RESEARCH ARTICLE

Association Between Accelerometer-Derived Physical Activity Measurements and Brain Structure

A Population-Based Cohort Study

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Abstract

Background and Objectives

While there is growing evidence that physical activity promotes neuronal health, studies examining the relation between physical activity and brain morphology remain inconclusive. We therefore examined whether objectively quantified physical activity is related to brain volume, cortical thickness, and gray matter density in a large cohort study. In addition, we assessed molecular pathways that may underlie the effects of physical activity on brain morphology.

Methods

We used cross-sectional baseline data from 2,550 eligible participants (57.6% women; mean age: 54.7 years, range: 30–94 years) of a prospective cohort study. Physical activity dose (metabolic equivalent hours and step counts) and intensity (sedentary and light-intensity and moderate-to-vigorous intensity activities) were recorded with accelerometers. Brain volumetric, gray matter density, and cortical thickness measures were obtained from 3T MRI scans using FreeSurfer and Statistical Parametric Mapping. The relation of physical activity (independent variable) and brain structure (outcome) was examined with polynomial multivariable regression, while adjusting for age, sex, intracranial volume, education, and smoking. Using gene expression profiles from the Allen Brain Atlas, we extracted molecular signatures associated with the effects of physical activity on brain morphology.

Results

Physical activity dose and intensity were independently associated with larger brain volumes, gray matter density, and cortical thickness of several brain regions. The effects of physical activity on brain volume were most pronounced at low physical activity quantities and differed between men and women and across age. For example, more time spent in moderate-to-vigorous intensity activities was associated with greater total gray matter volume, but the relation leveled off with more activity (standardized β [95% CIs]: 1.37 [0.35–2.39] and −0.70 [−1.25 to −0.15] for the linear and quadratic terms, respectively). The strongest effects of physical activity were observed in motor regions and cortical regions enriched for genes involved in mitochondrial respiration.

Discussion

Our findings suggest that physical activity benefits brain health, with the strongest effects in motor regions and regions with a high oxidative demand. While young adults may particularly profit from additional high-intensity activities, older adults may already benefit from light-intensity activities. Physical activity and reduced sedentary time may be critical in the prevention of age-associated brain atrophy and neurodegenerative diseases.

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GLOSSARY

AHBA = Allen Human Brain Atlas; **GCP** = Good Clinical Practice; **FDR** = false discovery rate; **FMWH** = full-width-half-maximum; **ICH** = International Council for Harmonization; **METs** = metabolic equivalents; **NADH** = nicotinamide adenine dinucleotide + hydrogen.

Physical activity may slow the rate of age-related cognitive decline and reduce the risk of developing neurodegenerative diseases.[1,2] It is unclear, however, which dose and intensity of physical activity is required to achieve brain health benefits.[2] Determining which physical activity components are linked to brain health and whether the effects vary across demographic factors could facilitate the development of targeted physical activity regimens as lifestyle interventions against neurodegeneration.

Several mechanisms underlying the neuroprotective effects of physical activity have been proposed, including enhancement of cerebral blood flow and stimulation of neurotrophin release, neuronal growth, and maturation,[3,4] but the underlying molecular pathways remain largely unknown. Moreover, previous studies examining the relation between physical activity and brain morphology, as a proxy of brain health, have reported inconsistent findings[5-12]: While some studies found both the gray and white matter structures to benefit from physical activity,[5,11] other studies reported an association with either only the gray matter[6,7,10] or the white matter volume.[8,13] Regional changes associated with physical activity were observed in the frontal, temporal, parietal, occipital, and motor regions.[7,10,12,14] Physical activity has also been suggested to induce hippocampal neurogenesis,[4] but findings on the effects of physical activity on hippocampal volume are equivocal.[7,8,10] The majority of previous studies relied on physical activity questionnaires,[7,9,14] which are a cost-efficient way to gather information on physical activity, but come with potential pitfalls such as social desirability and recall bias and cannot distinguish between different physical activity components.[15]

With the recent introduction of accelerometer-based assessments into cohort studies, an objective approach for measuring distinctive physical activity components at population scale has emerged.[8,10] We aimed to disentangle the association between physical activity components, including dose and intensity, and detailed brain morphological assessments of adults across a wide age range in a large population-based cohort study. To this end, we systematically investigated whether accelerometer-derived physical activity components were associated with (1) volumes and cortical thickness of predefined temporal, occipital, and motor regions, (2) whole-brain voxel-based regional gray matter density, and (3) vertex-based cortical thickness across the entire brain. To identify molecular pathways that potentially underlie the effects of physical activity on the brain, we linked vertex-based estimates of physical activity to gene expression profiles.

Methods

Study Participants

The study was based on cross-sectional baseline data from the first 5,000 participants (age range: 30–94 years) of the Rhineland Study, an ongoing community-based prospective cohort study.[16] Data were collected from March 2016 to June 2020. Invitations to participate were sent to inhabitants of 2 municipal districts in Bonn, Germany. To participate in the study, participants were required to have a sufficient command of the German language and be 30 years or older. They were not offered financial rewards for study participation.

We analyzed data of 2,550 participants in total of the first 5,000 participants (eFigure 1, links.lww.com/WNL/C218). Actimetry data of 1,028 participants were not available due to the following reasons: refusal to participate (n = 72), technical/acquisition failure (n = 190), or ineligibility (n = 766). Ineligibility criteria included astasis (inability to stand or walk), unrepresentative physical activity week, and/or allergy to medical adhesives. Based on self-reports, it was established whether participants anticipated a typical, representative activity and sleeping pattern during the recording time. Examples of unrepresentative physical activity weeks included vacation, untypical work travel, surgery, and hospital stays. To achieve reliable physical activity estimates,[17] we additionally excluded 127 participants with less than 5 valid actimetry recording days. Based on recommendations by Winkler et al.[18], we classified recording days as invalid when meeting 1 or more of the following criteria: (1) <500 steps/d, (2) ≥95% time spent in 1 posture, (3) <10 hours estimated waking wear time. Heatmaps of included and excluded data and wear diaries were visually checked to avoid incorrect exclusion. In addition, we excluded 1,040 participants who did not undergo an MRI scan and 238 participants with missing covariate data. Last, we flagged potential outliers and after visual inspection, excluded 15 participants with erroneous recordings.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Medical Ethics Committee of the University of Bonn and followed the recommendations of the International Council for Harmonization (ICH) Good Clinical Practice (GCP) standards (ICH-GCP). Participants provided informed consent in accordance with the principles of the Declaration of Helsinki.

Physical Activity

Physical activity was measured using the activPAL3 micro accelerometer (PAL Technologies, Glasgow, UK), a small

(55 × 25 × 5 mm) and lightweight (9 g) triaxial accelerometer with a sampling frequency of 20 Hz. Based on acceleration across the vertical, anteroposterior, and mediolateral axes, the activPAL can be used to estimate energy expenditure and posture (sitting/lying, standing, or stepping) across time. The accelerometer was fixed with a nitrile finger cot and attached on the middle-anterior right thigh with a waterproof transparent dressing (Tegaderm), which allowed the accelerometer to be worn continuously during 7 recording days. Participants were instructed to take off the accelerometer when being exposed to hot environments, strong magnetic fields, and before security checks. They were shown how to reattach the accelerometer and instructed to complete a nonwear diary.

