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Objectively measured physical activity, brain atrophy, and white matter lesions in older adults with mild cognitive impairment

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ABSTRACT

Physical activity may help to prevent or delay brain atrophy. Numerous studies have shown associations between physical activity and age-related changes in the brain. However, most of these studies involved self-reported physical activity, not objectively measured physical activity. Therefore, the aim of this study was to examine the association between objectively measured physical activity, as determined using accelerometers, and brain magnetic resonance imaging (MRI) measures in older adults with mild cognitive impairment (MCI). We analyzed 323 older subjects with MCI (mean age 71.4 years) who were recruited from the participants of the Obu Study of Health Promotion for the Elderly. We recorded demographic data and measured physical activity using a tri-axial accelerometer. Physical activity was classified as light-intensity physical activity (LPA) or moderate-to-vigorous physical activity (MVPA). Brain atrophy and the severity of white matter lesions (WML) were determined by MRI. Low levels of LPA and MVPA were associated with severe WML. Subjects with severe WML were older, had lower mobility, and had greater brain atrophy than subjects with mild WML (all $P < 0.05$). Multivariate analysis revealed that more MVPA was associated with less brain atrophy, even after adjustment for WML ($\beta = -0.126$, $P = 0.015$), but LPA was not ($\beta = -0.102$, $P = 0.136$). Our study revealed that objectively measured physical activity, especially MVPA, was associated with brain atrophy in MCI subjects, even after adjusting for WML. These findings support the hypothesis that physical activity plays a crucial role in maintaining brain health.

1. Introduction

Alzheimer disease (AD) is a serious health problem, and its prevalence is dramatically increasing worldwide. Because of the absence of disease-modifying treatments, numerous studies have sought to identify potentially modifiable risk factors for AD (Barnes and Yaffe, 2011). In particular, physical inactivity has been recognized as a significant risk factor for cognitive decline (Sofi et al., 2011) and cognitive impairments, including AD and mild cognitive impairment (MCI) (Barnes and Yaffe, 2011; Lautenschlager et al., 2010),

MCI is considered to be a clinical feature that typifies the prodromal phase of AD and most types of dementia (Petersen, 2004). MCI is associated with a relatively high rate of conversion to dementia, but may also revert to a healthy cognitive state (Brodaty et al., 2013). Physical activity (PA)-based interventions were tested to improve cognitive function in people with MCI, and studies have suggested associations between PA and preservation of cognitive function. However, a meta-analysis revealed some inconsistencies in the effects of PA (Gates et al., 2013). Thus, better understanding of the association between PA and cognition should allow us to refine PA interventions.

Emerging evidence also suggests that PA could protect against age-related changes in the brain, including structural changes observed on magnetic resonance imaging (MRI). Several studies have shown that greater PA is associated with larger brain volume or less atrophy (Benedict et al., 2013; Erickson et al., 2010; Flöel et al., 2010; Gow et al., 2012). Brain atrophy is strongly associated with the presence of white matter lesions (WML), but the association between WML and PA is still debated (Burzynska et al., 2014; Kooistra et al., 2014; Podewils et al., 2007; Wirth et al., 2014). The coexistence of WML and brain atrophy was thought to depend on underlying vascular risk factors

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; WML, white matter lesions; LPA, light-intensity physical activity; METs, multiples of the resting metabolic rate; MVPA, moderate-to-vigorous intensity physical activity; PA, physical activity; TE, echo time; TI, inversion time; TR, repetition time; TUG, timed up and go test

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or on a contribution of altered white matter integrity to the pathogenesis of brain atrophy, although the mechanisms were unclear (Appelman et al., 2009). The severity of WML was also associated with brain atrophy in older adults, including those with cognitive impairment (Appelman et al., 2009). However, it is still unclear whether the association between PA and brain atrophy is independent of the severity of WML. It is also notable that, in these earlier studies, PA was assessed using self-reported questionnaires. An earlier study reported that objectively measured PA was associated with cognitive function, but self-reported PA was not (Buchman et al., 2008). Even young adults had difficulty in evaluating PA because of recall bias with subjective assessments, and over- or under-estimated PA (Hagstromer et al., 2010).

Thus, we examined whether objectively measured PA is associated with brain atrophy, independent of WML, in older adults with MCI. Studies using objectively measured PA have revealed that the intensity of PA, rather than the amount of PA, is associated with cognitive performance in older people (Brown et al., 2012; Kerr et al., 2013). Therefore, we also examined whether the intensity of PA has an impact on the association between PA and brain atrophy. In this study, we objectively measured PA using tri-axial accelerometers and calculated the mean daily duration of PA for several intensity levels.

