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Moderate-Intensity Physical Activity, Hippocampal Volume, and Memory in Older Adults With Mild Cognitive Impairment

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Background. Greater physical activity (PA) is associated with better memory performance and greater hippocampal volume in older adults. However, most studies to date assessed PA via questionnaires and thereby lacked objective characterization of PA (eg, intensity, duration, etc.). Thus, we currently do not have a comprehensive understanding of PA characteristics that are important for neuroprotection, especially among older adults with mild cognitive impairment (MCI). Thus, using triaxial accelerometers, we examined the association between light- and moderate-intensity PA, total duration of PA, hippocampal volume, and memory in older adults with MCI.

Methods. This cross-sectional study involved 310 older adults with MCI who completed neuropsychological tests of memory, and structural magnetic resonance imaging. Participants were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. Average daily duration of light, moderate, and total PA (min/day) was calculated.

Results. Moderate PA was associated with hippocampal volume ($\beta = .167$, $p = .003$) after controlling for age, but light PA ($\beta = -.021$, $p = .713$) and total PA ($\beta = .011$, $p = .844$) were not. Both light and moderate PAs were not associated with memory performance. Structural equation modeling demonstrated that moderate PA was not directly associated with memory but significantly contributed to hippocampal volume; hippocampal volume loss was significantly and directly associated with poor memory performance.

Conclusions. Our results suggest that the benefits of moderate PA on memory among older adults with MCI are mediated by hippocampal volume. Furthermore, light PA may not reduce dementia risk among older adults with MCI.

Key Words: Physical activity—Brain—Memory.

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PHYSICAL activity (PA) has many well-known health benefits, including the reduction of chronic conditions, such as cardiovascular and cerebrovascular diseases, diabetes, obesity, and hypertension (1). There is also growing recognition that PA is associated with a reduced risk of dementia (2). Although more evidence should be accumulated (3), recent data from longitudinal studies and randomized controlled trails suggest associations of PA with preservation of cognitive function (4) and with brain volumes, including the hippocampus specifically (5–7). The hippocampus is crucial for memory, and significant atrophy of the hippocampus is a hallmark of Alzheimer's disease (AD). Smaller hippocampal volume is also associated with increased risk for progression from mild cognitive impairment (MCI) to AD (8,9).

MCI is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia and is a significant risk factor for dementia (10). To our knowledge, few studies have examined the effect of PA on memory in older adults with MCI (11) and none have

examined the effect of PA on hippocampal volume. A better understanding of PA characteristics (eg, intensity, duration) critical for neuroprotection would allow the refinement of PA interventions for older adults with MCI.

To objectively characterize PA, the use of technologies such as triaxial accelerometers is required. Triaxial accelerometers are objective, small, noninvasive tools for estimating PA intensities (12,13). However, majority of cohort studies to date have assessed PA via questionnaires. Although PA questionnaires is a highly feasible method to obtain data from large samples, PA levels may be over- or underestimated (14). Importantly, a previous study found that daily PA assessed using an accelerometer was associated with cognitive function, whereas self-report PA was not (15).

Thus, we aimed to examine the association of daily PA measured by triaxial accelerometers with memory and hippocampal volume in older adults with MCI. Specially, we assessed the effect of (i) total duration of daily PA (regardless of intensity), (ii) duration of light-intensity PA, and (iii) duration of moderate-intensity PA, with memory performance and hippocampal volume. Vigorous-intensity PA was not examined because we assumed that vigorous activity was not a common situation for participants in this study. Our focus on PA duration and intensity was justified as evidence suggested that intensity, not quantity (ie, duration), of PA was important for maintaining cognitive function in older adults (16–18).

Methods

Study Population

The current study involved a subset of participants who were enrolled in the Obu Study of Health Promotion for the Elderly (OSHPE). To enroll in the OSHPE, an individual was recruited from Obu, Japan, which is a residential suburb of Nagoya. For the OSHPE, we included individuals who were aged 65 years or older at study entry, lived in Obu, and was not participating in another study. We excluded individuals who required support or care by the Japanese public long-term care insurance system (care level ≥ 3/5), had disability in basic activities of daily living, and could not carry out performance-based assessments (19). A total of 5,104 community-dwelling older individuals participated in the OSHPE.

