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Association of objectively measured physical activity with brain structure: UK Biobank study

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Short title: Physical activity and brain health

Abstract

Background: Physical activity may be beneficial for cognition but mechanisms are unclear. We examined the association between objectively assessed physical activity and brain volume, with a focus on the hippocampus region.

Methods: We used data from UK Biobank (n=5,272 ; aged 55.4±7.5 yrs; 45.6% men) collected through 2013-2016. Participants wore the Axivity AX3 wrist-worn triaxial accelerometer for seven days to assess habitual physical activity. Structural magnetic resonance imaging was performed using a standard Siemens Skyra 3T running VD13A SP4 to obtain images of the brain.

Results: There was an association between physical activity (per SD increase) and grey matter volume after adjustment for a range of covariates, although this association was only detected in older adults (>60 yrs old). We also observed associations of physical activity with both left (B=0.52, 95% CI, 0.01, 1.03; p=0.046) and right hippocampal volume (B=0.59, 95% CI, 0.08, 1.10; p=0.024) in covariate adjusted models.

Conclusion: In summary, physical activity may play a role in the prevention of neurodegenerative diseases.

Keywords: Physical activity; neurodegeneration; hippocampus; population

Introduction

With treatments for dementia and cognitive impairment elusive, there is a parallel interest in prevention via modifiable risk factors. Position statements and systematic reviews of the literature have suggested a role for selected nutritional factors, cigarette smoking, certain somatic medical conditions and cognitive training, although the evidence base, while voluminous, is inconclusive. Given its cardioprotective properties, and an apparent vascular origin for cognitive decline and dementia, there is also interest in the potential role of physical activity [1-4]. Meta-analyses of cohort studies have demonstrated favourable associations between physical activity and cognitive outcomes [2,3]. The mechanisms underlying these relationships are, however, uncertain.

Hippocampal atrophy may be particularly relevant in relation to Alzheimer's disease [5], and several studies have demonstrated positive associations between physical activity, fitness and brain volume (grey and white matter) [6-13]. The existing studies are, however, small in scale (sample size range: 90 to 691 people). While offering imprecise results, small scale studies also fail to facilitate an examination according to important sub-groups such gender and age. It is also the case that in mechanistically-orientated studies of activity and cognition or dementia most [8-11], but not all [12,13], have relied on assessments of self-reported physical activity which are subject to measurement error.

Accordingly, the aim of this study was to examine associations between objective physical activity and brain structure using data from a large scale population imaging study of over 5,000 adults. We hypothesized an association between physical activity and greater brain volume, particularly in the hippocampus region. We hypothesized stronger associations in older adults where atrophy is more advanced.

Methods

Participants

We used data from UK Biobank consisting of participants aged 40–69 years when recruited in 2006–2010 [14]. Ethical approval was provided by the NHS National Research Ethics Service (Ref 11/NW/0382).

Physical activity assessment

Participants who had provided a valid email address were sent an invitation to wear an accelerometer for seven days. The participant email addresses were chosen randomly. From June 2013, participants were sent devices (the Axivity AX3 wrist-worn triaxial accelerometer) in order of acceptance. Details on the accelerometer protocol including data extraction and processing have been described elsewhere [15]. In brief, the accelerometers were programmed to start at 10am two working days after postal dispatch, and capture triaxial acceleration data over a seven day period at 100Hz with a dynamic range of +-8g. Participants were instructed to wear the device continuously and carry on with their normal activities. Physical activity was denoted as mean acceleration vector magnitude, representing overall activity as a continuous variable.