Raw data were uploaded using proprietary activPAL software. A customized version of the activpalProcessing package was used to extract physical activity dose and intensity.[19] Weighted daily average values were calculated to adjust for accelerometer wear time per day. Physical activity dose was defined as average weighted daily step counts and energy expenditure in average weighted daily metabolic equivalents (METs) per hour. Physical activity intensity was defined based on posture and energy expenditure across time: average weighted daily %time spent in sedentary (sitting/lying posture), light-intensity (standing or step-taking posture and METs <3.0), or moderate-to-vigorous activity (standing or step-taking posture and METs ≥ 3.0).[19,20]

Brain MR Imaging

MRI scans were obtained with a 3T Siemens MAGNETOM Prisma system (Siemens Healthcare, Erlangen, Germany) equipped with an 80 mT/m gradient system and a 64-channel head-neck coil. Using a multiecho Magnetization Prepared Rapid Acquisition Gradient Echo sequence,[21,22] T1-weighted images were acquired at 0.8 mm isotropic spatial resolution (TA = 6.5 minutes, TR = 2,560 ms, TI = 1,100 ms, flip angle = 7°, field-of-view = 256 × 256 mm, 224 sagittal slices). The standard FreeSurfer 6.0[23] preprocessing pipeline was used to extract brain structure volumes and thickness.[24-26] The segmentation quality was visually assessed in 1,872 participants, which were selected based on incidental findings, examination comments, age-adjusted extreme volumetric values, and 12% random selection. Cortical thickness was determined at each surface location based on the average closest distance between the white and pial surfaces.[24] Cortical structures were parcellated using the "Desikan-Killiany-Tourville" atlas.[25] Subcortical structures were segmented using the automatically segmented brain volume atlas.[26]

Our primary outcome measures were brain volume and cortical thickness of predefined regions of interest, which were selected based on a targeted literature research (eTable 1, links.lww.com/WNL/C218). In addition, we conducted an exploratory analysis of localized vertex-based thickness estimates across the whole cortex. Individual thickness maps were registered to a group surface and smoothed with a 10-mm full-width-half-maximum (FMWH) kernel. Cluster-wise inference and correction for multiple comparisons were performed using a permutation simulation.[27]

For the exploratory voxel-based morphological analysis, T1 images were first segmented into gray matter, white matter, and CSF images using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, UCL) and resampled to 1 × 1 × 1 mm3 voxel size.[28] Gray matter images were normalized into Montreal Neuroscience Institute (MNI) space using diffeomorphic anatomical registration through Geodesic shooting and Gauss-Newton optimization with Geodesic shooting template from CAT12 toolbox[29,30] and smoothed with an isotropic Gaussian kernel of 8 mm FMWH. Segmented images were checked visually for potential segmentation and registration errors. Estimated total intracranial volume was calculated by combining gray matter, white matter, and CSF images generated during segmentation.

Covariates

Participants' age, sex, and smoking status (current, former, or nonsmoker) were determined based on self-reports. Using the International Standard Classification of Education 2011, participants' highest educational level was classified as low (lower secondary education or below), middle (upper secondary education to undergraduate university level), and high (postgraduate university study). Participants' medical history of neurologic (including dementia, Parkinson disease, multiple sclerosis, stroke, and TIA) and psychiatric (including depression and anxiety) disorders was obtained based on self-reports and categorized as binary variables (yes/no).

Mapping Gene Expression to Vertex-Based Estimates of Physical Activity

Normalized microarray-based gene expression data from all 6 available donors were downloaded from the Allen Human Brain Atlas (AHBA).[31] The donor characteristics and approach used to obtain high-resolution gene expression data from the postmortem brains have been detailed earlier.[32] We linked vertex-based effect estimates of physical activity to gene expression data by first converting FreeSurfer surface-based coordinates (i.e., fsaverage) to MNI volumetric coordinates (i.e., right, anterior, superior coordinates in MNI152 space) using the registration fusion-advanced normalization approach developed by Wu et al.[33] Next, for each donor, we mapped gene expression data to vertex-based results using rounded MNI coordinates.

Statistical Analysis

Statistical analyses were performed in R (version 3.6.3, The R Foundation). Multivariable regression models were used to assess the association between physical activity (independent variable) and brain structure (outcome). To test for nonlinear effects, initial models also included a quadratic term for physical activity. In addition, we tested for interaction effects between physical activity and age and between physical activity and sex. All models were adjusted for age, age2, sex, education, and smoking. The quadratic physical activity and age terms were removed if they failed to reach significance (with $p \leq 0.05$). Volumetric analyses were also adjusted for estimated intracranial volume. Continuous independent variables were z-standardized to allow the comparison of effect

sizes. Model diagnostics were performed by visual inspection of the distribution of the residuals. We reported both multiple comparison–uncorrected and false discovery rate (FDR)-corrected results, assuming 24 tests for the corresponding number of preselected volumetric and cortical regions of interest. To assess the robustness of our findings, we ran a 5-fold cross-validation with 100 iterations. We split up our data set into 5 equal-sized, disjoint folds and examined the physical activity effects in 4 of the 5 folds each time.[34] In a further sensitivity analysis, we tested whether the association between physical activity and brain structure was altered after excluding participants with neurologic and psychiatric disorders.

For the voxel-based morphometry analysis, we performed 2-sample *t* test (women vs men) with each actimetry measure as covariate and controlled for age, age^2, education, smoking, and estimated intracranial volume. Resulting maps were corrected for multiple comparisons using probability threshold-free cluster enhancement method.[35] Statistical inferences were made at $p \leq 0.01$ family-wise error corrected for multiple comparisons across the whole brain and measures. For the vertex-wise analysis, a permutation-based correction for multiple comparisons was performed with a cluster-forming threshold of $p \leq 0.05$ and 1,000 iterations.[27] The threshold for statistical significance of cluster sizes was set at a 2-sided $p \leq 0.005$.

Generalized additive mixed-effects models were used to assess the association between gene expression (independent variable) and vertex-wise effect estimates of physical activity (outcome) across the brain. In these models, the spatial autocorrelation among the vertices was accounted for by including a smoothed interaction term (i.e. s[x,y,z]) for the MNI coordinates of each vertex. The intraindividual correlation within each donor was modeled through a random intercept for donor. Given the low number of donors, additional adjustments for age or sex were not possible. FDR correction was applied to adjust for multiple comparisons with $q < 0.05$ considered statistically significant.