For this current study, we included 310 participants who had normal general cognitive functioning (scored ≥24/30 on the Mini-Mental State Examination [MMSE]) (20), subjective memory complaints, objective cognitive impairment (indicated by an age-adjusted score at least 1.5 *SD*s below the reference threshold in one or more specific cognitive domains including memory, attention and executive function, processing speed, and visuospatial skill), and no evidence of functional dependency (no need for supervision or external help in performing activities in daily life) (21,22). We excluded participants who were diagnosed with dementia, had a history of major psychiatric illness (eg, schizophrenia or bipolar disorder), other serious neurological or musculoskeletal diagnoses, and clinical depression in this study. To identify objective cognitive impairment, the National Center for Geriatrics and Gerontology-Functional Assessment Tool (NCGG-FAT) (19,23) were conducted. The NCGG-FAT consists of multidimensional neurocognitive tests to assess memory, attention and executive function, processing speed, and visuospatial skill. High test–retest reliability and moderate to high validity were confirmed in community-dwelling older adults for all task components of the NCGG-FAT (23). We defined objective cognitive impairment using established standardized thresholds one or more tests included the NCGG-FAT (score <1.5 *SD*s below the age-specific mean of any of the tests) for the population-based OSHPE cohort consisting of older adults.

Informed consent was obtained from all participants prior to their inclusion in the study, and the Ethics Committee of the National Center for Gerontology and Geriatrics approved the study protocol.

Measures

All participants completed a face-to-face interview, memory performance tests, measurements of PA, and magnetic resonance imaging (MRI).

PA measurements.—We used a triaxial accelerometer (modified HJA-350IT, Active style Pro, Omron Healthcare Co., Ltd.) for continuous measure of daily PA pattern (13). This small (74 × 46 × 34 mm) and light (60 g) device can accumulate data for a maximum of 30 days with the direct current power supply from a commercial button-type lithium battery. Participants were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks.

The accelerometer measured the number of steps taken and the intensity of PA every 4 seconds, and intensities were estimated based on the pattern of the accelerometer signal (12,13). The output was expressed in metabolic equivalents (METs; multiples of resting metabolic rate). Periods of time in which accelerometer data were not recorded for less than or equal 1 minute were defined as the nonwear time. Before calculating parameters, the data during activity hours were inspected by an arbitrary computer program to detect any consecutive intervals with no recorded body movement to indicate periods when the monitor had been removed (for such reasons as bathing, showering, napping, or sleeping). Participants who did not record 75% and over of each daytime activity, this being from 6 AM to 6 PM, for 7 days during the 2-week period were excluded from this study. During the 2-week period, the displays of accelerometers were blinded to prevent checking their counts and values to assess normal daily activity.

We defined light PA as 1.5–2.9 METs and moderate PA as 3.0–5.9 METs (24). Strong relationships between measured MET using indirect calorimetry and filtered synthetic accelerations for household ($r = .91$, $p < .001$) and locomotive ($r = .96$, $p < .001$) activities were reported (12). For example, slow-pace walking with light effort (1.0–2.0 mph) would be classified as light PA and brisk walking with moderate effort (3.0–4.0 mph) would be considered moderate PA (12,24). Total PA was all activity equal to or greater than 1.5 METs (25). In addition, we examined the categories of light PA (1.5–2.9 METs) and moderate PA (3.0–5.9 METs). Vigorous PA (≥6.0 METs) was not examined because approximately 90% participants of our sample did not perform any daily vigorous activities. Mean duration of each intense PA (min/d) was calculated.

Memory performance.—Participants underwent memory performance tests including measures of logical, visual, and verbal memory (26,27). The memory performance tests had a standardized format and were administered by licensed and trained clinical speech therapists in controlled environmental conditions. Logical memory was tested using the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R) (26). In the WMS-R Logical Memory, two short stories (stories A and B) were read aloud to the participant, who was instructed to recall details of the stories immediately (Logical Memory I) and after 30 minutes (Logical Memory II). The Logical Memory II score was calculated (ie, sum score of stories A and B) and used for statistical analysis.

Visual memory was examined using the visual reproduction subtest of the WMS-R (26). This test measures immediate (Visual Reproduction I) and delayed retention (Visual Reproduction II) of geometric figures. The Visual Reproduction II score was used for statistical analysis.

