ORIGINAL ARTICLE
https://doi.org/10.30773/pi.2020.0214
Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Effects of Moderate Intensity Exercise on the Cortical Thickness and Subcortical Volumes of Preclinical Alzheimer's Disease Patients: A Pilot Study

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Objective We aimed to explore the impact of moderate intensity exercise on the cortical thickness and subcortical volumes of preclinical Alzheimer's disease (AD) patients.

Methods Sixty-three preclinical AD patients with magnetic resonance imaging (MRI) and 18-florbetaben positron emission tomography (PET) data were enrolled in the study. Information on demographic characteristics, cognitive battery scores, self-reported exercise habits were attained. Structural magnetic resonance images were analyzed and processed using Freesurfer v6.0.

Results Compared to Exercise group, Non-Exercise group demonstrated reduced cortical thickness in left parstriangularis, rostral middle frontal, entorhinal, superior frontal, lingual, superior parietal, lateral occipital, inferior parietal gyrus, temporal pole, precuneus, insula, fusiform gyrus, right precuneus, superiorparietal, lateral orbitofrontal, rostral middle frontal, medial orbitofrontal, superior frontal, lingual, middle temporal gyrus, insula, supramarginal, parahippocampal, paracentral gyrus. Volumes of right thalamus, caudate, putamen, pallidum, hippocampus, amygdala were also reduced in Non-Exercise group.

Conclusion Moderate intensity exercise affects cortical and subcortical structures in preclinical AD patients. Thus, physical exercise has a potential to be an effective intervention to prevent future cognitive decline in those at high risk of AD.

Psychiatry Investig 2020;17(6):613-619

Key Words Alzheimer's disease, Exercise, Cortical thickness, Subcortical volume, Structural MRI.

INTRODUCTION

Alzheimer's disease (AD) is a major global health burden, with doubled world-wide prevalence in 26 years due to increase in aging population.[1] Despite numerous efforts to unravel the exact mechanism of the disease, effective treatment and prevention options remain elusive.[2] Instead of the single view of amyloid cascade hypothesis in understanding AD, many researchers are beginning to advocate 'multifactorial hypothesis,' calling for the need to consider multiple targets when developing prevention or treatment strategies for AD.[3] In this regard, individual life style factors, environmental stress and resultant 'allostatic load' has been suggested as a major influencing factors in the disease trajectory of AD.[4] In line with this stance, recent major trials reported significant benefits of lifestyle interventions in those with high risk of AD.[5]

Among many lifestyle and nonpharmacological interventions frequently discussed,[6] physical exercise is increasingly accentuated as a potential therapeutic strategy for AD,[7] with its beneficial effects on mitochondrial function, brain plasticity, neurogenesis and cerebral blood flow.[7,8] One randomized controlled trial conducted to evaluate the effects of moderate-to high intensity aerobic exercise on mild AD patients demonstrated significantly reduced neuropsychiatric symptoms and cognition.[9] Another randomized study on mild to moderate AD patients reported rather a contradicting result, demonstrating

Received: June 5, 2020 **Accepted:** June 9, 2020

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that a 4 month structured, moderate to high intensity aerobic exercise did not influence cognition, quality of life, or caregiver burden.[10] According to recent systematic reviews, the impact of physical exercise on AD is inconclusive, due to lack of large sample sizes, methodological disparities across studies and lack of prospective designs.[11,12] Moreover, studies on preclinical AD population remain relatively scarce.

Neuroimaging studies are also too scarce to demonstrate the impact of physical exercise on AD trajectory. There have been evidences of increased cortical thickness and attenuated influence of amyloid on cognition in older adults who have higher cardiorespiratory fitness, but sample sizes were small.[13,14] There were no brain volume changes of AD patients after a 16-week aerobic exercise with duration of 60 minutes.[15] Meanwhile, 12-week moderate intensity walking in mild cognitive impairment (MCI) patients was significantly associated with increased cortical thickness. However, the study lacked a modest sample size and information on amyloid deposition.[16] Another study reported similar results, with 12-week multimodal physical exercise program only proven to be effective for MCI patients but not in AD patients.[17] Contradicting results on AD and MCI patients may be due to the differential impact of exercise in the different stages of AD trajectory.

In this study, we aimed demonstrate the impact of physical exercise on the cortical thickness and subcortical volume of preclinical AD patients, who are cognitively normal but with amyloid deposition. We hypothesized that cortical thickness and subcortical volumes of preclinical dementia patients with physical exercise will be reduced when compared with their counterparts.