In Silico Functional Analyses

To gain insight into the underlying molecular mediators and functional pathways in the brain that are affected by physical activity, we first selected the set of genes whose expression was significantly associated with vertex-wise effects of physical activity (i.e., FDR $q < 0.05$). These genes were used as an input for further functional enrichment analyses with the WebGestalt tool[36,37] using the built-in reference set of the human genome for overrepresentation analysis. As look-up databases for gene enrichment analyses, we queried the Kyoto Encyclopedia of Genes and Genomes (KEGG),[38] Reactome,[39] WikiPathways,[40] and DrugBank[41] resources.

Data Availability

The data set of Rhineland Study is not publicly available because of data protection regulations. Access to data can be provided to scientists in accordance with the Rhineland Study's Data Use and Access Policy. Requests for further information or to access the data set of Rhineland Study should be directed to RS-DUAC@dzne.de.

Results

Characteristics of the Sample

Participants were aged 30–94 years and had a relatively high education level (Table 1). In comparison with men, women had a lower body mass index, education level, and brain volume, were less sedentary, and spent more time in light-intensity activities. They also had a higher energy expenditure than men. Age-stratified brain volumetric and physical activity characteristics are summarized in eTable 2, links.lww.com/WNL/C218.

Effects of Physical Activity on Predefined Brain Regions of Interest

Predefined regions of interest included the temporal, occipital, and motor regions (eTable 1, links.lww.com/WNL/C218). Given our hypothesis-driven approach, in this study, we focused on multiple comparison–uncorrected findings. Model statistics and FDR-corrected findings are summarized in eTable 3–6, links.lww.com/WNL/C218.

Higher step counts and energy expenditure, as expressed in MET-hour, were associated with greater total gray matter volume, cerebellar gray matter volume, and precentral thickness (Figures 1, A and B and 2A). The positive effect of increasing step counts and energy expenditure on brain volumes was most pronounced at the lower end of the physical activity spectrum. Total brain, total gray matter, cerebellar gray matter, and hippocampal and precentral volume also increased with a higher proportion of time spent on light-intensity and moderate-to-vigorous intensity activities, whereas the opposite effect was found for sedentary activities (Figures 1, C and D and 2C). We found the opposite effect for the cortical thickness of the lateral occipital cortex (Figure 1D). These results did not change materially after the exclusion of participants with neurologic or psychiatric disorders (eFigure 2, eFigure 3A and C, links.lww.com/WNL/C218). The mean and SD values of the cross-validation results for the physical activity parameters are summarized in eTable 7, links.lww.com/WNL/C218.

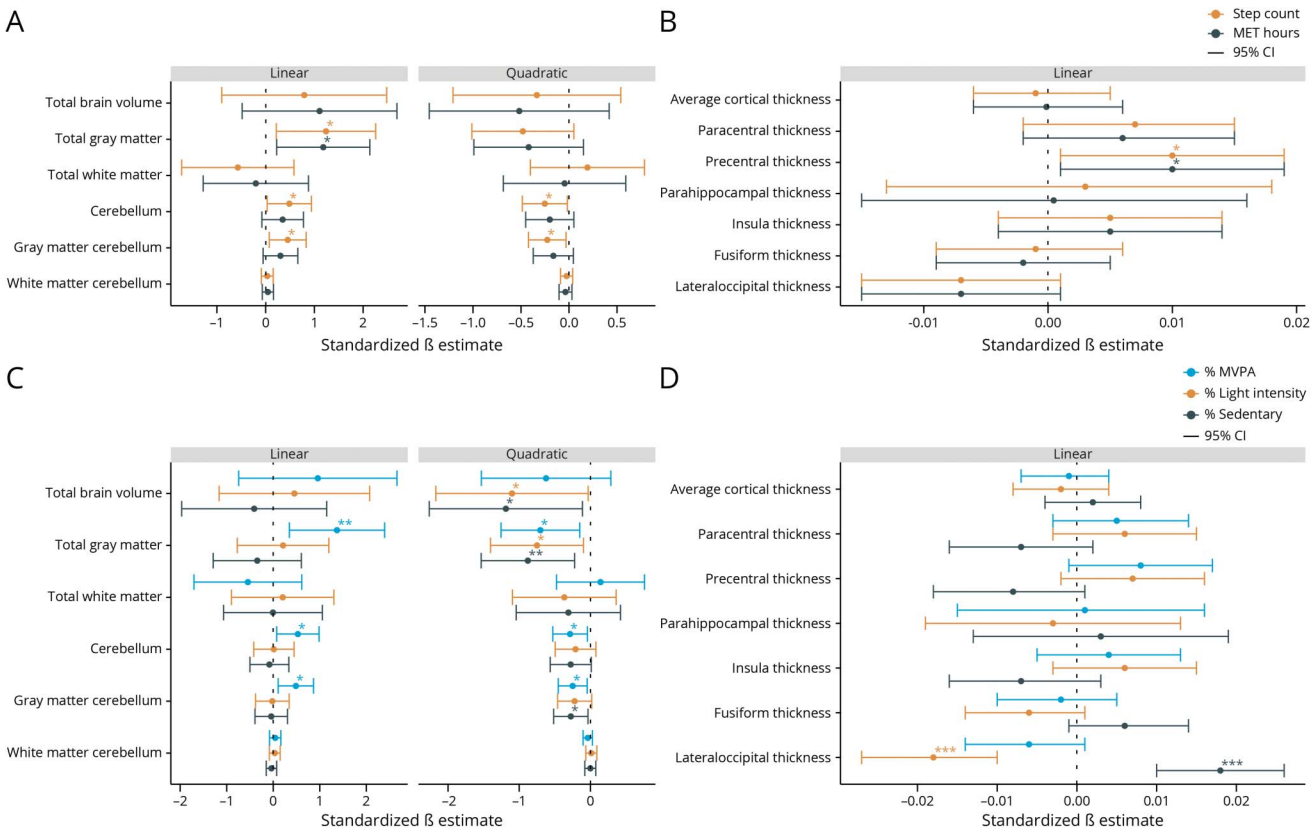
Next, we examined whether the effects of physical activity on these predefined brain regions changed across age and differed between men and women. We observed no differences in the effects of physical activity dose on brain volume and cortical thickness across age and between men and women (Figures 2B and 3, A and B). For physical activity intensities, we found that with increasing age, the association between more light-intensity activities with higher total brain volume and lower amygdalar volume became more pronounced, whereas the association with lower lateral occipital volume weakened (Figures 2D and 3, C and D). The effect of light-intensity activities on total brain and amygdalar volume was strongest in our oldest age group (70+ years, eFigure 4A