Rey Auditory Verbal Learning Test (RAVLT) performance was measured to assess verbal memory (27). The test was administered according to its original standards: 15 nouns (list A) were read five times by the examiner. The subjects then conducted free recall five times consecutively (A1–A5). After the fifth recall period, the examiner read a second list (list B) of 15 new words (a list of interference), followed by free recall (B1). After the B1, the examiner asked the individual to recall the words from list A, without reading it again (A6). After 30 minutes later, the examiner asks the individual to remember the words from list A (30-minute delayed recall) without reading this list. In this study, we analyzed subjects' performance in the List A 30-minute delayed recall.

MRI Acquisition and Image Analysis

MRI was performed on a 3-T system (TIM Trio, Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient-echo sequence (inversion time [TI], 800 ms; echo time [TE]/repetition time [TR], 1.98 ms/1800 ms; 1.1 mm slice thickness). Then axial T2-weighted SE images (TR, 4200 ms; TE, 89.0 ms; 5 mm slice thickness) and axial Fluid Attenuated Inversion Recovery images (TR, 9000 ms; TE, 100 ms; TI, 2500 ms; 5 mm slice thickness) were obtained for diagnosis.

For segmentation and volumetric analysis of the hippocampus, we used the Oxford Centre for Functional MRI of the Brain (FMRIB)'s Integrated Registration and Segmentation Tool (FIRST) in FMRIB's Soft-ware Library (FSL) version 5.0 (28,29). FIRST is a semiautomated model-based subcortical segmentation tool using a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston. In the analysis of FIRST, volumetric labels are parameterized by a 3D deformation of a surface model based on multivariate Gaussian assumptions. FIRST then searches through linear combinations of shape modes of variation for the most probable shape given the intensity distribution in the T1-weighted image (30).

Statistical Analysis

Statistical analyses were performed using SPSS (version 17.0) in conjunction with Analysis of Moment Structures (AMOS 7.0) Graphics. Continuous variables were summarized by means and *SD*s, whereas categorical variables were summarized by frequency and percentage. Student's *t* tests and chi-square tests were used to compare characteristics between participants who were included in ($n = 310$) and excluded from ($n = 79$) the main analyses. Pearson's correlation coefficients were calculated to assess simple correlations of duration of PA divided light- and moderate-intensity with hippocampal volume and memory performance tests. Linear regression analysis was used to assess the relationships between the variables while controlling for age to minimize the confounding influence of age-related changes in these variables, and standardized β values were calculated. Structural equation modeling in AMOS was performed to provide estimates of the magnitude and significance of the hypothetical model including duration of moderate PA and hippocampal volume as observed variables, and memory (created from WMS-R Logical Memory-II, WMS-R Visual Reproduction-II, and RAVLT delayed recall) as a latent variable.

Structural equation modeling is an optimal statistical technique for testing these hypotheses as it can evaluate a priori models, identify mediators, and elucidate direct and indirect paths between variables. Two types of models were considered: First, a direct effects model had direct paths from moderate PA and hippocampal volume on memory (Figure 1a). Second, an indirect effects model

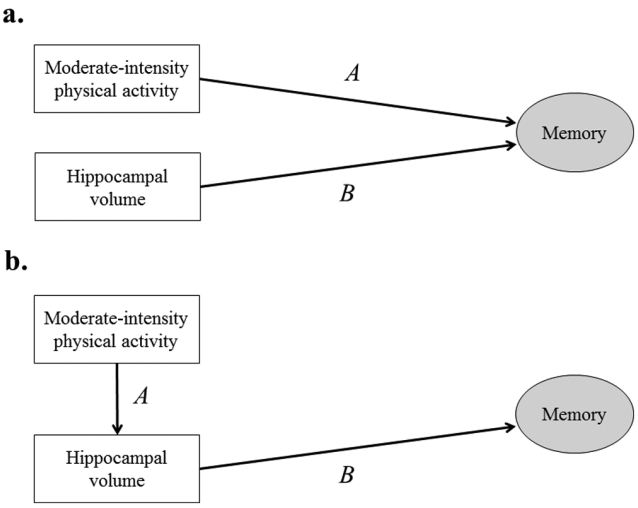

Figure 1. Two types of models in this study. (**a**) A direct effects model had direct paths from moderate-intensity physical activity (PA) and hippocampal volume on memory. (**b**) An indirect effects model had the effects of moderate-intensity PA on memory be transmitted indirectly through hippocampal volume.

