NeuroImage 221 (2020) 117150

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Objectively measured physical activity is associated with dorsolateral prefrontal cortex volume in older adults

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ARTICLE INFO

Keywords:
SenseWear armband
hippocampus
Gray matter
Cognition

ABSTRACT

Background: Epidemiological studies suggest physical activity (PA) can slow or prevent both cognitive decline and age-related atrophy in frontal and hippocampal gray matter volumes. However, much of this evidence is based on self-reported measures of PA.

Methods: PA was measured objectively with a SenseWear™ Armband to examine the cross-sectional associations between the duration of light, moderate and vigorous intensity PA with gray matter volume in the dorsolateral prefrontal cortex (DLPFC) and hippocampus in 167 (female: 43%) cognitively healthy older adults aged 73 to 78.

Results: The duration of objective moderate to vigorous intensity physical activity (MVPA) was associated with a greater volume of the right DLPFC ($\beta = 0.16$; $p = 0.04$). In addition, objective moderate-intensity PA alone was also associated with greater volume of the left ($\beta = 0.17$; $p = 0.03$) and right ($\beta = 0.19$; $p = 0.01$) DLPFC after controlling for covariates and adjustment for multiple comparisons. In contrast, there were no significant associations between light- or vigorous-intensity PA and gray matter volumes (all $p > 0.05$). No associations between PA and cognitive performance were detected, and self-reported PA was not associated with any of the outcomes investigated.

Conclusions: These findings suggest that an intensity-dependent relationship may exist, whereby a greater duration of MVPA, perhaps driven by moderate-intensity PA, is associated with preserved gray matter volume in frontal regions of the brain. Future research should investigate the mechanisms of this dose-effect and determine whether greater brain volumes associated with objective PA convey protective effects against cognitive decline.

1. Introduction

Older age is associated with a progressive decline in cognitive function, which increases the risk of neurological diseases such as dementia and impacts on quality of life. Age-related cognitive decline is attributable, in part, to gray matter atrophy, which occurs earlier and progresses faster in the dorsolateral prefrontal cortex (DLPFC) and hippocampal regions of the brain (Raz et al., 2005; Fraser et al., 2015; Gunning-Dixon and Raz, 2003). However, significant inter-individual variability has been extensively reported (Raz et al., 2005) and this has led to the hypothesis that differences in brain ageing trajectories might be due to different exposure to risk factors across individuals. This, in turn, has prompted a greater investigation of modifiable lifestyle factors which may promote healthy brain ageing. Physical activity (PA), in particular, has received widespread attention due to its apparent protective effects for brain and cognitive health (Northey et al., 2018; Erickson et al., 2014).

Although the DLPFC and hippocampus are prone to age-related atrophy, there is also evidence to show these regions are particularly sensitive to PA. Much of this evidence comes from studies of aerobic fitness (Erickson et al., 2009; Weinstein et al., 2012) or epidemiological studies which utilise self-report measures of PA (Benedict et al., 2013; Bugg and Head, 2011; Erickson et al., 2010; Head et al., 2012; Kooistra et al., 2014; Floel et al., 2010). The DLPFC and hippocampus have both been

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https://doi.org/10.1016/j.neuroimage.2020.117150
Received 8 April 2020; Received in revised form 12 June 2020; Accepted 4 July 2020
Available online 12 July 2020

demonstrated to mediate the relationship between aerobic fitness and cognitive function (Erickson et al., 2009; Weinstein et al., 2012). While this demonstrates that greater fitness, and presumably higher physical activity levels, are associated with less age-related cognitive decline, it does not provide information on the quantity or intensity of physical activity which is required to inform population-based guidelines. Although generally supportive of a link between PA and gray matter volume, questionnaire-based measures are also limited in that they often have questionable validity compared to PA measured objectively with an activity monitor (Northey et al., 2019). To address the limitations of self-report measures of PA, recent studies have incorporated accelerometers to record the dose of PA objectively (Alosco et al., 2015; Arnardottir et al., 2016; Halloway et al., 2018; Varma et al., 2016). In these studies, total daily activity, usually calculated as the total number of steps, is associated with greater subcortical gray matter volume (Alosco et al., 2015; Halloway et al., 2018; Varma et al., 2016) and total gray matter (Arnardottir et al., 2016; Halloway et al., 2018). However, to date little is known of the association between objectively measured PA and the DLPFC (Weinstein et al., 2012).