Table 1 Sample Demographics

	Women (n = 1,469)	Men (n = 1,081)	*p* Value
Age (y), mean (SD)	55.03 (13.38)	54.24 (13.96)	0.151
30–39	238 (16.20)	215 (19.89)	0.194
40–49	258 (17.56)	180 (16.65)	
50–59	409 (27.84)	291 (26.92)	
60–69	343 (23.35)	224 (20.72)	
70–79	182 (12.39)	137 (12.67)	
80–89	38 (2.59)	34 (3.15)	
90+	1 (0.07)	0 (0.00)	
Body mass index (kg/m^2), mean (SD)	25.29 (4.65)	26.12 (3.50)	<0.001
Smoking, n (%)			0.072
Current	182 (12.4)	154 (14.3)	
Former	560 (38.1)	440 (40.7)	
Never	727 (49.5)	487 (45.1)	
Education ISCED11, n (%)			<0.001
High	689 (46.9)	696 (64.4)	
Middle	743 (50.6)	375 (34.7)	
Low	37 (2.5)	10 (0.9)	
Neurologic disorders, n yes (%)	34 (2.31)	26 (2.41)	0.986
Psychiatric disorders, n yes (%)	293 (19.95)	134 (12.40)	<0.001
Daily sensor hours worn (h), mean (SD)	23.83 (0.47)	23.81 (0.54)	0.440
Daily energy expenditure (MET-hours), mean (SD)	34.10 (1.29)	33.9 (1.38)	<0.001
Daily step count, mean (SD)	8,958.25 (3,038.77)	8,796.33 (3,327.51)	0.202
% daily light-intensity physical activity, mean (SD)	0.23 (0.06)	0.19 (0.06)	<0.001
% daily moderate-to-vigorous physical activity, mean (SD)	0.05 (0.02)	0.05 (0.02)	0.964
% daily sedentary, mean (SD)	0.72 (0.07)	0.76 (0.06)	<0.001
Actimetry examination season, n (%)			0.153
Spring	305 (20.76)	219 (20.26)	
Summer	343 (23.35)	236 (21.83)	
Autumn	431 (29.34)	295 (27.29)	
Winter	390 (26.55)	331 (30.62)	
Total brain volume (cm^3), mean (SD)	1,052.76 (92.51)	1,178.09 (107.61)	<0.001
Gray matter volume (cm^3), mean (SD)	596.77 (49.00)	661.24 (56.91)	<0.001
White matter volume (cm^3), mean (SD)	430.27 (47.20)	489.64 (54.28)	<0.001
Cerebellar volume (cm^3), mean (SD)	129.50 (12.04)	143.04 (14.46)	<0.001
Hippocampal volume (cm^3), mean (SD)	7.60 (0.80)	8.23 (0.90)	<0.001

Abbreviations: ISCED = International Standard Classification of Education; MET = metabolic equivalents.
To assess group differences, a χ^2 test was used for categorical variables and a 2-sample *t* test for continuous variables.

Figure 1 Association Between Physical Activity and Predefined Brain Regions



(A and B) Standardized effect estimates of association between physical activity dose (step counts and MET-hours) and (A) larger brain volumes and (B) cortical thickness of predefined regions. (C and D) Standardized effect estimates of association between physical activity intensity (% moderate-to-vigorous [MVPA], % light-intensity and sedentary activities) and (C) larger brain volumes, and (D) cortical thickness of predefined regions. ***$p \leq 0.001$ **$p \leq 0.01$ *$p \leq 0.05$ $p \leq 0.06$. MET = metabolic equivalents.

and B, links.lww.com/WNL/C218). Similarly, the effect of sedentary time on greater amygdalar volume strengthened in older age groups (eFigure 4D, links.lww.com/WNL/C218). However, the opposite was found for the relationship of increasing lateral occipital volume with more sedentary time (eFigure 4E, links.lww.com/WNL/C218). Compared with women, men showed a weaker association between more light-intensity activities and greater total cerebellar and cerebellar gray matter volume (Figure 3C). By contrast, the association between more sedentary activities and lower total cerebellar and cerebellar gray matter volume was stronger in men (Figure 3C). These effects were also observed after excluding individuals with neurologic or psychiatric disorders (eFigure 3B and D, eFigure 5, links.lww.com/WNL/C218). Cross-validation of these interaction models revealed relatively robust interaction effects. For cerebellar volume, the interaction between physical activity and sex remained statistically significant across all iterations (eTable 8, links.lww.com/WNL/C218).

Effects of Physical Activity on Regional Gray Matter Density

Higher step counts and energy expenditure were associated with greater gray matter density in the right temporal pole and bilateral cerebellum (Figure 4, A and B). More time spent on light-intensity and moderate-to-vigorous intensity activities was predominantly associated with higher temporal and cerebellar but lower occipital gray matter density (Figure 4, C and D). This was reversed for sedentary activities (Figure 4E). Overall, we observed the strongest effects of all the physical activity components on the right cerebellum (eFigure 6, links.lww.com/WNL/C218). Results corrected for multiple comparisons are summarized in eTable 9, links.lww.com/WNL/C218.

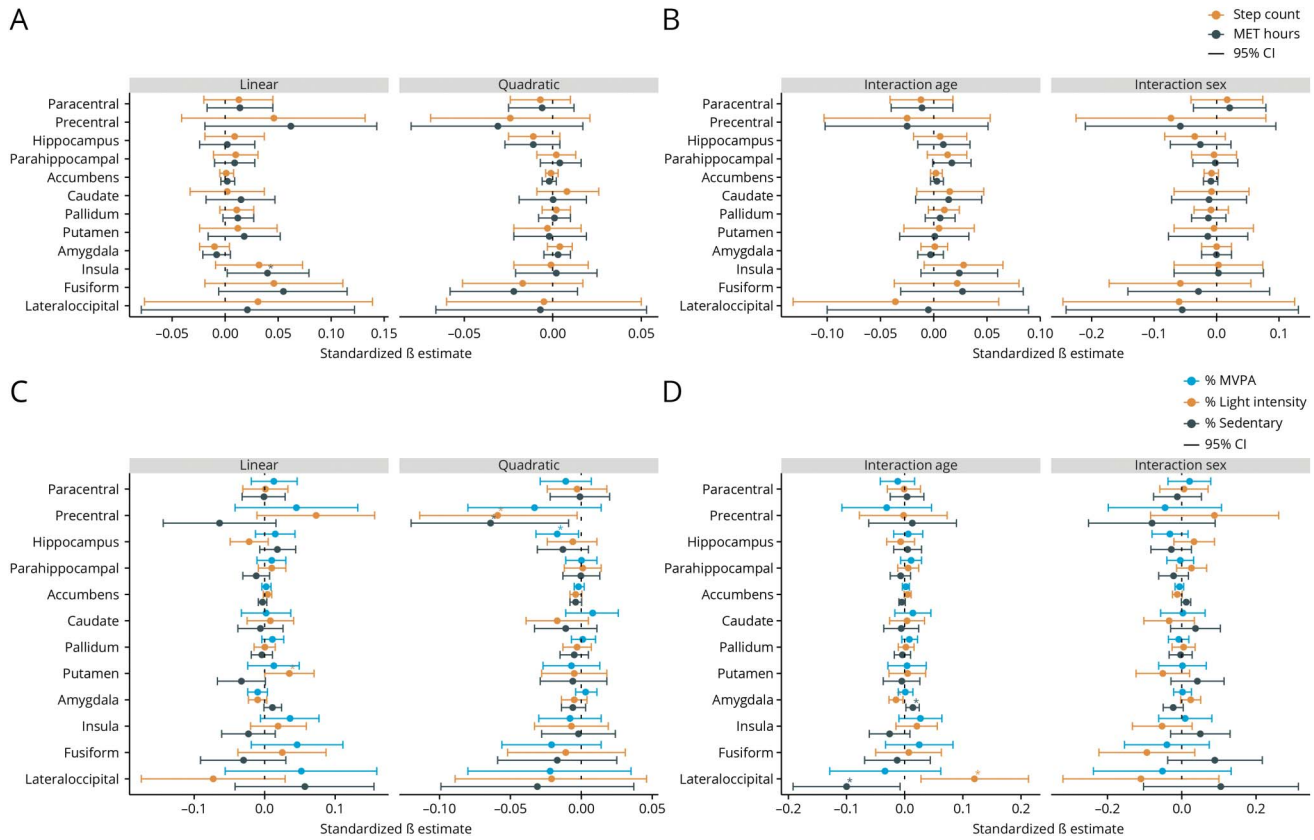
Effects of Physical Activity on Regional Cortical Thickness