METHODS

Subjects

Sixty-three preclinical AD subjects were included in this study. They were recruited from the normal control volunteers of the Catholic Dementia Brain Imaging Database, which holds brain scans of outpatients and inpatients at the Department of Geriatric Psychiatry, the Saint Vincent's Hospital, the Catholic University of Korea from 2010 to 2016. The inclusion criteria of the Exercise group were as follows: 1) subjects aged ≥60 years; 2) Mini-Mental Status Examination score ≥27; 3) Clinical Dementia Rating=0;[18] 4) amyloid retention corresponds to global mean standard value uptake ratio (SUVR) ≥1.4. 5) Doing moderate intensity aerobic exercise (e.g., mountain climbing, dancing, and swimming) more than one hour per day, 5 days per weeks.[19] Most of the inclusion criteria of the Non-Exercise group were the same as the Exercise group [1)−4)], except for the criteria that the Non-Exercise group had a history of doing walking less than 10 min or no exercise per day, 5 days per weeks were included.[19] The cognitive functions of the subjects were evaluated with the Korean version of Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K),[20] which assess the following cognitive domains: verbal fluency, 15-item Boston naming test (BNT), the Korean version of Mini Mental Status Examination (MMSE-K),[21] constructional praxis (CP), word list memory (WLM), word list recall (WLR), word list recognition (WLRc), constructional recall (CR). The study was conducted in accordance with the ethical and safety guidelines set forth by the local Institutional Review Board of the Catholic University of Korea and written informed consent was obtained from all study subjects.

PET acquisition

FBB [(F-18) florbetaben] was produced and FBB-PET data were collected and analyzed as previously described.[22] Each individual participant's MRI was utilized for co-registration and defining the ROI and for correcting partial volume effects from expanding cerebrospinal spaces accompanying cerebral atrophy.[23,24] Analysis of the FBB PET data utilized a standardized uptake value ratio (SUVR) 90 min post-injection, using the cerebellar cortex region of interest as the reference. Global Aβ burden was expressed as the average SUVR of the mean for the following 5 cortical ROIs: frontal, superior parietal, lateral temporal, and anterior and posterior cingulate cortex/precuneus as described in previous study.[24]

The FBB PET data were acquired within 4 weeks of clinical screening and cognitive function test. We used a cut-off for 'high' or 'low' neocortical SUVR of 1.4, consistent with cut-off values used in previous FBB-PET study.[25]

MRI acquisition

Imaging data were collected at the Department of Radiology, St Vincent's Hospital, The Catholic University of Korea, using a 3T Siemens Verio machine and eight channel Siemens head coil (Siemens Medical Solutions, Erlangen, Germany). The parameters used for the T1-weighted volumetric magnetization-prepared rapid gradient echo scan sequences were TE=2.5 ms, TR=1,900 ms, inversion time=900 ms, FOV=250 mm, matrix=256×256, and voxel size=1.0×1.0×1.0 mm.[3]

Data analysis

For cortical reconstruction and volumetric segmentation of the whole brain, Freesurfer image analysis suite (version 6.0, http://surfer.nmr.mgh.harvard.edu), which is documented and freely available online, was used. The technical details of these procedures have been described in previous publications.[26,27] Briefly, the processing stream includes a Talairach transform of each subject's native brain, removal of the non-brain tissue, and segmentation of the gray matter/white matter (GM/WM)

tissue. The cortical surface of each hemisphere was inflated to an average spherical surface to locate both the pial surface and the GM/WM boundary. The entire cortex of each subject was visually inspected, and any topological defects were corrected manually, blind to the subject's identity. The cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. The global mean cortical thickness for each subject was computed by averaging the cortical thickness at each vertex, right and left hemispheres separately, and was used in the statistical analyses. The regional thickness value at each vertex for each subject was mapped to the surface of an average brain template allowing visualization of data across the entire cortical surface (described at http://surfer. nmr.mgh.harvard. edu/fswiki/FsAverage). In addition, the entire cerebral cortex was parcellated into 34 regions,[28,29] and a variety of surface-based data, including maps of cortical volume and surface area as well as curvature and sulcal depth, were created. Data were resampled for all subjects onto a common spherical coordinate system.[30] The cortical map of each subject was smoothed with a Gaussian kernel of 10-mm full width at half-maximum for the entire cortex analyses. The subcortical volumes were obtained from the automated procedure for volumetric measures of the brain structures implemented in Freesurfer. In all, 27 volumetric measures were investigated and extracted seven subcortical structures (white matter, caudate, thalamus, pallidum, putamen, hippocampus, and amygdala) from each hemisphere.