Another important research gap is the lack of evidence on the most appropriate intensity of PA which may promote brain health and protect against neurodegeneration. Only a small number of epidemiological studies with objective measures have examined the association between PA intensity and gray matter volume and have provided mixed findings. In one study of cognitively healthy older adults, a greater number of steps at low intensity was associated with greater hippocampal volume, but this relationship was not present for moderate to vigorous intensity PA (MVPA) (Varma et al., 2015). In comparison, in older adults with mild cognitive impairment, more time spent at moderate intensity, but not light intensity or total PA, has been associated with greater hippocampal volume (Makizako et al., 2014). Meanwhile, initial intervention studies have shown increased volume in the hippocampus and DLPFC following moderate-intensity aerobic exercise (Colcombe et al., 2006; Erickson et al., 2011), although other intensities have not been investigated. These contradictory findings are problematic and prevent practitioners and policymakers from providing robust, evidence-based recommendations for healthy brain ageing.

To address these questions, the current study investigated the associations between the duration of PA at light, moderate and vigorous intensities, measured objectively, and brain health through volumetric analyses of the DLPFC and hippocampus. These regions of interest (ROI) were selected a priori based on their implication in age-related cognitive decline and memory loss (Raz et al., 2005; Gunning-Dixon and Raz, 2003), as well as their apparent sensitivity to PA interventions (Colcombe et al., 2006; Erickson et al., 2011) and aerobic fitness (Erickson et al., 2009; Weinstein et al., 2012). Secondly, we examined the relationship between PA and cognitive performance in tasks assessing executive function, processing speed, working memory and episodic memory. These cognitive processes were selected because their performance is supported by the DLPFC and hippocampus (Gunning-Dixon and Raz, 2003; Head et al., 2008). Thirdly, we investigated whether the relationship between PA and brain differed when PA was measured by self-report.

2. Methods

2.1. Study population

Participants were sampled from the magnetic resonance imaging (MRI) sub-study (Cherbuin et al., 2015) of the Personality and Total Health through life (PATH) project, which is described in detail elsewhere (Anstey et al., 2012). Briefly, two thousand five hundred and fifty-one participants were enrolled at baseline (the year 2001) into the older (60–64 years at baseline) PATH study cohort. Of those, 622 randomly selected participants were offered, and 478 eventually underwent a structural MRI scan. At the fourth assessment (12 years after baseline), 275 participants underwent a repeat MRI scan and were offered to participate in a cross-sectional sub-study examining the cognitive, PA, and diet habits of older adults (Northey et al., 2019). Of those participants, 184 participants accepted and completed the PA component of the sub-study. After exclusion of participants with MRI images of poor quality or who wore a SenseWear™ Armband (SWA; BodyMedia, PA, USA) for less than five valid days (>20 h on-body time), or with a history of neurological disorders (stroke, Parkinson's disease, epilepsy or dementia), Mini-Mental State Examination score $\leq$25, or without valid FreeSurfer data (n = 10) were excluded, leaving 167 participants available for inclusion. The final study sample did not differ from the larger PATH study cohort in terms of age and sex, but had completed more years of education (14.2 vs 13.7 years; p = 0.01). The study was approved by the Australian National University Human Research Ethics Committee and participants provided written informed consent.

2.2. Objective physical activity

Participants were fitted with a SWA on the day of their MRI scan and wore it over the triceps muscle of their left arm for a continuous seven-day period to objectively record PA. The SWA incorporates a tri-axial accelerometer with galvanic skin response, skin temperature, near-body ambient temperature, and heat flux to noninvasively measure PA (Liden et al., 2002) with greater accuracy than accelerometry alone (Welk et al., 2007). The SWA was set to record data at 1-min intervals and was only removed during water submersion. Data from the SWA were downloaded to the proprietary software (SenseWear™ Professional version 8.0, BodyMedia, PA) where energy expenditure was calculated (Liden et al., 2002). Subsequently, every minute-by-minute data point across the week was coded by its intensity using metabolic equivalents (METs). METs provide a standardised measure of PA intensity relative to an individual's resting energy expenditure.

Five outcomes were calculated from the weekly SWA data. Weekly totals (mins·week^{-1}) were computed for time spent in light (1.5–2.99 METs), moderate (3.00–5.99 METs), and vigorous (6.00 or greater METs) intensity PA (Berntsen et al., 2010). As moderate to vigorous intensity PA (MVPA) is commonly recommended in population guidelines, the time spent engaging in moderate and vigorous intensity PA was also calculated. To create an overall metric of PA that accounts for relative intensity, MET-values $\geq$ 1.5 were summed across the 7-day period (Total PA; MET:mins·week^{-1}).

2.3. Self-report physical activity

Prior to the MRI scan, participants were asked to report time in the past week engaging in PA of light, moderate and vigorous intensity as part of the standard PATH questionnaire. This questionnaire has been used in several studies investigating the relationship between PA and brain health (Lamont et al., 2014). Each question asked the participants to report the time spent on average undertaking PA at intensity levels comparable to activities or sports (Northey et al., 2019). The three questions provided examples of common activities and sports for light (e.g. walking), moderate (e.g. dancing) and vigorous (e.g. running) intensities.