had the effects of moderate PA on memory be transmitted indirectly through hippocampal volume (Figure 1b). Model selection was determined by comparison of the following model fit indices: chi-square (χ^2), goodness-of-fit index (GFI), comparative fit index (CFI), and the root mean square error of approximation (RMSEA) (31,32). The chi-square value is the traditional measure for evaluating overall model fit, and a good model fit would provide an insignificant result at a 0.05 threshold (31). The value of the GFI and CFI should be high (>0.95) and RMSEA should be small (<0.07) for a good-fitting model (31,32). In the case that the indirect effects model demonstrated superior fit to the data, the indirect effect of moderate PA on memory was tested by determining the product of paths *A* and *B* (Figure 1b), and then calculating the bootstrapped 95% confidence interval (CI) around the product term (2,000 bootstrapped resamples). The indirect effect is determined to be significant when the 95% CI does not contain the value 0.

Results

Sample Characteristics

Of the 945 older individuals who met the MCI criteria in the OSHPE (n = 5,104), 389 (41.2%) agreed with participation in this study and met the MRI eligibility. Of the 389 participants, 79 were excluded from analysis: 65 who provided insufficient or/and inaccurate accelerometer data, 13 for whom hippocampal segmentations could not be created by FIRST in FSL, and 1 who did not complete memory performance tests. After exclusions, 310 participants remained. Table 1 summarizes the characteristics of participants. The mean age of the participants who were included in the main analyses (n = 310) was 71.3 years (SD = 4.4; range 65–94 years), and over half (55.5%) were women. Individuals who were excluded from the main analyses (n = 79) were significantly older (73.0±6.4 years, p = .006) and less likely to be female (39.2%, p = .010). There were no differences in education levels or MMSE scores between individuals who were included in versus excluded from the main analyses. Of the 310 participants, 120 (38.7%) had hypertension, 35 (11.3%) had diabetes, and 38 (12.3%) had heart disease.

Table 1. Sample Characteristics (N = 310)

Variable	Mean (*SD*)
Age, mean (*SD*), y	71.3 (4.4)
Female, *n* (%)	172 (55.5)
Education, mean (*SD*), y	10.9 (2.2)
Diagnosis, *n* (%)	
Hypertension	120 (38.7)
Diabetes mellitus	35 (11.3)
Heart disease	38 (12.3)
Medication (3 and over)	116 (37.4)
Global cognition score (MMSE), mean (*SD*)	26.7 (1.9)
Duration of physical activity, mean (*SD*), min/d	
Total*	370.1 (101.1)
Light-intensity†	347.3 (97.0)
Moderate-intensity‡	22.6 (18.3)
Hippocampal volume, mean (*SD*), mm^3	7255.1 (826.0)
Memory performance, mean (*SD*)	
WMS-R Logical Memory-II	10.3 (6.4)
WMS-R Visual Reproduction-II	22.7 (8.5)
RAVLT 30-min delayed recall	7.5 (3.3)

Notes: Values are mean (*SD*) and numbers (%) for sex and diagnosis. MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; WMS-R = Wechsler Memory Scale-Revised.
*Total physical activity, ≥1.5 METs.
†Light-intensity, 1.5–2.9 METs.
‡Moderate-intensity, 3.0–5.9 METs.

Relationship of Hippocampal Volume and Memory With PA

Duration of total PA (r = .035, p = .544) and light PA (r = –.003, p = .961) were not associated with hippocampal volume (Table 2 and Figure 2a). There were no significant correlations between duration of total PA and light PA and memory performance tests. Moderate PA was significantly associated with hippocampal volume (r = .195, p = .001), and this association remained significant after adjusting for age (β = .167, p = .003) (Figure 2b). However, duration of moderate PA was not significantly associated with any of the memory performance tests (Table 2).

