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Association between exercise habits and subcortical gray matter volumes in healthy elderly people: A population-based study in Japan

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ABSTRACT

Background and aims: The relationship between exercise and subcortical gray matter volume is not well understood in the elderly population, although reports indicate that exercise may prevent cortical gray matter atrophy. To elucidate this association in the elderly, we measured subcortical gray matter volume and correlated this with volumes to exercise habits in a community-based cohort study in Japan.

Methods: Subjects without mild cognitive impairment or dementia ($n = 280$, 35% male, mean age 73.1 ± 5.9 years) were evaluated using the Mini-Mental State Examination (MMSE), an exercise habit questionnaire, and brain magnetic resonance imaging. Subcortical gray matter volume was compared between groups based on the presence/absence of exercise habits. The MMSE was re-administered 3 years after the baseline examination.

Results: Ninety-one subjects (32.5%) reported exercise habits (exercise group), and 189 subjects (67.5%) reported no exercise habits (non-exercise group). Volumetric analysis revealed that the volumes in the exercise group were greater in the left hippocampus ($p = 0.042$) and bilateral nucleus accumbens (left, $p = 0.047$; right, $p = 0.007$) compared to those of the non-exercise group. Among the 195 subjects who received a follow-up MMSE examination, the normalized intra-cranial volumes of the left nucleus accumbens ($p = 0.004$) and right amygdala ($p = 0.014$)showed significant association with a decline in the follow-up MMSE score.

Conclusion: Subjects with exercise habits show larger subcortical gray matter volumes than subjects without exercise habits in community-dwelling elderly subjects in Japan. Specifically, the volume of the nucleus accumbens correlates with both exercise habits and cognitive preservation.

1. Introduction

Exercise and/or physical fitness may be protective against the development of dementia. A number of studies that examined the effects of exercise in elderly people with or without dementia have been summarized by meta-analyses [1–5]. These meta-analyses showed that aerobic exercise training is associated with modest improvements in cognitive function such as attention, processing speed, executive function and memory. Based on studies using animal models and human subjects, several hypotheses have been proposed to describe the mechanisms behind the beneficial effects of exercise on cognition; these include a reduction in oxidative stress [6], an increase in growth factor levels (e.g., brain-derived neurotrophic factor, insulin-like growth factor, and vascular endothelial growth factor) [7–10], and reduced levels of amyloid-β (Aβ), a key pathogenic factor in Alzheimer's disease (AD) [11].

In regard to brain volume, several studies of elderly subjects revealed that exercise intervention for 6 to 12 months increased gray matter volumes in the hippocampus and the prefrontal and anterior cingulate cortices [7,8,12]. However, few studies have examined the relationship between subcortical gray matter volume and exercise habits. In this study, we examined the association between exercise habits and

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subcortical gray matter volume in healthy elderly subjects in a population-based cohort study in Japan.

2. Methods

2.1. Subjects

The subjects included in this study were a sub-population of those from the Ama-cho study, a population-based cohort study of individuals aged 65 years or older in Japan. A detailed account of the Ama-cho study has been described previously [13]. The subject inclusion criteria for the present study were as follows: (1) no indications of dementia, or mild cognitive impairment (MCI) at baseline; (2) underwent brain magnetic resonance imaging (MRI); (3) answered questionnaires that included information on exercise habits; (4) received a neuropsychological examination by a neurologist or clinical psychologist. The exclusion criteria for the study subjects were as follows: (1) a Clinical Dementia Rating (CDR) score of 0.5 or more or (2) a medical history of head trauma, brain tumor, stroke, neurological disease, or psychiatric illness.

The study was approved by the Committee for Medical Research Ethics at Tottori University, and followed the principles outlined in the Declaration of Helsinki. All participants provided written informed consent to participate in the study.

2.2. Demographics and medical history

Information on education level, medical history of hypertension, hyperlipidemia, diabetes mellitus, alcohol consumption and/or smoking, and exercise habits were obtained from a self-administered questionnaire and a review of electronic databases in the healthcare system. Blood pressure (BP) was assessed during medical examinations by neurologists [14]. High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and 1,5-anhydroglucitol (1,5-AG) were measured for this investigation [15].