Weekly totals were calculated for time spent in light, moderate, and vigorous PA, as well as MVPA. Additionally, Total PA was calculated with the formula MET:mins·week^{-1} = light mins·week^{-1} + (2 x moderate mins·week^{-1}) + (3 x vigorous mins·week^{-1}) in accordance with previous research with this questionnaire (Northey et al., 2019; Lamont et al., 2014). As such, the same five PA outcomes were available for both the objective and self-report measures of PA.

2.4. MRI data acquisition

Participants were scanned on a Siemens 1.5T Espree scanner (Siemens Medical solutions) for T1-weighted 3-dimensional structural

MRI. The T1-weighted MRI was acquired in sagittal orientation using an MPRAGE sequence with repetition time, echo time, flip angle and slice thickness equal to 1160 ms/4.24 ms/15° and 1 mm, respectively, with matrix size 512 × 512 for a final voxel size of 1 × 0.5 × 0.5 mm (Shaw et al., 2017).

2.5. Image processing

Image processing, which included intensity and inhomogeneity correction, skull stripping, tissue segmentation, and parcellation according to the FreeSurfer atlas (Desikan et al., 2006) was carried out using the FreeSurfer 5.3 (Fischl, 2012) cross-sectional pipeline, including automated segmentation and parcellation to delineate ROI and estimation of cortical surfaces and cortical thickness for each participant. Processing quality control was implemented via an in-house script that identified outliers based on total gray and white matter volumes. Potential outliers were visually checked, and those that had failed FreeSurfer processing were removed from the analysis.

2.6. Regions of interest

In the current study, total brain volume and regional volumes of the DLPFC and hippocampus were selected a priori for analysis in accordance with the aims of the study due to their sensitivity to physical activity interventions (Colcombe et al., 2006; Erickson et al., 2011) and role in mediating the relationship between aerobic fitness and cognitive function (Erickson et al., 2009; Weinstein et al., 2012; Das et al., 2017). DLPFC volume was computed by summing the volume of the superior frontal, rostral mid-frontal and caudal mid-frontal gyri (Das et al., 2017).

2.7. Cognitive assessment

Executive function and processing speed were assessed using the Symbol Digit Modalities Test (SDMT) (Smith, 1982) and the Trail Making Test Part B (TMT-B) (Reitan and Wolfson, 1985). Processing speed was independently assessed using the Trail Making Test Part A (TMT-A) (Reitan and Wolfson, 1985). Verbal working memory was assessed using the Digits-Span Backwards Task, a sub-test of the Weschler memory scale (Wechsler, 1945). Episodic memory was assessed with the first list of the California Verbal Learning Test for both immediate and delayed recall (Delis et al., 1988). For the cognitive assessments, a higher score indicates better performance, except for the TMT-A and TMT-B where a higher score reflects poorer performance.

2.8. Health and sociodemographic covariates

Total years of education, smoking, alcohol consumption and depressive symptoms were assessed by self-report. Alcohol consumption was estimated with the Alcohol Use Disorders Identification Test (Saunders et al., 1993). For men, weekly alcohol consumption was categorised as light (1–13 units), moderate (14–27 units), hazardous (28–42 units), or harmful (>42 units). For women, weekly alcohol consumption was categorised as light (1–7 units), moderate (8–13 units), hazardous (14–28 units), or harmful (>28 units). One unit is equal to 10 g of pure alcohol. Depressive symptomatology was assessed with the Goldberg Depression and Anxiety Scale (Goldberg et al., 1988). Brachial blood pressure was measured twice in a seated position after resting for at least 5 min. Participants were classified as hypertensive if they had an average systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or were on anti-hypertensive medication. Participants were considered to have diabetes if they reported having diabetes or were receiving drug treatment or consuming a special diet for diabetes, or if their fasting glucose plasma level was ≥10 mmol/L (Cherbuin et al., 2012). Body mass index was computed using the formula weight in kilograms divided by height in meters squared, where height and weight were measured by a trained anthropometrist. APOE*E4 genotype was determined from DNA collected by cheek swab.

Table 1
Demographic and health characteristics of the study population.