Statistical analysis

Statistical analyses for demographic data were performed with the Statistical Package for Social Sciences software (SPSS, version 20.0, IBM Corp., Armonk, NY, USA). Assumptions for normality were tested for all continuous variables. Normality was tested using the Kolmogorov-Smirnov test. All variables were normally distributed. The independent t-test and the χ^2 test were used to assess potential differences between the Exercise groups and Non exercise groups for all demographic variables. All statistical analyses had a two-tailed a level of <0.05 for defining statistical significance. The general linear model (GLM) was implemented at each vertex in the whole brain to identify the brain regions in which the Exercise groups showed significant differences in cortical thickness relative to Non exercise group, using the FreeSurfer's mri_glmfit (described at http://surfer.nmr.mgh.harvard. edu/fswiki/mri_glmfit). The All analyses were performed for the right and left hemispheres separately. The threshold was set at p<0.05 [false discovery rate (FDR)] to resolve the problem of multiple comparisons. The seven subcortical structure volumes (i.e., total white matter volumes, thalamus, caudate nucleus, putamen, pallidum, hippocampus, and amygdala) were imported into the SPSS 20.0 software for statistical analyses (IBM Corp.). To assess the main effects of diagnosis on the volume of subcortical structures, we used analysis of covariance (ANCOVA) with TIV, education, gender, and age as nuisance variables.

RESULTS

Demographic and clinical characteristics of the study participants are summarized in Table 1. There was no significant difference in age, education, gender and CDR scores between Exercise group and Non-Exercise group. Among the cognitive domains of CERAD-K, there were significant differences in WLM, WLR, WRLc, and CR scores between the two groups, with Non Exercise group concordantly displaying lower scores.

When compared with Exercise group, Non-Exercise group

Table 1. Demographic and clinical characteristics of the study participants

	Exercise group (N=33)	Non Exercise group (N=30)	p value
Age (years±SD)	70.1±8.1	70.2±7.9	NS
Education (years±SD)	11.2±4.8	10.4±5.1	NS
Sex (M:F)	12:21	13:17	NS
CDR (SD)	0	0	
SUVR (SD)			NS
ACC	1.48±0.12	1.42±0.21	NS
FRC	1.34±0.13	1.32±0.12	NS
PAR	1.12±0.08	1.24±0.10	NS
LT	1.40±0.11	1.34±0.10	NS
PRC	1.44±0.12	1.43±0.12	NS
PCC	1.62±0.15	1.64±0.11	NS
Mean	1.50±0.12	1.48±0.10	NS
CERAD-K battery (SD)			
VF	13.4±3.9	11.8±4.1	NS
BNT	10.9±2.7	10.0±2.7	NS
MMSE	27.9±2.7	27.2±2.3	NS
WLM	16.9±4.3	13.7±4.7	0.004
CP	10.2±1.1	10.4±1.1	NS
WLR	4.5±2.2	2.3±2.4	<0.001
WLRc	8.0±2.2	5.9±2.7	<0.001
CR	5.3±3.3	2.6±2.2	<0.001

SD: standard deviation, NS: not significant, CDR: Clinical Dementia Rating, SUVR: standard value uptake ratio, ACC: anterior cingulate, FRC: frontal cortex, PAR: parietal cortex, LT: lateral temporal cortex, PRC: precuneus, PCC: posterior cingulate, CERAD-K: the Korean version of Consortium to Establish a Registry for Alzheimer's disease, VF: verbal fluency; BNT: 15-item Boston Naming Test, MMSE: Mini Mental Status Examination, WLM: word list memory, CP: constructional praxis, WLR: word list recall, WLRc: word list recognition, CR: constructional recall

demonstrated significantly reduced cortical thickness in left parstriangularis, rostral middle frontal, entorhinal, superior frontal, lingual, superior parietal, lateral occipital, inferior parietal gyrus, temporal pole, precuneus, insula, and fusiform gyrus (Table 2, Figure 1). Moreover, reduced cortical thickness in right precuneus, superiorparietal, lateral orbitofrontal, rostral middle frontal, medial orbitofrontal, superior frontal, lingual, middle temporal gyrus, insula, supramarginal, parahippocampal, paracentral gyrus was noted in Non-Exercise group (Table 2, Figure 1).

As for subcortical volumes, reduced subcortical volumes were noted in left thalamus, putamen, pallidum, hippocampus, amygdala in Non-Exercise group when compared with Exercise group (Table 3). Volumes of right thalamus, caudate, putamen, pallidum, hippocampus, amygdala were also reduced in Non-Exercise group (Table 3).

