and capability in elderly healthy adults.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102767.

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