Characteristics	All (n = 167)	Men (n = 95)	Female (n = 72)	*P* value for men vs. women
Age, y (SD)	75.1 (1.3)	75.1 (1.4)	75.0 (1.3)	0.61[a]
Range	73–78	73–78	73–78	
BMI, kg·m^2 (SD)	27.9 (4.3)	28.3 (4.6)	27.3 (3.9)	0.12[a]
Education, years (SD)	14.4 (2.6)	15.0 (2.4)	13.6 (2.7)	0.001[a]
Ever smoker, n (%)	75 (44.9%)	48 (50.5%)	27 (37.5%)	0.13[b]
MMSE, score (SD)	29.2 (1.1)	29.0 (1.2)	29.3 (0.9)	0.08[a]
Hypertension, n (%)	127 (76.1%)	71 (74.7%)	56 (77.8%)	0.79[b]
Alcohol intake, n (%)				<0.01[b]
Abstain/ occasional	54 (32.3)	22 (23.2)	32 (44.4)	
Light/moderate	107 (64.1)	69 (72.6)	38 (52.8)	
Hazardous/ harmful	6 (3.6)	4 (4.2)	2 (2.8)	
Diabetes, n (%)	26 (15.6%)	17 (17.9%)	9 (12.5%)	0.46[b]
APO*E4 carrier, n (%)	50 (29.9%)	30 (31.6%)	20 (27.8%)	0.72[b]
Objective physical activity, mins·wk^{-1} (SD)				
Light, mins·wk^{-1} (SD)	1550 (584)	1593 (510)	1493 (668)	0.29[a]
Moderate, mins·wk^{-1} (SD)	370 (301)	448 (293)	268 (283)	<0.001[a]
Vigorous, mins·wk^{-1} (SD)	39 (78)	45 (82)	30 (72)	0.20[a]
MVPA, mins·wk^{-1} (SD)	409 (352)	493 (336)	298 (344)	<0.001[a]
Total PA, MET:mins·wk^{-1} (SD)	4447 (2292)	4939 (2165)	3797 (2307)	0.001[a]
Region of interest, mm^3 (SD)				
L DLPFC	37,629 (4239)	39,404 (4029)	35,287 (3277)	<0.001[a]
R DLPFC	37,024 (4206)	38,726 (4088)	34,779 (3200)	<0.001[a]
L hippocampus	3854 (413)	3895 (455)	3801 (347)	0.13[a]
R hippocampus	3820 (396)	3838 (420)	3796 (364)	0.49[a]
Total brain volume	1,119,249 (118,125)	1,178,197 (109,559)	1,041,470 (771, 22)	<0.001[a]
Cognitive performance, SD				
SDMT, score	47.3 (8.4)	47.6 (8.2)	47.0 (8.6)	0.67[a]
TMT-B, sec	92.2 (42.5)	84.6 (29.7)	102.3 (53.6)	0.01[a]
TMT-A, sec	37.0 (15.6)	36.5 (10.4)	37.6 (20.6)	0.69[a]
Digit backwards, words	5.1 (2.1)	5.4 (2.1)	4.7 (2.0)	0.03[a]
Immediate recall, words	5.4 (1.9)	5.1 (1.6)	5.8 (2.1)	0.03[a]
Delayed recall, words	7.6 (3.2)	7.2 (2.9)	8.1 (3.5)	0.08[a]

Notes: All region of interest volumes are corrected for intracranial volume.
Abbreviations: BMI, body mass index; MMSE, Mini-mental state examination; MVPA, moderate to vigorous physical activity; L, left; R, right; DLPFC: dorsolateral pre-frontal cortex; SDMT, Symbol Digits Modalities Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B.
[a] t test.
[b] X^2 test.

2.9. Statistical analysis

Statistical analysis was conducted with R version 3.4.2 (R Core Team, 2013). Means and standard deviations were calculated for age, sociodemographic and health, PA, brain volume, and cognitive performance variables. Students *t*-tests for continuous and X^2 tests for categorical data were conducted to compare groups. The association between PA and ROI or cognitive function were examined with general linear models. In each model, the dependent variable was ROI or cognitive performance and the

Table 2
Multiple linear regression of brain volume on objectively measured moderate-intensity physical activity.

	L DLPFC			R DLPFC			Total brain volume		
Predictors	b (SE)	β	P^*	b (SE)	β	P^*	b (SE)	β	P^*
Age	−237.6 (213.7)	−0.08	0.26	−206.5 (212.5)	−0.07	0.33	−4303.2 (5470.8)	−0.05	0.43
Sex[a]	−3528.3 (617.0)	−0.83	<0.01	−3242.7 (613.7)	−0.77	<0.01	−115432.1 (15796.8)	−0.98	<0.01
Education	143.7 (106.1)	0.09	0.22	184.4 (105.6)	0.12	0.17	5912.5 (2717.2)	0.14	0.03
Moderate intensity PA	**2.4 (1.0)**	**0.17**	**0.03**	**2.7 (1.0)**	**0.19**	**0.01**	**77.4 (25.3)**	**0.20**	**<0.01**
R^2	0.27			0.27			0.37		

b: unstandardised regression coefficient; β: standardised regression coefficient; DLPFC: dorsolateral pre-frontal cortex; PA: physical activity.
*adjusted p-values.
[a] Compared to male sex.

independent variable was PA with age, sex and education included as covariates. Both age and education were mean centred. ROI volumes were adjusted for ICV using the residual method (adjusted volume = raw volume – *b* x [ICV – mean ICV]; where *b* is the slope of regressing an ROI volume on ICV) (Pintzka et al., 2015; Sanfilipo et al., 2004). Initially, the interaction between PA and the covariates was included, and non-significant terms were dropped from the final model's for ease of interpretation. Additionally, non-linear relationships were investigated by separately adding a quadratic and cubic term for PA in each model. The normality of residuals was tested via visual inspection of Q-Q plots. To reduce the risk of Type-I errors associated with multiple comparisons, p-values from the general linear models underwent a Simes-Benjamini-Hochberg false discovery rate adjustment (Benjamini and Hochberg, 1995). Statistical significance was accepted at adjusted $p < 0.05$.