Structural Equation Models

The chi-square test of the direct effects model was significant, indicating a poorly fitting model (χ^2 = 19.344, df = 5, p = .002). The GFI, CFI, and RMSEA values were 0.976, 0.922, and 0.096, respectively. In this model (Figure 3a), hippocampal volume was significantly associated with

Table 2. Relationship of Hippocampal Volume and Memory With Physical Activity ($N = 310$)

	Total Physical Activity*				Light-Intensity Physical Activity†				Moderate-Intensity Physical Activity‡			
Dependent Variable	Simple Correlation (r)	p	Age-Controlled (β)	p	Simple Correlation (r)	p	Age-Controlled (β)	p	Simple Correlation (r)	p	Age-Controlled (β)	p
Brain volume												
Hippocampus	.035	.544	.011	.844	−.003	.961	−.021	.713	.195	.001	.167	.003
Memory performance												
Logical Memory-II	.018	.757	−.014	.813	.003	.959	−.022	.715	.081	.154	.038	.513
Visual Reproduction-II	−.010	.857	−.050	.401	−.025	.661	−.057	.343	.071	.213	.021	.762
RAVLT delayed recall	.048	.396	.015	.800	.036	.525	.011	.851	.072	.205	.022	.703

Notes: RAVLT = Rey Auditory Verbal Learning Test.
*Total physical activity, ≥1.5 METs.
†Light-intensity, 1.5–2.9 METs.
‡Moderate-intensity, 3.0–5.9 METs.

memory (β = .266), but there was no significant direct association of moderate PA (β = .059) with memory. The indirect effects model (Figure 3b) provided an excellent fit to the data ($\chi^2 = 8.091$, $df = 5$, $p = .151$; GFI = 0.989, CFI = 0.983, RMSEA = 0.045). This model showed that moderate PA was not directly associated with memory but contributed significantly to hippocampal volume (β = .195). Furthermore, hippocampal volume loss was significantly and directly associated with poor memory performance (β = .277). The indirect effect of moderate PA on memory performance was significant (β = .054, 95% CI [0.020, 0.104], $p = .001$).

Discussion

In this cross-sectional study of community-dwelling older adults with MCI, duration of moderate PA, as measured objectively by a triaxial accelerometer, was significantly correlated with hippocampal volume. Specially, longer duration of moderate PA was associated with greater hippocampal volume. Our findings from structural equation modeling indicated that moderate PA had a beneficial influence on hippocampal volume, and in turn, hippocampal volumes was directly associated with memory. In other words, the association between moderate of PA and memory was mediated by hippocampal volume.

MCI is a heterogeneous condition associated with the transitional phase between normal cognitive aging and dementia, and those progression rates to dementia and AD have been reported as being in the range of 6%–25% per year (33). Although rates of progression varies according to study populations, these are higher than the 1%–2% annualized incidence rates of dementia and AD in the general older population (34). Smaller hippocampal volume is associated with increased risk for progression from MCI to AD (8,9). In contrast, greater hippocampal volume is one of associated factors with reversion from MCI to normal cognition (35). Therefore, identifying factors that are associated with the maintenance of hippocampal volume among older people with MCI have important implications for dementia prevention and disease progression.