2.3. Assessment of cognitive function, motor function, and mood

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) [16], and the CDR [17]. Motor function was assessed using an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (modified UPDRS) [14]. Depressed mood was assessed using the Japanese version of the Geriatric Depression Scale (GDS) with 15 questions [18,19].

A diagnosis of dementia or MCI was determined by neurologists [19] according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM-IV) [20] and the International Working Group on MCI criteria, respectively [21].

2.4. Definition of exercise habits

We used the definition of exercise habits published by the Minister of Health, Labor and Welfare in Japan (http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kenkenkounip21.html). The exercise habits criteria were as follows: (1) >30 min; (2) more than twice a week; (3) maintained for >1 year.

2.5. Brain MRI

Brain MRI was performed between March and May 2010 using a 1.5 Tesla scanner (Gyroscan Intera; Philips Electronics Japan, Tokyo, Japan) with a multi-channel head coil system. A sagittal volumetric magnetization-prepared rapid gradient echo sequence was used to acquire a three-dimensional T1-weighted image with the following parameters: repetition time/echo time/inversion time (TR/TE/TI), 8.5/4/1000 ms; flip angle, 8°; 240 mm field of view; 192 × 192 acquisition; 256 × 256 reconstruction matrix; and a 1.2 mm slice thickness. Axial proton-density (TR/TE, 3000/12 ms) and T2-weighted (TR/TE, 3000/96 ms) images were also acquired for diagnostic purposes. This scanning protocol followed the MRI methods used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) [22].

2.6. Survey procedure

The baseline study was conducted from 2008 to 2010 and the follow-up study was conducted from 2011 to 2013. During the baseline study, we collected personal and demographic information, and administered the MMSE, the GDS, and brain MRI. The MMSE was re-evaluated during the follow-up study.

2.7. Subcortical segmentation using the FMRIB's Integrated Registration and Segmentation Tool (FIRST)

Fourteen subcortical gray matter regions (bilateral nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus) were automatically segmented using the FMRIB's Integrated Registration and Segmentation Tool (FIRST) [23], and their volumes were calculated using the functions of the FMRIB Software Library (FSL) package [24] (Fig. 1). For each subject, the subcortical gray matter volumes were divided by the intra-cranial volume (ICV) for normalization to the individual's head size. The ICV was calculated by summing the segmented gray/white matter and cerebrospinal fluid (CSF) volume output using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) implemented in the SPM8 software package (http://fil.ion.ucl.ac.uk/spm), running under a MATLAB environment (version 8.0; MathWorks, Natick, MA, USA).

2.8. Statistical analyses

Differences in demographic and clinical variables, MMSE scores, and GDS scores between the groups were analyzed using Student's *t*-tests or a chi-square test. A paired Student's *t*-test was used to analyze differences between the baseline and follow-up MMSE scores for each group. Multiple regression analyses, including age, sex and education level as covariates, were used to examine the effects of exercise habits on the ICV-normalized subcortical gray matter volumes, and to evaluate the relationship between changes in MMSE score (ΔMMSE) and subcortical gray matter volumes. The ΔMMSE value was obtained by subtracting the baseline MMSE score from the follow-up MMSE score. Also, medical history or demographics variables that showed a tendency toward significance ($p < 0.05$) in the univariate analysis were entered as explanatory variables in the logistic regression model. The Statistical Package for the Social Sciences (SPSS) program version 20.0 (release 20; Tokyo, Japan) was used for all data analyses.

3. Results

3.1. Study flow chart

Fig. 2 shows a flow chart of the number of subject involved in this study. The total number of residents (aged 65 years or older) in the town was 924, which represented 38.0% of the total population at baseline. Twenty-four subjects were deceased or had moved outside of the town at the start of the investigation. Therefore, 900 individuals were considered eligible for the study. Among the 900 subjects, 689 (76.6%) underwent brain MRI, and 390 subjects (43.3%) were judged to be cognitively healthy without a diagnosis of dementia or MCI. One hundred and ten subjects were subsequently excluded from the analysis based on the inclusion/exclusion criteria, a lack of answers pertaining to exercise habits, or poor quality MR images. Thus, 280 subjects (31.1% of the eligible residents and 71.8% of the 390 cognitively healthy subjects) were selected for this study. The 110 subjects excluded from the study