2.10. Exploratory analysis of cortical thickness

An exploratory investigation of the relationship between objective physical activity and cortical thickness was conducted. The cortical thickness data for all participants were resampled into a common space, and surface-based smoothing was applied (10-mm FWHM). Then, general linear model analyses of the cross-sectional association between physical activity and surface-based thickness measurements were performed separately for each hemisphere using FreeSurfer mri-GLMFIT. As with the volumetric analysis, the model was controlled for the confounding effects of age, sex, education and ICV. False Discovery Rate (FDR) was applied at the 0.05 level to correct for Type-I errors.

3. Results

The demographic and health characteristics of the study sample are presented in Table 1.

3.1. Associations between ROI, cognitive function and objective PA

There were significant positive associations for objective moderate-intensity PA with the left and right DLPFC and total brain volume (Table 2 and Fig. 1). Greater objective MVPA was positively associated with the right DLPFC and total brain volume, although the regression coefficient for PA was reduced compared to the model with moderate PA alone (Table 3 and Fig. 2). However, there were no significant relationships between light-intensity PA, vigorous-intensity PA, or Total PA and brain volumes, and neither the left or right hippocampus was associated with any PA variables. The duration of objective PA was not associated with cognitive function, regardless of intensity (all $p > 0.05$; see supplementary material eTable 1). For all models, there were no significant interaction effects between PA and the covariates and no evidence of non-linear relationships. A sensitivity analysis including all of the demographic and health variables reported in Table 1 produced the same results for objective PA, however, the association between MVPA and total brain volume was no longer significant (see supplementary material eTable 2 and eTable 3).

3.2. Associations between ROI, cognitive function and self-report PA

Self-report PA was not associated with any of the brain regions of interest or cognitive performance variables investigated here (see supplementary material eTable 4 and eTable 5).

3.3. Exploratory analyses of cortical thickness

Analysis of objectively measured moderate-intensity PA controlling for age, sex, education and ICV did not identify any statistically significant results after FDR adjustment for multiple comparisons (FDR < 0.05). Prior to adjustment, both moderate-intensity PA and MVPA were associated ($p < 0.05$) with greater cortical thickness in several regions (see Fig. 3).

4. Discussion

The key finding of this study is that greater duration of objectively measured MVPA, and particularly moderate-intensity PA, is associated with greater gray matter volume within the DLPFC and total brain volume. However, neither light nor vigorous-intensity PA showed the same relationships with brain volume. While previous studies have investigated the relationship between PA and gray matter volume, we are not aware of any previous investigation of the association between objectively measured PA intensity and DLPFC volume in older adults. Although MVPA and moderate-intensity PA was associated with brain volume, objective PA was not associated with cognitive performance in this study sample, which is consistent with previous findings in the area. Finally, we found no associations between the self-report measure of PA and any of the outcome measures investigated here, highlighting the potential importance of integrating robust measures of PA into epidemiological research design.

While this study is unique in investigating the relationship between objectively measured PA intensity and the DLPFC, this brain region has previously been shown to increase in volume following a moderate-intensity aerobic exercise intervention (Colcombe et al., 2006), as well as mediate the relationship between aerobic fitness and cognitive function (Weinstein et al., 2012). The current study adds to these findings by demonstrating an association between MVPA, and particularly moderate-intensity PA, with the DLPFC, but not for light or vigorous intensity PA. This finding suggests that the significant associations found for MVPA might be largely attributable to moderate-intensity PA, rather than any additional benefits from obtaining vigorous-intensity PA. However, it is also possible that there was insufficient variability in vigorous PA with relatively few participants reporting extensive activity in this range.