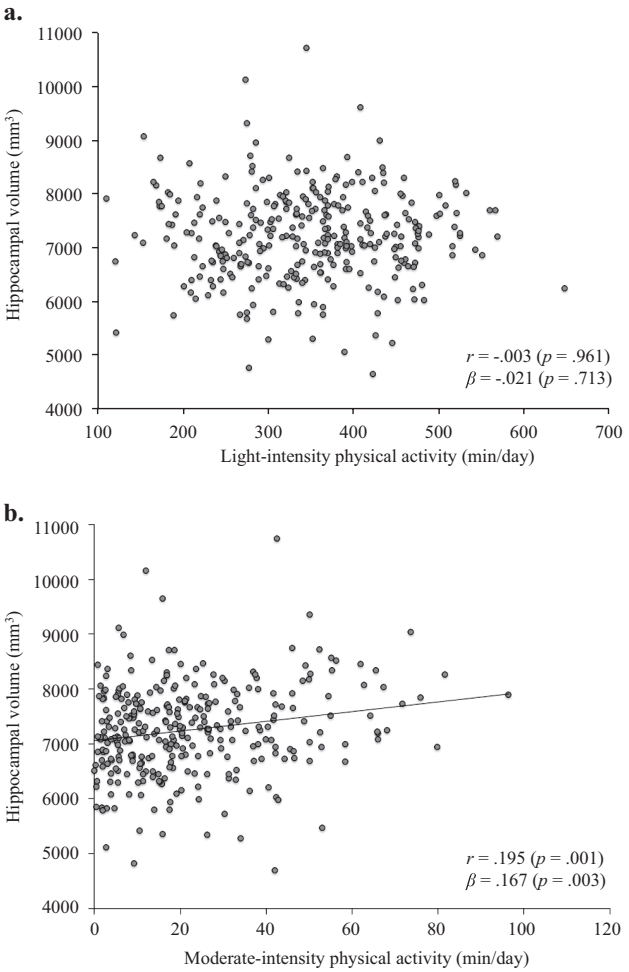

Figure 2. Correlations between duration of physical activity and hippocampal volume. Pearson correlation coefficients (r) and standardized beta values (controlling for age) are presented. (**a**) Light-intensity physical activity. (**b**) Moderate-intensity physical activity.

Our study results concern and extend our current understanding of the benefits of PA on the brain. The results of a previous longitudinal study indicated that greater PA assessed by a questionnaire (the number of blocks walked

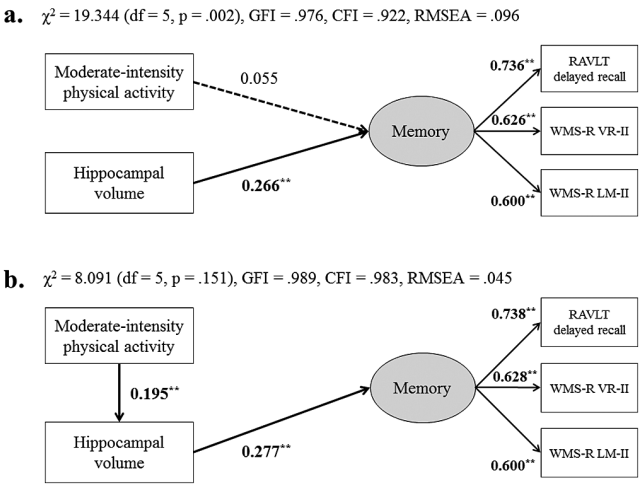

Figure 3. Results of structural equation models of the correlations among moderate-intensity physical activity, hippocampal volume, and memory. The direct effects model (**a**) and the indirect effects model (**b**) are represented. The estimated standardized coefficients are shown. Latent variables (Memory) are represented with ovals and observed variables are represented with rectangles. The dashed line indicates an association that was not significant ($p > .05$). In the indirect effects model (**b**), the indirect effect of moderate PA on memory performance was significant (β = .054, 95% CI [0.020, 0.104], $p = .001$). *Notes*: LM = Logical Memory; RAVLT = Rey Auditory Verbal Learning Test; VR = Visual Reproduction; WMS-R = Wechsler Memory Scale-Revised. **$p < .01$.

over 1 week) predicted greater volume of hippocampus 9 years later among healthy older people (5). Recent results of randomized trials suggest that moderate-intensity physical exercise increases hippocampal perfusion (36) and the size of hippocampus (6) among healthy older adults. A randomized trial demonstrated by Erickson and colleagues (6) found that, in the exercise group, increased hippocampal volume was directly related to improvements in memory performance. The indication that increase in hippocampal volume after exercise augments memory function in late adulthood was mentioned. However, these previous studies did not include objectively measured PA data and older adults with MCI. Our current study findings suggest that the benefits of PA, specifically moderate PA, on hippocampal volume and memory performance extend to older adults with MCI.