With higher physical activity intensity and dose, precentral and entorhinal thickness increased, whereas lateral occipital and frontal thickness decreased (Figure 5A). The opposite was found for sedentary activities. After multiple comparison correction, only 1 cluster in the lateral occipital region retained significance, showing a negative association with light-intensity and a positive association with sedentary activities (Figure 5B).

Gene Expression Profiles Associated With the Effects of Physical Activity

Using MET-hours as an outcome, the spatial expression patterns of 4,504 gene probes were significantly related to the

Figure 2 Physical Activity Effects and Interaction Effects With Age and Sex for Additional Smaller Predefined Brain Regions



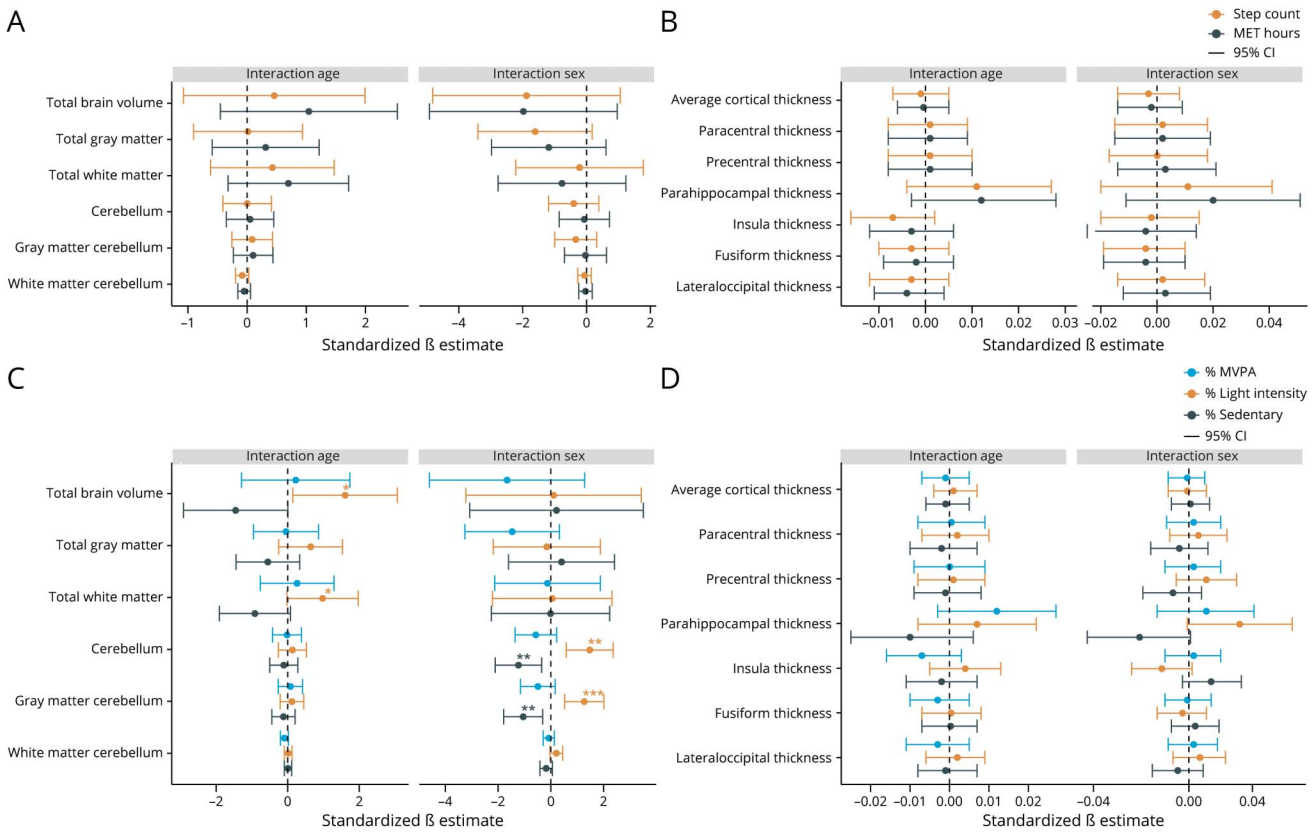
(A) Standardized effect estimates of association between physical activity dose (step counts and MET-hours) and additional smaller predefined brain regions. (B) Standardized effect estimates of interaction between physical activity dose, age, and sex for smaller predefined brain regions. (C) Standardized effect estimates of association between physical activity intensity (%moderate-to-vigorous [MVPA], %light-intensity and %sedentary activities) and additional smaller predefined brain regions. (D) Standardized effect estimates of interaction between physical activity intensity, age, and sex for additional smaller predefined brain regions. ***$p \leq 0.001$ **$p \leq 0.01$ *$p \leq 0.05$ $p \leq 0.06$. MET = metabolic equivalents.

vertex-wise effects of physical activity (FDR q < 0.05). Of these, 2,887 could be unambiguously mapped to unique Entrez gene IDs (eFigure 7, links.lww.com/WNL/C218). Over-representation analysis with gene ontology terms related to cellular processes, functions and components, demonstrated that these genes were predominantly enriched in pathways related to mitochondrial constituents and function (Figure 6A, eFigure 8A, links.lww.com/WNL/C218). Other pathways in which these genes were enriched included (mitochondrial) ribosomal subunits and protein-containing complex disassembly (Figure 6A, eFigure 8A, links.lww.com/WNL/C218). Using the KEGG database resource as a reference also highlighted mitochondrial, ribosomal, and proteosomal pathways as significantly enriched in genes related to physical activity levels (Figure 6B, eFigure 8B, links.lww.com/WNL/C218). It is of interest that KEGG pathway analysis also demonstrated an over-enrichment of these genes in pathways related to neurodegenerative diseases, including Alzheimer disease, Parkinson disease, and Huntington disease (Figure 6B, eFigure 8B, links.lww.com/WNL/C218). Using Reactome and WikiPathways as reference databases highlighted the involvement of mitochondrial and proteostasis pathways (data not shown). In addition, using the "DrugBank" resource as reference, we identified 2 compounds (i.e., phenethyl isothiocyanate and nicotinamide adenine dinucleotide + hydrogen [NADH]), which induced transcriptional changes significantly enriched for genes whose cortical expression patterns coincided with those of physical activity (eFigure 8C, links.lww.com/WNL/C218).