The observed PA intensity dose-effect is not unexpected. Indeed, low-intensity PA does not increase circulating levels of brain-derived neurotrophic factor (BDNF) (Nofuji et al., 2012), whereas moderate and vigorous-intensity PA tend to show increases of a similar magnitude (Nofuji et al., 2012; Schmolesky et al., 2013). Cerebral blood flow also tends to display an inverted-U relationship with PA intensity, similar to

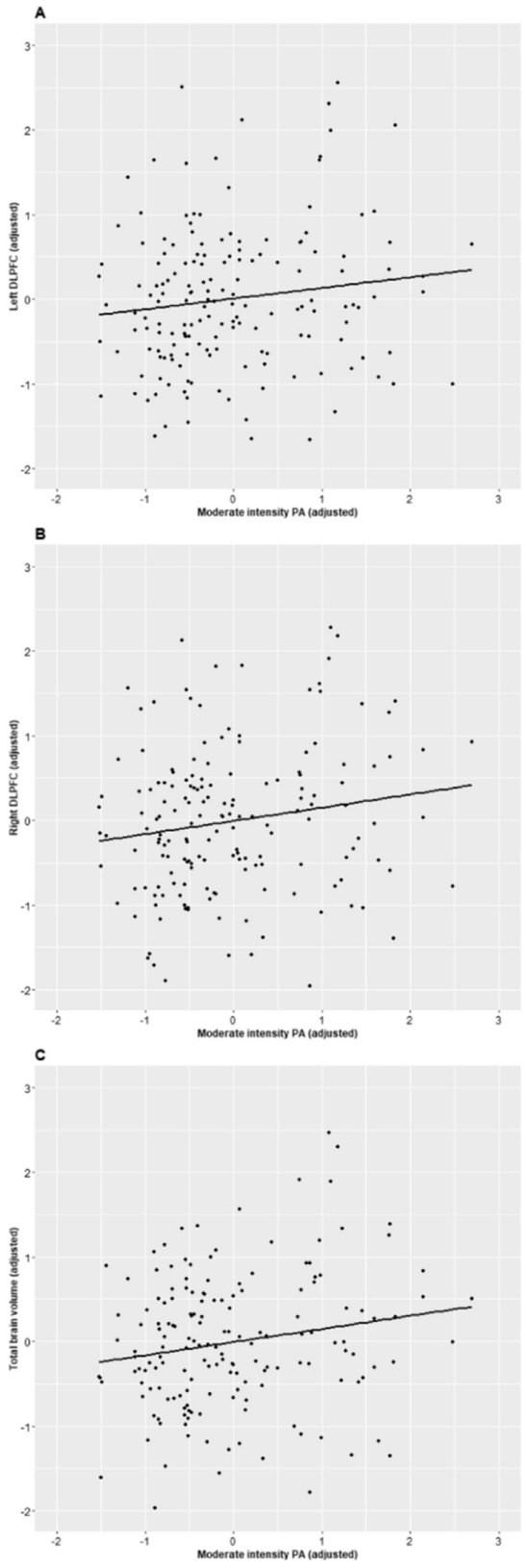

Fig. 1. Partial regression plots displaying the relationship between residuals of (Panel A) left dorsolateral prefrontal cortex (L DLPFC) (Panel B) right dorsolateral prefrontal cortex (R DLPFC) and (Panel C) total brain volume with the residuals of moderate intensity PA adjusting for the effects of age, sex and education.

Table 3
Multiple linear regression of brain volume on objectively measured moderate to vigorous intensity physical activity.

	R DLPFC			Total brain volume		
Predictors	b (SE)	β	P*	b (SE)	β	P*
Age	−217.5 (213.7)	−0.07	0.31	−4586.9 (5503.8)	−0.05	0.41
Sex	−3346.8 (613.7)	−0.80	<0.01	−118108.2 (15803.7)	−1.00	<0.01
Education	184.5 (106.2)	0.12	0.10	5921.2 (2735.7)	0.14	0.04
MVPA	**1.9 (0.8)**	**0.16**	**0.04**	**57.8 (21.7)**	**0.17**	**0.01**
R^2	0.26			0.38		

b: unstandardised regression coefficient; β: standardised regression coefficient; DLPFC: dorsolateral pre-frontal cortex; PA: physical activity.
*adjusted p-values.
compared to male sex.

the results for PA intensity on brain volumes observed in the current study. During PA cerebral blood flow increases from rest and peaks at an intensity corresponding to ~60% of maximal aerobic capacity, before declining towards resting values as the intensity exceeds ventilatory capacity, a physiological indicator commonly used to distinguish between moderate and vigorous intensity (Ogoh and Ainslie, 2009). Given that the mean duration of vigorous-intensity PA was quite low in this cohort, it may be that moderate-intensity PA causes a sufficient physiological response to stimulate mechanisms associated with brain health, whilst being accumulated for sufficient time to maximise exposure. Future research designed to investigate the relative contributions of both intensity and duration of PA to brain health is needed to better explain these effects.

Although PA was related to gray matter volume in the DLPFC, no associations with the hippocampus were identified. In contrast, Varma et al. found associations between PA and hippocampal volume in cognitively healthy older adults (Varma et al., 2015). Differences between the study populations may explain these conflicting findings. In comparison to Varma et al. (2015), the participants in the current study were substantially more active (408 vs ~48 min week^{-1} of MVPA) and had greater mean hippocampal volume and MMSE scores (see Table 1). These differences are relevant as the neurocognitive status of study participants seems to influence the strength of PA-hippocampal associations. For example, the relationship between aerobic fitness and hippocampal volume is stronger in early-Alzheimer's disease compared to cognitively healthy older adults (Burns et al., 2008), and Makizako et al. (2014) demonstrated associations with moderate intensity PA in older adults with mild cognitive impairment. Therefore, it is possible that any protective effects of PA on the hippocampus are more discernible after tissue loss has become prevalent which may have limited our ability to distinguish benefits in this relatively high-functioning cognitively healthy sample of older adults.