The strengths of our study include the objectively measured data of PA and neuroimaging data of hippocampal volume. In addition, well-sampled data from MCI subjects could be another strength. Although some previous studies examined relationships between objectively measured PA levels and cognition in aged population (16,37,38), these studies did not indicate participants defined as MCI or if they did, and the sample size was relatively small. These strengths in the present study may extend the role of promotion of moderate PA among older adults with MCI. However, we recognize our study limitations. This is a cross-sectional study, and thus the temporal direction of the associations among PA, hippocampus volume, and memory cannot be determined. To clarify those causal relationships, we would need to implement a longitudinal design and consider other factors that might be related to the relationship between moderate PA and hippocampal volume, such as the etiology and severity of MCI and physical functional status. We should note the potential for selection bias. Over 15% of the cohort was unable to comply with accelerometry. We found that individuals who were excluded from the main analyses ($n = 79$) were significantly older and more likely to be male relative to participants who were included in the main analyses. In addition, although vigorous activity might promote healthy aging including cognitive status (39), we were unable to assess a separate category for vigorous PA (≥6.0 METs) in the current analysis. Because 270 participants of our sample ($n = 310$) did not perform any daily vigorous activities, and mean (±*SD*) duration of vigorous activity was 0.2 (±1.6) min/d. Ignoring vigorous activity could potentially have led to overestimation of the effect of moderate activity if those who engaged in moderate activity were also more likely to engage in vigorous activity. Finally, we recognize that the lack of generalizability is a potential limitation and that future longitudinal studies with relevant cohorts are needed to add weight to our findings.

In summary, this study of data from older adults with MCI found that higher level of moderate rather than light PA is associated with hippocampal volume. In addition, moderate PA is not associated directly with memory, but mediated through hippocampal volume. Our findings strongly imply that regular PA of moderate-intensity levels at even at the MCI stage may have a beneficial influence on hippocampal volume, and in turn, hippocampal volumes may affect memory loss. Longitudinal studies and clinical trials are needed to understand the temporal direction of associations among PA, hippocampal volume, and memory, and the efficacy of moderate PA on memory mediated through the changing size of hippocampus in older adults with MCI.

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References

1. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39:1435–1445. doi:10.1249/mss.0b013e3180616aa2
2. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med*. 2009;39:3–11. doi:10.1017/S0033291708003681