2. Materials and methods

2.1. Subjects

Overall, 649 subjects participating in the Obu Study of Health Promotion for the Elderly (Shimada et al., 2013) were considered for this study, and met the following criteria: age > 65 years; diagnosis of MCI; no specific medical history of cerebrovascular disease, Parkinson disease, connective tissue disease, or depression; no severe visual or auditory impairment; no current symptoms of depression defined as Geriatric Depression Scale ≥ 6 (Yesavage, 1988); not participating in other research projects; and not receiving support from the Japanese public long-term-care insurance system, which certifies a person as "Support Level 1 or 2" if they need support for daily activities or "Care Level 1, 2, 3, 4, or 5" if they need continuous care (Tsutsui and Muramatsu, 2007). MCI was defined based on the criteria established and revised by Petersen (2004) as follows: 1) subjective memory complaints; 2) objective cognitive impairment; 3) no dementia; and 4) independent function in daily life activities. The subjects with MCI included in our study were not diagnosed with dementia and their general cognitive function was considered intact with a Mini-Mental State Examination score of >23 (Folstein et al., 1975). Objective cognitive impairment was defined as a cognitive function score at least 1.5 standard deviations below the normal score (Shimada et al., 2013). Cognitive function was assessed in multiple domains (attention, executive function, processing speed, visuospatial skill, and memory) using the National Center for Geriatrics and Gerontology Functional Assessment Tool (Makizako et al., 2013). Subjects with cognitive impairment in the memory domain were classified as having amnestic MCI; the remaining subjects were classified as having non-amnestic MCI. Overall, 409 people responded to the invitation to participate, 400 participated after providing informed consent in accordance with the ethical policy, and 336 completed all examinations and the MRI analysis. The ethics committee of the National Center for Geriatrics and Gerontology approved this study.

2.2. MRI

MRI was performed on a 3T system (TIM Trio; Siemens, Berlin, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient-echo sequence produced a gapless series of thin sagittal sections using a magnetization preparation with rapid-acquisition (inversion time [TI], 800 ms; echo time [TE], 1.98 ms; repetition time [TR], 1800 ms; slice thickness, 1.1 mm). Then, axial T2-weighted, spin-echo images (TR, 4200 ms; TE, 89.0 ms; slice thickness, 5 mm) and axial fluid-attenuated inversion recovery images (TI, 2500 ms; TR, 9000 ms; TE, 100 ms; slice thickness, 5 mm) were obtained for diagnosis. WML were assessed based on periventricular hyperintensity and deep and subcortical white matter hyperintensity. Subjects were classified as having severe WML if periventricular hyperintensity or white matter hyperintensity was classified as grade III (Fazekas et al., 1993).

Brain atrophy was evaluated using the voxel-based, specific regional analysis system for Alzheimer's disease advance, which has been validated and described in more detail elsewhere (Hirata et al., 2005; Matsuda et al., 2012). Normalized MRI images were segmented into gray matter, white matter, cerebrospinal fluid, and other components. The segmented gray matter images were then subjected to affine and non-linear anatomical standardization using a gray matter template established a priori. Then, gray matter images were smoothed with an isotropic Gaussian kernel with a full-width-at-half-maximum of 12 mm. We compared the gray matter images of each subject with the mean and standard deviation of gray matter images obtained from healthy older adults using voxel-by-voxel Z-score analysis (Hirata et al., 2005; Matsuda et al., 2012). Regions of brain atrophy were defined as voxels with a Z-score >2. A brain atrophy index was defined as the proportion of atrophic voxels relative to the total number of voxels for the entire brain.

2.3. Physical activity

To objectively measure PA, we used a small tri-axial accelerometer (74 × 46 × 34 mm; modified HJA-350IT, Active style Pro; Omron Healthcare Co., Ltd., Kyoto, Japan) (Kim et al., 2013; Oshima et al., 2010) according to a previously described protocol (Makizako et al., 2014). The number of steps and the intensity of PA were measured every 4 s throughout each day. The intensity of PA was calculated in multiples of the resting metabolic rate (METs). Subjects were instructed to wear the accelerometer on an elastic band on their hip at all times for 2 weeks. To assess normal daily activity, the displays of the accelerometers were masked to the subjects. We excluded the data for 13 subjects lacking activity data for ≥75% of the daytime period (6 am to 6 pm) on 7 days or more in the 2-week period. Accelerometer data were classified as light-intensity physical activity (LPA; 1.5–2.9 METs) or moderate-to-vigorous physical activity (MVPA; more than 3.0 METs), which were calculated from the mean duration of each intensity of PA in min/day.

2.4. Other covariates

Age, sex, and body mass index (weight/height^2) were recorded as demographic characteristics. Comorbidities including hypertension, diabetes mellitus, lipidemia, and current medications were also recorded.

Table 1
Characteristics of subjects according to the severity of white matter lesions.

Variables	Non-severe WML ($n = 263$)	Severe WML ($n = 60$)	P
Age, years	70.7 ± 4.1	74.3 ± 5.2	<0.001
Sex (women), %	54.7	50.0	0.499
BMI, kg/m^2	23.3 ± 2.9	23.6 ± 2.5	0.509
Subjects with non-amnestic MCI, %	48.2	54.8	0.343
Hypertension, %	39.2	43.5	0.528
Diabetes mellitus, %	10.3	12.9	0.544
Lipidemia, %	28.6	24.2	0.487
Number of medications	2.0 ± 1.9	2.4 ± 1.8	0.143
TUG, s	8.4 ± 1.7	9.0 ± 1.7	0.013
LPA, min/day	353.6 ± 96.0	324.4 ± 96.7	0.035
MVPA, min/day	24.1 ± 18.7	18.6 ± 17.5	0.039
Brain atrophy, %	1.6 ± 1.0	2.7 ± 1.6	<0.001

Values are means ± standard deviation or % of subjects.
WML: white matter lesions; BMI: body mass index; MCI: mild cognitive impairment; TUG: timed up and go test; LPA: low-intensity physical activity. MVPA: moderate-to-vigorous intensity physical activity.