In this study, no relationships were identified between PA and cognitive function. Whilst this may again be related to the characteristics of the study sample, it may also be a limitation of the cross-sectional design of the study or the sensitivity of the cognitive performance tests to detect differences in non-clinical populations. Cross-sectional studies show both positive (Buchman et al., 2008) or no (Halloway et al., 2018) association between objectively measured PA and cognitive function. However, baseline PA tends to be positively related to longitudinal cognitive function and the risk of cognitive impairment (Erickson et al., 2010). As gray matter atrophy also tends to precede declines in cognitive performance, it may be that the beneficial effects of PA on the DLPFC observed here will translate into cognitive benefits in the future. Promisingly, total brain volume, a global marker of brain atrophy associated with neurological health and cognitive function (Lamont et al., 2014), was also related to MVPA and moderate-intensity PA. While improving precision through objective measures of PA is important, the same

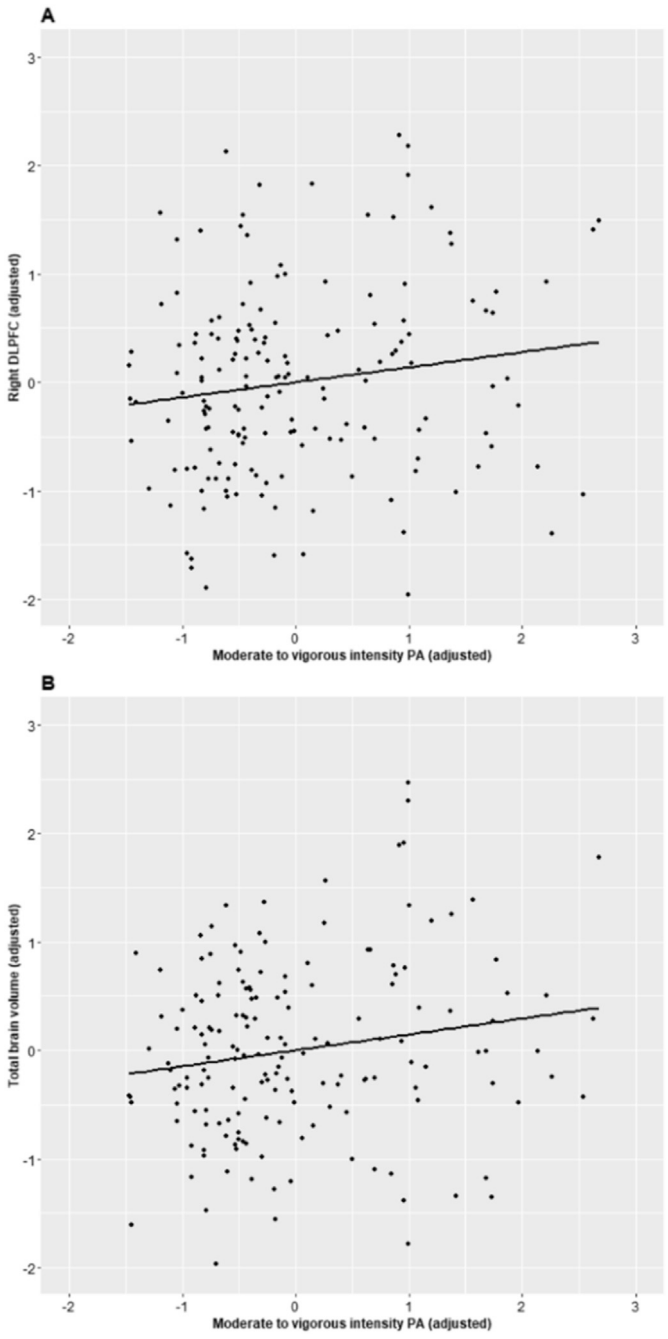

Fig. 2. Partial regression plots displaying the relationship between residuals of (Panel A) right dorsolateral prefrontal cortex (R DLPFC) and (Panel B) total brain volume with the residuals of moderate to vigorous intensity PA adjusting for the effects of age, sex and education.

consideration could also be applied to the testing of cognitive performance, particularly in non-clinical samples. It cannot be discounted that a lack of precision or ceiling effects in the traditional "pen-and-paper" assessments used here may have been a limiting factor. Although not without limitations, there are now computerised cognitive testing batteries which have good compariability to validated neurophyscological tests and may improve the sensitivity of measures in older adults (Zygouris and Tsolaki, 2015). As such, future research examining objectively measured PA intensity should include longitudinal follow-ups and could consider incorporating more sensitive computer-based cognitive testing to investigate these relationships.