Structural Magnetic Resonance Imaging

In 2014, UK Biobank began inviting back 100,000 of the original volunteers for brain, heart and body imaging. Imaging data for 10,000 volunteers scanned between 2014-16 has

already been processed, which is utilised in the present analyses. Total grey and white volume were estimated using structural magnetic resonance (MR) imaging. The MR imaging protocols have been described in detail elsewhere [16]. In brief, the study used a standard Siemens Skyra 3T running VD13A SP4 with a standard Siemens 32-channel RF receive head coil. For each scan, the field-of-view was automatically determined based on Siemens' auto-align software, which aligns a scout scan to an atlas. In the infrequent situation where auto-align failed, alignment was set by the radiographer. Structural images were acquired using straight sagittal orientation (i.e., with the field-of-view aligned to the scanner axes), with resolution of 1x1x1 mm, field-of-view, 208x256x256 matrix, over a duration of 5 minutes, with 1 mm isotropic resolution using a 3D MPRAGE acquisition. Full details on structural image segmentation and data normalization are provided elsewhere [17]. Data were processed using publicly available image processing tools, primarily taken from FSL (the FMRIB Software Library). Here we used the output of the standard biobank processing pipeline. All data were normalised for head size.

Covariates

During the clinic visit data were collected on age, sex, smoking history, frequency of alcohol intake (daily or almost daily, 1-2 times a week or monthly, never or almost never), education (college/degree; A-level; O-level; CSEs or equivalent; NVQ/HND or equivalent; other professional qualification; none), sleep duration (≤ 6; 7; 8; ≥9 hr per night), self-rated health (excellent; very good; good; fair; poor), and physician diagnosed cardiovascular diseases (including hypertension), major depression. Body weight was measured using electronic scales without shoes and in light clothing, and height was measured using a Stadiometer.

Body mass index (BMI) was calculated using the standard formula [weight (kilograms)/height (meters) squared].

Statistical analysis

We modelled the associations between physical activity (per SD increase) and brain structure (total grey and white volume) using multiple linear regression. We also specifically examined associations between physical activity and hippocampal volume. Beta coefficients were initially adjusted for age, sex, and accelerometer wear time (Model 1), then for confounders such as smoking, alcohol consumption, body mass index, sleep, education, and health indicators (Model 2). We examined effect modification by fitting interaction terms for age (three categories) and sex. Analyses were performed using SPSS Version 22, with statistical significance (p) <0.05.

Results

The analytical sample comprised 5,272 adults (aged 55.4±7.5 yrs; 45.6% men). Compliance was high: on average, participants wore the accelerometer device for 6.4 ±1.4 days. More active participants (highest tertile) were younger, less likely to smoke, more likely to be degree educated, reported better self-rated health and lower prevalence of cardiovascular diseases, and lower BMI (Table 1).

As illustrated in Table 2, covariates associated with grey matter volume included age, sex, smoking, alcohol and BMI. There was an association between physical activity and grey matter which was apparent after adjustment for age and sex, and persisted after covariates were added into the model (Table 2). Age significantly modified the association between physical activity and grey matter (Table S1); associations were evident in the older adults aged 60 − 69 [n=2,108] (p=0.028), but not in younger age groups (50 − 59 year olds, [n=1,656] p=0.12; 40 − 49 year olds,[n=1,508] p=0.29). There were no gender differences in the activity-grey matter relation.

We observed associations of physical activity with both left (B=0.52, 95% CI, 0.01, 1.03; p=0.046) and right hippocampal volume (B=0.59, 95% CI, 0.08, 1.10; p=0.024) in covariate adjusted models. We did not observe any associations between physical activity and total white matter (p=0.30).

Sensitivity analyses

We restricted all analyses to participants providing at least 3 days of accelerometry data (n= 5,027), as a minimum of 72 hours of wear was shown to be closely reflective (within 10%) of a complete seven day measure [15]. Results, however, remained unchanged. In a sub-sample of participants (n=1,828) data on 'fluid intelligence' (a task with thirteen logic/reasoning-type questions and a two-minute time limit), and prospective memory [18] were available. Since cognitive status may influence brain structure and the ability to participate in physical activity we adjusted the models for fluid intelligence and memory

although the association between physical activity and grey matter volume was largely unchanged (standardised β = 0.04, p=0.06).

We conducted exploratory analysis to examine associations between physical activity and volumes of other specific brain regions using partial correlations adjusted for age and sex (Table S2). Physical activity was associated with various regional brain volumes, and associations with the pallidum (β=0.030, p=0.03) and accumbens regions (β=0.037, p=0.006) were robust to further covariate adjustments (including smoking, alcohol, BMI, self-rated health, CVD, depression, sleep, education).