DISCUSSION

To the best of our knowledge, this is the first study to explore the effects of physical exercise on cortical thickness of preclinical AD patients. According to our results, WLM, WLR, WRLc and CR scores were reduced in Non-Exercise group. Moreover, cortical thickness, subcortical volumes of certain brain regions were reduced in Non-Exercise group when compared with Exercise group.

Reasons for the disparities in the CERAD-K scores between the two groups may be attributable to the benevolent effects of moderate-to high intensity exercise in daily life. Our results are in line with previous results, where there was a dose-response relationship between the amount of physical activity and cognitive function among the elderly.[31] Moreover, across the lifespan, subjects who reported that they have been phys-

Table 2. Voxel wise group comparison results where a significant cortical thinning was observed in Non-Exercise group relative to Exercise group (FDR corrected, p<0.05)

Region	Cluster size (mm^2)	Number of vertex	T max	Talairach coordinates		
				X	Y	Z
Left						
Parstriangularis	184.75	264	5.836	-48.2	33.3	1.5
Rostral middle frontal	192.58	346	5.714	-41.0	31.1	19.4
Entorhinal	162.01	348	4.565	-32.2	-9.8	-31.8
Superior frontal	112.62	183	4.041	-10.4	29.8	30.7
Lingual	101.41	215	3.875	-26.2	-45.6	-6.2
Superior parietal	29.77	80	3.741	-27.6	-60.8	44.1
Lateral occipital	44.07	80	3.721	-42.2	-68.1	6.5
Inferior parietal	59.10	102	3.707	-39.6	-79.3	15.2
Temporal pole	77.58	91	3.559	-38.4	8.7	-36.9
Precuneus	125.61	236	3.537	-18.2	-71.4	30.4
Insula	34.88	101	3.512	-37.4	-1.1	-14.4
Fusiform	34.75	61	3.501	-32.7	-36.6	-21.6
Right						
Precuneus	58.37	164	5.254	7.2	-51.5	62.7
Superiorparietal	82.11	134	4.622	18.7	-78.4	41.6
Lateral orbitofrontal	290.44	573	4.406	37.2	28.2	-16.6
Rostral middle frontal	412.33	575	4.224	30.6	49.5	2.5
Medial orbitofrontal	151.07	271	4.189	12.6	43.9	-4.6
Superior frontal	62.55	123	3.925	10.4	29.3	33.7
Lingual	67.47	166	3.636	23.3	-53.1	-2.2
Middle temporal	34.27	56	3.623	54.4	-17.3	-24.2
Insula	22.02	82	3.605	32.7	-24.8	19.1
Supramarginal	33.98	70	3.456	55.4	-37.0	19.1
Parahippocampal	21.11	72	3.328	21.6	-14.8	-27.8
Paracentral	47.66	131	3.279	13.9	-24.6	46.3

FDR: false discovery rate

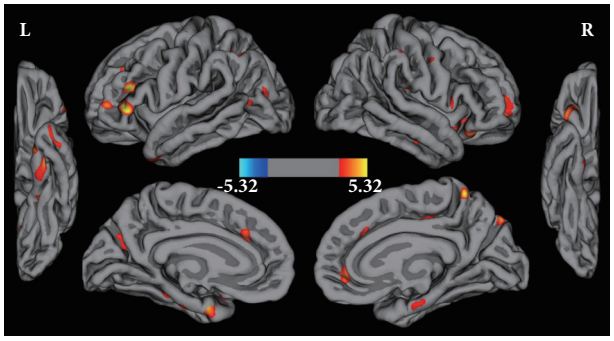

Figure 1. Statistical maps corrected for age, education, and gender showing increased cortical thickness in the Exercise group relative to the Non-exercise group (p<0.05 FDR corrected). FDR: false discovery rate.

Table 3. Group analysis results of subcortical volumes

Region (mm^3±SD)	Exercise group (N=33)	Non-exercise group (N=30)	p value
Left			
Thalamus	6,697±666	6,286±421	0.004
Caudate	3,242±450	3,129±463	0.301
Putamen	4,221±445	3,910±503	0.007
Pallidum	1,884±197	1,768±202	0.016
Hippocampus	3,635±367	2,972±346	<0.001
Amygdala	1,389 ±182	1,139±152	<0.001
Right			
Thalamus	6,669±665	6,230±415	0.002
Caudate	3,275±496	3,108±361	0.117
Putamen	4,328±541	4,012±387	0.007
Pallidum	1,816±208	1,769±199	0.332
Hippocampus	3,826±463	3,227±468	<0.001
Amygdala	1,573±224	1,322±206	<0.001