3. Snowden M, Steinman L, Mochan K, et al. Effect of exercise on cognitive performance in community-dwelling older adults: review of intervention trials and recommendations for public health practice and research. *J Am Geriatr Soc*. 2011;59:704–716. doi:10.1111/j.1532-5415.2011.03323.x
4. Daviglus ML, Bell CC, Berrettini W, et al. National Institutes of Health State-of-the-Science Conference statement: preventing Alzheimer disease and cognitive decline. *Ann Intern Med*. 2010;153:176–181. doi:10.7326/0003-4819-153-3-201008030-00260
5. Erickson KI, Raji CA, Lopez OL, et al. Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study. *Neurology*. 2010;75:1415–1422. doi:10.1212/WNL.0b013e3181f88359
6. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci U S A*. 2011;108:3017.–3022 doi:10.1073/pnas.1015950108
7. Head D, Singh T, Bugg JM. The moderating role of exercise on stress-related effects on the hippocampus and memory in later adulthood. *Neuropsychology*. 2012;26:133–143. doi:10.1037/a0027108
8. Apostolova LG, Dutton RA, Dinov ID, et al. Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps. *Arch Neurol*. 2006;63:693–699. doi:10.1001/archneur.63.5.693
9. Devanand DP, Pradhaban G, Liu X, et al. Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology*. 2007;68:828–836. doi:0.1212/01.wnl.0000256697.20968.d7
10. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58:1985–1992. doi:10.1001/archneur.58.12.1985
11. Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatr*. 2013;21:1086–1097. doi:10.1016/j.jagp.2013.02.018
12. Ohkawara K, Oshima Y, Hikihara Y, Ishikawa-Takata K, Tabata I, Tanaka S. Real-time estimation of daily physical activity intensity by a triaxial accelerometer and a gravity-removal classification algorithm. *Br J Nutr*. 2011;105:1681–1691 doi:10.1017/S0007114510005441.
13. Oshima Y, Kawaguchi K, Tanaka S, et al. Classifying household and locomotive activities using a triaxial accelerometer. *Gait Posture*. 2010;31:370–374. doi:10.1016/j.gaitpost.2010.01.005
14. Hagstromer M, Ainsworth BE, Oja P, Sjostrom M. Comparison of a subjective and an objective measure of physical activity in a population sample. *J Phys Act Health*. 2010;7:541–550.
15. Buchman AS, Wilson RS, Bennett DA. Total daily activity is associated with cognition in older persons. *Am J Geriatr Psychiatr*. 2008;16:697–701. doi:10.1097/JGP.0b013e31817945f6
16. Brown BM, Peiffer JJ, Sohrabi HR, et al.; AIBL research group. Intense physical activity is associated with cognitive performance in the elderly. *Transl Psychiatr*. 2012;2:e191. doi:10.1038/tp.2012.118
17. Angevaren M, Vanhees L, Wendel-Vos W, et al. Intensity, but not duration, of physical activities is related to cognitive function. *Eur J Cardiovasc Prev Rehabil*. 2007;14:825–830. doi:10.1097/HJR.0b013e3282ef995
18. Kerr J, Marshall SJ, Patterson RE, et al. Objectively measured physical activity is related to cognitive function in older adults. *J Am Geriatr Soc*. 2013;61:1927–1931. doi:10.1111/jgs.12524
19. Shimada H, Makizako H, Doi T, et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. *J Am Med Dir Assoc*. 2013;14:518–524. doi:10.1016/j.jamda.2013.03.010
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198. doi:10.1016/0022-3956(75)90026-6
21. Yaffe K, Middleton LE, Lui LY, et al. Mild cognitive impairment, dementia, and their subtypes in oldest old women. *Arch Neurol*. 2011;68:631–636. doi:10.1001/archneurol.2011.82
22. Hänninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. *Acta Neurol Scand*. 2002;106:148–154. doi:10.1034/j.1600-0404.2002.01225.x
23. Makizako H, Shimada H, Park H, et al. Evaluation of multidimensional neurocognitive function using a tablet personal computer: test-retest reliability and validity in community-dwelling older adults. *Geriatr Gerontol Int*. 2013;13:860–866. doi:10.1111/ggi.12014
24. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402–407. doi:10.1001/jama.1995.03520290054029
25. Unick JL, Bond DS, Jakicic JM, et al. Comparison of two objective monitors for assessing physical activity and sedentary behaviors in bariatric surgery patients. *Obes Surg*. 2012;22:347–352. doi:10.1007/s11695-011-0491-1
26. Wechsler D. *Wechsler Memory Scale—Revised Manual*. San Antonio, TX: The Psychological Corporation; 1987.
27. Lezak M, Howieson D, Loring D. *Neuropsychological Assessment*. 4th ed. New York, NY: Oxford University Press; 2004.
28. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001;20:45–57. doi:10.1109/42.906424
29. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 2004;23(suppl 1):S208–S219. doi:10.1016/j.neuroimage.2004.07.051
30. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage*. 2011;56:907–922. doi:10.1016/j.neuroimage.2011.02.046
31. Barrett P. Structural equation modelling: adjudging model fit. *Pers Indiv Differ*. 2007;42:815–824. doi:10.1016/j.paid.2006.09.018
32. Steiger JH. Understanding the limitations of global fit assessment in structural equation modeling. *Pers Indiv Differ*. 2007;42:893–898. doi:10.1016/j.paid.2006.09.017
33. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56:1133–1142. doi:10.1212/WNL.56.9.1133
34. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56:303–308. doi:10.1001/archneur.56.3.303
35. Sachdev PS, Lipnicki DM, Crawford J, et al.; Sydney Memory, Ageing Study Team. Factors predicting reversion from mild cognitive impairment to normal cognitive functioning: a population-based study. *PLoS One*. 2013;8:e59649. doi:10.1371/journal.pone.0059649
36. Burdette JH, Laurienti PJ, Espeland MA, et al. Using network science to evaluate exercise-associated brain changes in older adults. *Front Aging Neurosci*. 2010;2:23. doi:10.3389/fnagi.2010.00023
37. Buchman AS, Wilson RS, Yu L, James BD, Boyle PA, Bennett DA. Total daily activity declines more rapidly with increasing age in older adults. *Arch Gerontol Geriatr*. 2014;58:74–79. doi:10.1016/j.archger.2013.08.001
38. Wilbur J, Marquez DX, Fogg L, et al. The relationship between physical activity and cognition in older Latinos. *J Gerontol B Psychol Sci Soc Sci*. 2012;67:525–534. doi:10.1093/geronb/gbr137
39. Almeida OP, Khan KM, Hankey GJ, Yeap BB, Golledge J, Flicker L. 150 minutes of vigorous physical activity per week predicts survival and successful ageing: a population-based 11-year longitudinal study of 12 201 older Australian men. *Br J Sports Med*. 2014;48:220–225. doi:10.1136/bjsports-2013-092814