Discussion

The aim of the present analyses was to examine associations between objective physical activity and brain structure using data from a large, population-based imaging study. A key finding was an apparent link between physical activity and higher grey matter volume that was only evident in older (>60yr old) participants. We also observed associations of physical activity with both left and right hippocampal volumes, which may have particular relevance to neurodegenerative diseases such as Alzheimer's.

In previous small scale longitudinal studies, self-reported physical activity at baseline was associated with larger grey matter volume [9-11], larger white matter volume [10] and higher total brain volume [10,11] at follow up. In a study of 352 older adults (mean age 79.1 yrs) objectively assessed activity was associated with 5 year changes in grey and white matter volumes [12]. The present study builds on existing data by examining these

associations using objective physical activity measures in a much larger population sample. Our findings are consistent with existing evidence suggesting stronger associations between physical activity and grey matter than with white matter. Our findings relating to hippocampal volume are partly consistent with evidence from exercise trials showing positive effects on left hippocampal volume but not total volume [19].

The main strength of our study was the vastly superior sample size compared with other studies, giving us sufficiently greater statistical power to explore, for example, effect modification by age and sex. There are also limitations. Since this study was cross-sectional we cannot discount the possibility that greater grey matter beneficially drives physical activity behaviour as opposed to the hypothesized direction. Indeed, recent data has suggested cognitive decline may lead to reduced activity [20], although when we adjusted for fluid intelligence the association between physical activity and grey matter volume was largely unchanged. Physical activity and imaging data were not collected concurrently and there may be variation in the time lag between the two measures. Numerous biomedical data have been shown to correlate with brain derived variables in the UK Biobank study [16], although our analyses took a theory driven approach where covariates were selected on an *a priori* basis.

Conflict of interest
None declared.

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Table 1. Characteristics of sample according to level of physical activity (n=5,272)

Variable	Physical activity tertile based on mean acceleration data (mg)		
	Lower (≤24)	Middle (25 – 30)	Upper (≥31)
Age at examination, yrs (mean, SD)	57.1±7.4	55.7±7.4	53.4±7.3
Sex (%) Women Men	47.6 52.4	57.0 43.0	58.5 41.5
Education (% degree/college)	40.9	43.3	46.4
Smoking (%current)	7.1	5.7	4.9
Alcohol (%Daily)	24.0	22.4	20.0
Self-rated health (% excellent)	18.5	24.8	27.7
Sleep (hrs per night) 6 or less 7 8 9 or more	21.4 40.7 29.7 8.3	20.9 42.4 31.2 5.5	22.0 45.3 28.3 4.4
Doctor diagnosed cardiovascular disease	29.4	22.4	16.5
Major depression	2.6	2.8	2.6
Body mass index	28.0±4.8	26.5±4.0	25.3±3.7

Whole brain Grey matter	784419± 49095	795720± 47075	805730± 46614
Whole brain White matter	708171± 41434	709695± 47075	714103± 42079

Table 2. Association between physical activity and grey matter volume (n=5,272)

	Model 1 Standardized coefficient β (p-value)	Model 2 Standardized coefficient β (p-value)
Objective Physical activity (per SD of acceleration)	0.05 (<0.001)	0.03 (0.01)
Age (per unit)	-0.55 (<0.001)	-0.54 (<0.001)
Sex (women=1; men=2)	-0.30 (<0.001)	-0.28 (<0.001)
Smoking (never=1; ex-smoker=2; smoker=3)		-0.05 (0.001)
Alcohol (ranging from, daily = 1 through to never =5)		0.05 (0.001)
Self rated health (ranging from excellent=1 through to poor = 4)		-0.01 (0.46)
Doctor diagnosed CVD (none=1; heart disease=2; hypertension =3)		-0.01 (0.33)
Body mass index		-0.09 (<0.001)
Major depression (none=1; yes=2)		0.007 (0.48)
Sleep		0.02 (0.08)
Education (ranging from degree=1 through to none		0.006 (0.59)

=7)		

Model 1; adjusted for age, sex, and accelerometer wear time.

Model 2; mutually adjusted for all variables presented.