Discussion

Physical activity plays an important role in the prevention of age-associated neurodegeneration and promotes health and well-being.[1,2] By combining high-resolution structural brain imaging with continuous accelerometer-based quantification of physical activity patterns in a large community-based sample of adults across a wide age range, we could disentangle the relation of distinct physical activity components and brain health to an unprecedented level of detail. It is of importance that we observed that the effects of physical activity on brain volume are most pronounced at low physical activity quantities. This indicates that relative health gains from additional physical activity are greatest for people leading sedentary lifestyles when compared with those who already engage in at least moderate amounts of physical activity.

Figure 3 Interaction Between Physical Activity, Age, and Sex for Predefined Brain Regions



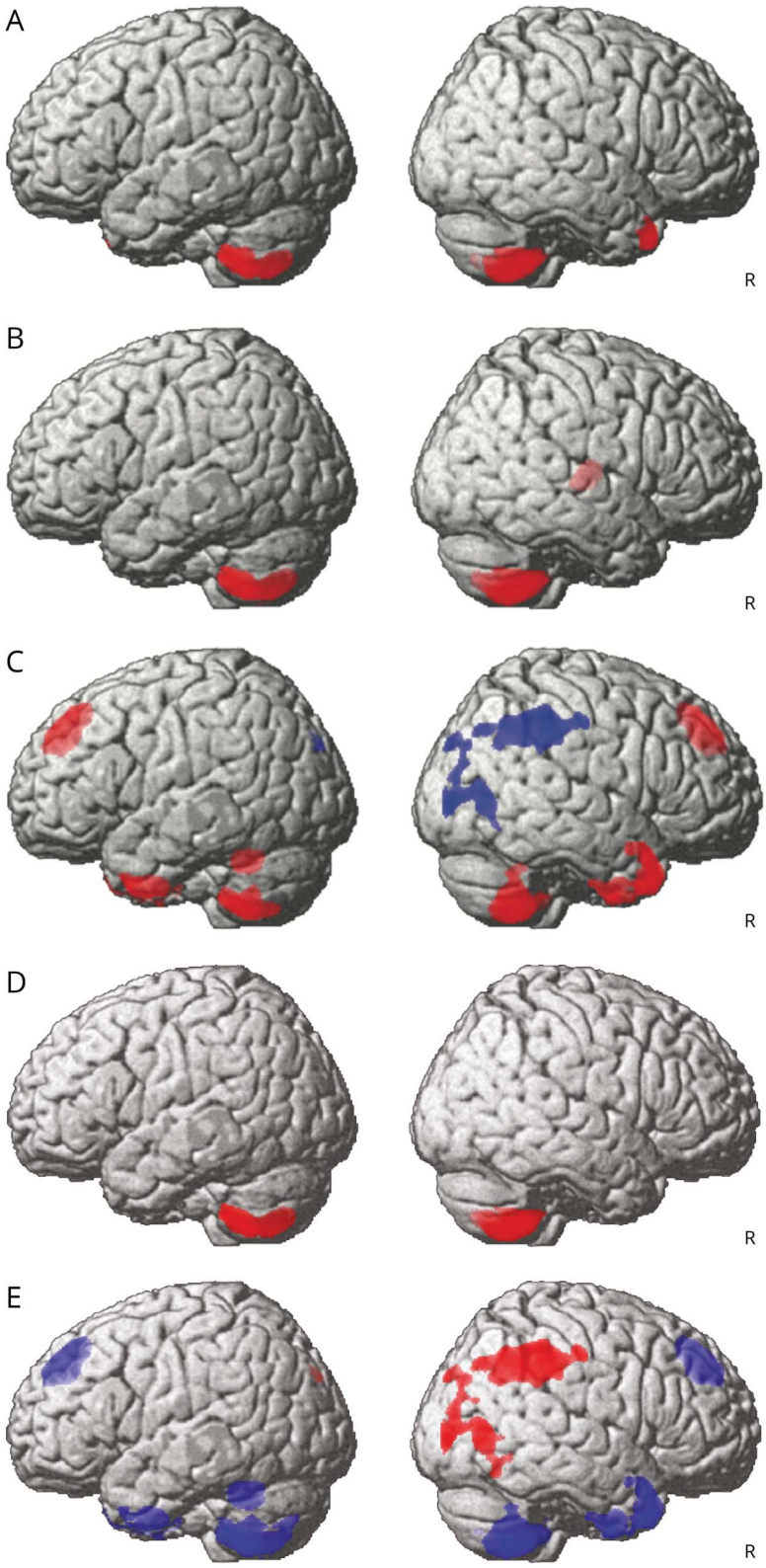
(A and B) Standardized effect estimates of interaction effects of physical activity dose (step counts and MET-hours) with age and sex for (A) larger brain volumes and (B) cortical thickness of predefined regions. (C and D) Standardized effect estimates of interaction effects of physical activity intensity (% moderate-to-vigorous [MVPA], %light-intensity and sedentary activities) with age and sex for (C) larger brain volumes, and (D) cortical thickness of predefined regions. ***$p \leq 0.001$ **$p \leq 0.01$ *$p \leq 0.05$ $p \leq 0.06$. MET = metabolic equivalents.

Findings from previous population studies were inconsistent regarding which brain structures are most affected by physical activity. In line with some previous studies, we observed a rise in the total gray, but not white, matter volume with increasing physical activity.[6,7,10] Specifically, we observed an increase in gray matter volume and density of motor regions including the precentral cortex and cerebellum with higher physical activity dose and across intensities. Animal studies also found angiogenesis, synaptogenesis, and neuronal growth in these motor regions in response to regular exercise.[3] Motor and cognitive skills have been proposed to be anatomically and functionally tightly linked.[42] However, whereas physical activity has been proposed to promote hippocampal neurogenesis,[4] studies examining the association between physical activity and hippocampal volume reported inconsistent findings.[8,10] Discrepancies may be attributable to examining dissimilar physical activity components and using different subjective and objective measurement instruments. In our study, we examined the relation between hippocampal volume and accelerometer-derived physical activity dose and intensity. We observed only a small increment in hippocampal volume with increasing relative time spent on moderate-to-vigorous intensity physical activities but not with increased light-intensity or reduced sedentary time. This parallels findings from exercise studies, which also did not detect major changes in hippocampal volume after exercise interventions.[43,44] Thus, although physical activity may particularly benefit both motor and cognitive regions, its effects on the latter are likely to be comparatively modest.