SD: standard deviation

ically active both in the early adulthood and mid-to-late adulthood were at lower risk of subjective cognitive decline.[32] Another study on the sample from the national survey reported that in those with family history of AD, subjective reports of higher physical activity was associated with greater cognitive function.[33] Even higher 'perceived' physical activity in subjective reports were associated with increased cognitive ability.[34] Meanwhile, Non-Exercise group in our study demonstrated lower scores in WLM, WLR, WRLc, and CR scores of the CERAD-K battery, which are closely related to the episodic memory assessment. They are domains where AD patients typically score less than their counterparts. Our results could imply that effects of exercise directly influence cognitive domains that are typically attacked by AD. Biological mechanisms explaining how exercise beneficially affects cognitive function are scarce. Many predict that exercise-induced elevations in physical function in turn results in cognitive function.[35] This is thought to be mediated by increased serum levels of brain-derived neurotropic factors (BDNF), insulin-like growth factor type-1 (IGF-1) and vascular endothelial growth factors (VEGF) often noted after physical exercise.[36]

The aforementioned increased markers of neurogenesis may explain the disparities in the cortical thickness between Exercise and Non-Exercise group in our study. Indeed, one study on healthy elders found that BDNF elevation was higher after physical exercise when compared with those measured after cognitive training.[37] Another explanation for the different results of cortical thickness between the two groups is the protective effects of exercise on neurovascular function. Exercise significantly improved blood brain barrier integrity in elderly women,[38] and exercise significantly increased endothelial function and cerebral blood flow, which can prevent neuronal hypoxia and degeneration.[39,40] Meanwhile, many of the regions that showed reduced cortical thickness in Non-Exercise group are components of default mode network (DMN), encompassing posterior cingulate cortex, precuneus, medial prefrontal cortex, mesial and inferior temporal cortex and inferior parietal cortex.[41] It is significant that important hubs of DMN, bilateral precuneus were all affected in None-Exercise group. It is in with a previous study where increased functional connectivity of DMN was observed in MCI patients after 12-week aerobic exercise.[42] DMN is a well-known for its vulnerability to disruption due to incipient AD pathology, and our results imply the preventive effects of physical exercise may be exerted through maintaining structural components of DMN in preclinical AD patients.

As for the results on subcortical volumes of the two groups, non-exercise group demonstrated reduced volumes of thalamus, caudate, putamen, pallidum, hippocampus, amygdala. Thalamic volume loss was proposed to be an early indicator of poorer cognitive performance in amnestic MCI patients in one study,[43] and early involvement of thalamus and striatum were noted in familial AD patients.[44] Moreover, subcortical volume loss increased the risk of conversion from MCI to AD.[45] Subcortical structures are proposed to be involved in the early stages of AD trajectory. In this regard, how exercise impacts those in the incipient stage of AD trajectory is of critical issue, but relevant studies are still scarce. A Japanese study on healthy elders demonstrated a meaningful result, with larger volumes of left hippocampus and bilateral nucleus accumbens in those exposed to frequent exercise habits.[46] Our study results are in line with the aforementioned result, and disparities in the subcortical volumes of the two groups in our study suggest the beneficial effects of exercise not only impact cortical structures, but also core subcortical structures in preclinical AD patients.

There are several limitations that must be taken into con-

sideration. First, subjects were recruited from a single center, which limits generalizability of results. Second, sample sizes were small. Third, assessment of quantity and intensity of exercise were solely based on patients' report, which is subject to recall bias. Fourth, the study was a retrospective, cross-sectional design. Fourth, information on apolipoprotein E (APOE) genotype was not provided, which limits more detailed interpretation of interactive effect of APOE and exercise on patients at high risk of AD.

There have been numerous interventional studies trying to explore the effects of exercise on cognition.[47-50] However, many are inconclusive due to heterogeneity of the study design and methods. Future studies should consider well-controlled and stringent selection of study population, structured, uniform exercise protocol and adequate sample sizes to achieve more conclusive findings on the relationship between exercise and AD.[35] Moreover, additional neuroimaging studies will be conducive to understanding the actual effect of exercise in patients at high risk of AD.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2019R1A2C2009100).

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Yoo Hyun Um, Hyun Kook Lim. Data curation: Hyun Kook Lim. Formal analysis: Hyun Kook Lim. Funding acquisition: Hyun Kook Lim. Investigation: Sheng-Min Wang, Dong Woo Kang, Nak-Young Kim, Hae-Ran Na. Methodology: Hyun Kook Lim. Project administration: Hyun Kook Lim. Resources: Hyun Kook Lim. Supervision: Chang Uk Lee. Writing—original draft: Yoo Hyun Um. Writing—review& editing: Sheng-Min Wang, Dong Woo Kang, Nak-Young Kim, Hae-Ran Na.

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