A novel component of the current study was independently assessing the association of objective and self-reported PA with neurocognitive health. The validity of the self-report measure compared to an objective measure is acceptable and comparable to the available literature (Northey et al., 2019). However, the associations with brain health were exclusive to objectively measured PA. These differential findings are consistent with previous research showing stronger associations of objective versus self-reported PA for a range of health measures and biomarkers (Atienza et al., 2011). The results of the current study add further weight to evidence that self-report and objective measures of PA are not equivalent and are likely to be capturing different information.

This study has several strengths in that it employed an objective measure to assess the duration of PA by intensity, controlled the statistical analysis for sociodemographic and health variables known to be associated with neurocognitive health, and included a large sample size. We also undertook an exploratory analysis of cortical thickness which identified several regions of the brain which may be influenced by moderate-intensity PA and MVPA. Although these areas did not survive adjustment for FDR, this offers a potential avenue of investigation in future longitudinal studies in this area. Despite these strengths, the findings of this study must be considered in the context of several limitations. As previously discussed, whilst participants in the current study are representative of the population they are randomly drawn from, they tend to have a higher socioeconomic status and education level compared to national averages and as such may not be fully representative of the general population (Anstey et al., 2012). The cross-sectional nature of the study design does not allow causal inferences to be made. The SWA, which was used to objectively measure PA, although validated is still an estimate of activity intensity and is known to underestimate MVPA (Berntsen et al., 2010). However, the SWA is ideal for use in older adults as its additional physiological sensors make it more accurate than accelerometry alone, especially when activity is of low-intensity and intermittent (Calabro et al., 2014).

In conclusion, this study suggests that greater duration of MVPA and moderate-intensity PA is associated with preserved gray matter volume in regions of the DLPFC, as well as more global effects on brain volume in older adults in their seventies. These effects were not present for light nor vigorous intensity PA, and only when measured with an objective PA monitor. A longitudinal follow-up of this cohort to determine if greater DLPFC volume associated with PA is related to future cognitive function and neurological health will further our understanding of the differential

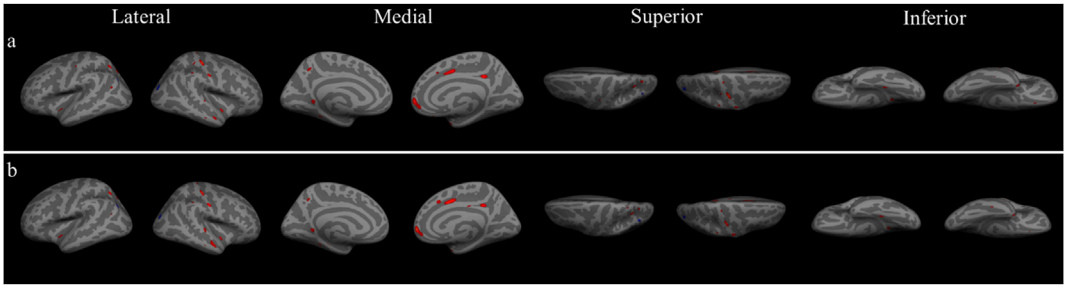

Fig. 3. Associations for objectively measured (**a**) moderate intensity physical activity or (**b**) moderate-to-vigorous-intensity physical activity and cortical thickness in the left and right lateral, medial, superior, and inferior planes. All regions were significant prior to false discovery rate correction at $p < 0.05$.

effects of PA intensity on the brain.

Funding

This work was supported by the Dementia Collaborative Research Centre Early Diagnosis and Prevention as part of an Australian Government Initiative and NHMRC Grant No. 1002160. MAF is supported by an Australian Government Research Training Program (RTP) Scholarship. KJA is funded by NHMRC Fellowships No. 1002560.

Declaration of competing interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Joseph M. Northey: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft. **Ben Rattray:** Conceptualization, Methodology, Data curation, Writing - review & editing, Funding acquisition. **Kate L. Pumpa:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Disa J. Pryor:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Mark A. Fraser:** Methodology, Data curation, Formal analysis, Writing - review & editing. **Marnie E. Shaw:** Methodology, Data curation, Writing - review & editing. **Kaarin J. Anstey:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition. **Nicolas Cherbuin:** Conceptualization, Methodology, Data curation, Writing - review & editing, Funding acquisition.

Acknowledgements

The authors are grateful to Anthony Jorm, Helen Christensen, Peter Butterworth, Andrew McKinnon, and the PATH project interviewers. This research was partly undertaken on the National Computational Infrastructure (NCI) facility in Canberra, Australia, which is supported by the Australian Commonwealth Government.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.117150.

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