In contrast to previous population studies, we did not observe an effect of physical activity on total white matter volume.[5,8] A systematic review identified tentative evidence in favor of a small, positive association between physical activity and white matter.[13] Particularly, white matter microstructure has been suggested to be affected by physical activity.[13] A recent population-based study observed motor cortex and basal ganglia structural connectivity to be positively associated with physical activity.[45] Thus, the effects of physical activity on white matter microstructure may be largely confined to structural connectivity between regions involved in motor functions.

Thus far, region-specific effects of distinct physical activity components on cortical thickness had also received little scrutiny. In line with findings of Raffin et al.[12] (2021), we found physical activity levels to be associated with a modestly

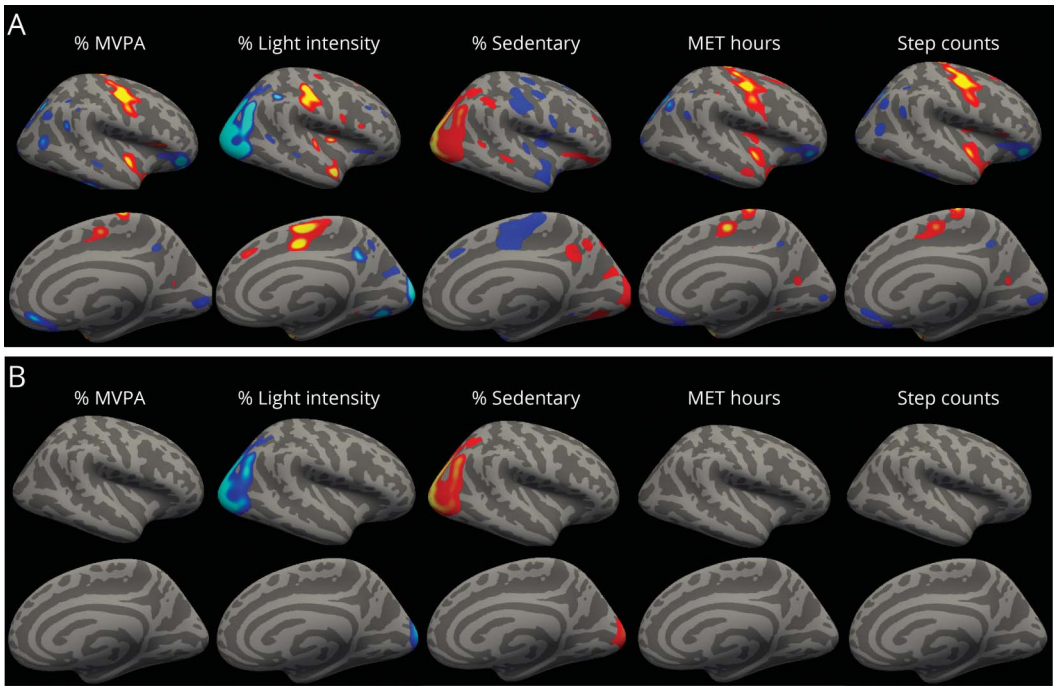
Figure 4 Physical Activity Effects on Gray Matter Density



(A–E) Effects of physical activity on gray matter density for (A) MET-hours, (B) step count, (C) % light-intensity physical activity, (D) % moderate-to-vigorous physical activity, and (E) % sedentary activity are rendered on a template brain using a height threshold of $p < 0.001$ uncorrected and extent threshold of >200 voxels. Positive corrections are depicted in red and negative correlations in blue. MET = metabolic equivalents.

thicker entorhinal cortex. Similarly, medial temporal lobe thickness has been found to be inversely associated with self-reported sedentary time.[46] It has been suggested that physical activity may protect against β-amyloid–associated thinning of regions, which are particularly affected in Alzheimer diseases.[47] It is of interest that we observed lateral occipital

Figure 5 Physical Activity Effects on Vertex-Based Cortical Thickness



(A and B) Effects of physical activity on vertex-based cortical thickness. (A) Cluster threshold–uncorrected results. (B) Cluster threshold results (cluster-forming threshold of $p \leq 0.05$, 1,000 iterations).

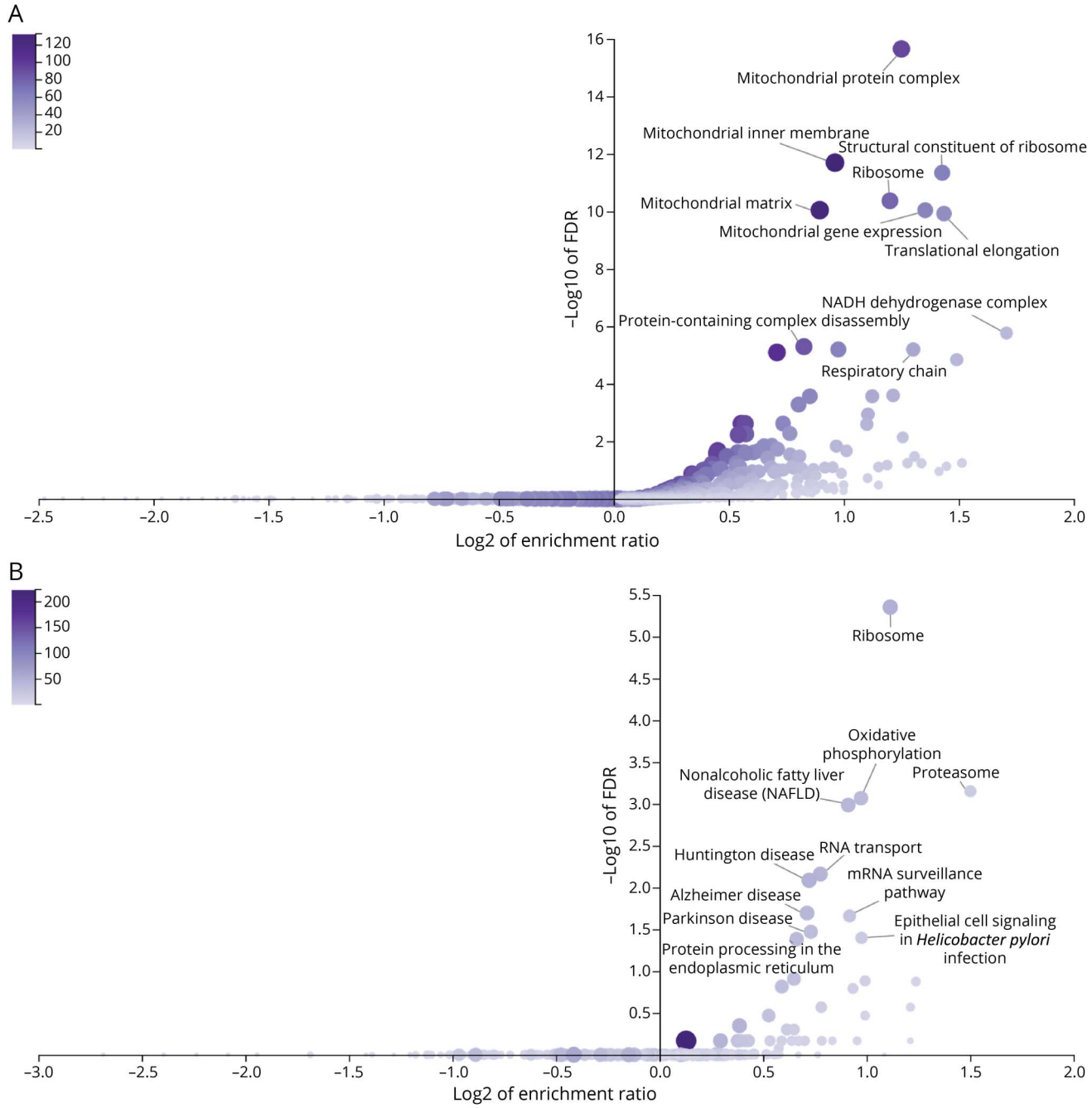
thickness to decrease with more light-intensity activity and to increase with more sedentary time. As the lateral occipital cortex is one of the major hubs for visual processing,[48] it could be speculated that longer sedentary time may be associated with relatively more engagement in visual activities and concomitantly, more stimulation of visual brain areas. Taken together, our findings suggest that the effects of physical activity are not uniformly distributed across the brain and by inference, may cause remodeling rather than an increase of overall brain tissue.

Both age and sex were found to influence the association of light-intensity physical activity and sedentary time with brain structure. The moderating effects of sex on the relation of physical activity and brain structure had not been assessed before, whereas some studies have examined the moderating effects of age.[8,10] In line with findings from the UK biobank and the Framingham Study, we observed the association between light-intensity physical activity and total brain volume to be strongest in our oldest participants (older than 70 years).[8,10] Similarly, the association of longer sedentary time with increasing amygdala volume and more light-intensity physical activities with lower amygdala volume became more pronounced with age. The amygdala is believed to play a key role in emotional processing and regulation, and its volume has been linked to anxiety levels. However, findings on whether the amygdala volume increases or decreases with higher anxiety levels have been inconsistent.[49,50] Physical activity has been proposed to have an anxiolytic effect by acting on the 5-HT_{2C}R receptor in the amygdala.[51] Accordingly, our findings suggest that the anxiolytic effect of physical activity may vary across age.

We also observed differences in the effects of light-intensity activity and sedentary time on cerebellar volume between men and women. Compared with women, in men, we observed a weaker association between additional light-intensity activities and greater cerebellar volume, but a stronger association between longer sedentary time and lower cerebellar volume. The cerebellum has been found to present a sexually dimorphic anatomy and functional asymmetry.[52] Little is known about the causal link between physical activity and cerebellar structure and function, and further research is warranted to establish whether the effect of physical activity on the cerebellum may differ between men and women.

The molecular changes induced in the human brain by physical activity have long eluded detection due to difficulties to extract molecular data from the brain in living individuals. We addressed this challenge by linking our vertex-wise estimates of the effects of physical activity to detailed gene expression data from the Allen Brain Atlas, which enabled the identification of a large number of genes whose spatial expression patterns correlated with those of physical activity. It is important that further in silico functional pathway analysis yielded several key insights: First, our findings indicate that the effects of physical activity are strongest in cortical regions with the highest expression levels of genes involved in

Figure 6 Functional Enrichment Analyses of Genes, Whose Expression Was Significantly Associated With Vertex-wise Effects of Physical Activity



(A) Volcano plot of -log(FDR) vs enrichment ratio of gene ontology terms related to cellular processes, functions, and components with the size and color of the dots proportional to the number of overlapping genes of that category; (B) Volcano plot of -log(FDR) vs enrichment ratio of KEGG pathways enriched in genes whose expression levels are associated with physical activity levels, with the size and color of the dots proportional to the number of overlapping genes of that category. FDR = false discovery rate.

mitochondrial structure and function. This finding closely parallels the central role of exercise-induced enhancement of mitochondrial function in skeletal muscles[53] and implies that brain regions with a comparatively high oxidative demand are likely to benefit most from physical activity. Indeed, blood flow to specific brain regions has been shown to increase by almost twofold in response to exercise.[3] Notably, these regions include the motor cortex and the cerebellum,[54] largely coinciding with regions that exhibited the strongest associations with physical activity in our study. Second, pathways previously associated with the Alzheimer and Parkinson disease, the 2 most common neurodegenerative diseases, and those associated with the Huntington disease, one of the most common genetically determined neurodegenerative diseases,

were enriched for genes whose expression patterns coincided with regional effects of physical activity on the brain. These findings further support the beneficial effects of physical exercise in the prevention and treatment of neurodegenerative diseases.[1,2] Last, we identified 2 potentially interesting compounds, phenethyl isothiocyanate and NADH, whose application may partly mimic the cortical gene expression changes induced by physical activity. Of these, it is noteworthy that supplementation with NAD(+) precursors has been proposed as a potential therapy for neurodegenerative diseases[55] and was shown to be highly effective in an Alzheimer disease mouse model.[56] Therefore, further experimental studies assessing the potential efficacy of these 2 compounds for maintaining or restoring brain health are warranted.

Several limitations of our study should be acknowledged. Our study was based on cross-sectional baseline data of a large population-based study, which did not allow the assessment of longitudinal associations. We did not assess the association between physical activity and cognitive and motor function, which could have provided more insights into the effects of physical activity on brain health. Owing to lack of more detailed information, we could not account for leisure-time exercise or the time of day of the MRI assessments. We also excluded participants who were ineligible for MRI scanning because of extreme obesity and who did not complete an accelerometer recording of at least 5 days. Recordings were made during regular activity weeks to ensure representativeness of overall activity patterns. Nonetheless, participants may have consciously or unconsciously adapted their physical activities. It also cannot be excluded that our findings may partly have been influenced by selection bias. Our participants were highly educated and comparatively physically active across all age groups. However, one could argue this may have led to an underestimation of the effects of physical activity on brain structure. Finally, for our in silico functional pathway analysis, we used data from the AHBA, which is based on genetic expression data of a limited number of donors.

In summary, we provide a detailed characterization of the effects of physical activity on brain morphology, indicating that physical activity is particularly beneficial to brain regions involved in motor functions. It is of importance that we found increases across all physical activity modalities to be associated with larger brain volumes, gray matter density, and cortical thickness. The strongest associations between physical activity and brain volumes were observed for additional time spent in moderate-to-vigorous activities and reduced sedentary time. However, in older adults, the association between light-intensity activities and brain volumes was comparatively stronger. Our findings thus indicate that whereas in young and middle-aged adults, brain health may particularly profit from additional high-intensity activities, additional light-intensity activities may be sufficient to maintain brain health in older adults. Overall, sedentary behavior was associated with worse structural markers of brain health and should be reduced across all age groups. Therefore, in line with the new World Health Organization guideline slogan "every move counts,"[57] our findings suggest that incorporating even small increments of additional movement into everyday life is likely to benefit brain health and aid in the prevention of neurodegenerative diseases.

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Continued

Appendix *(continued)*

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