Hippocampal Response to a 24-Month Physical Activity Intervention in Sedentary Older Adults

Caterina Rosano, M.D., M.P.H., Jack Guralnik, M.D., Ph.D., M.P.H., Marco Pahor, M.D., Nancy W. Glynn, Ph.D., Anne B. Newman, M.D., M.P.H., Tamer S. Ibrahim, Ph.D., Kirk Erickson, Ph.D., Ronald Cohen, Ph.D., C. Elizabeth Shaaban, M.P.H., Rebecca L. MacCloud, B.S., Howard J. Aizenstein, M.D., Ph.D.

Background: *Greater hippocampal volume is observed in healthy older adults after short-term structured exercise. Whether long-term exposure to real-world physical activity (PA) programs has similar effects for sedentary older adults with impaired mobility and comorbid conditions is not known.* **Hypothesis:** *A long-term moderate intensity regimen of PA is related to larger volume of the hippocampus in older adults at risk for mobility disability. We further explore whether these associations are modified by factors known to be related to dementia.* **Methods:** *Twenty-six sedentary adults at risk for mobility disability participated in a 24-month randomized intervention program of physical activity (PA, N = 10, age: 74.9 years, 7 women) or health education (HE, N = 16, age: 76.8 years, 14 women). Volumes of total hippocampus, dentate gyrus, and cornu ammonis were measured at baseline and at 24-month follow-up using 7-Tesla magnetic resonance imaging. Between-group volumetric differences at 24 months were adjusted for sessions attended and baseline volumes. The contribution of each dementia-related factor was tested separately for education, APOE, diabetes, cardiovascular diseases, white matter hyperintensities, and brain atrophy.* **Results:** *Between-group differences were significant for left hippocampus, left cornu ammonis, and right hippocampus. Adjustment for regional baseline volume attenuated the associations to statistically nonsignificant for right hippocampus and left conru ammonis; associations for left hippocampus were robust for all adjustments. Results were similar after adjustment for dementia-related factors.* **Conclusions:** *In this group of sedentary older adults there was a hippocampal response to a long-term program of moderate-intensity PA. Future studies should examine whether hippocampal response could explain the beneficial effects of PA on cognition for vulnerable older adults.* (Am J Geriatr Psychiatry 2017; 25:209–217)

Key Words: Hippocampal, physical activity, ultra high field, mobility

Received April 8, 2016; revised October 7, 2016; accepted November 3, 2016. From the Graduate School of Public Health (CR, NWG, ABN, CES); Departments of Bioengineering and Radiology, Swanson School of Engineering and School of Medicine (TSI); Department of Psychology (KE); Department of Psychiatry (RLMC, HJA), University of Pittsburgh, Pittsburgh, PA; Department of Epidemiology & Public Health (JG), University of Maryland School of Medicine, Baltimore, MD; and College of Medicine (MP, RC), University of Florida, Gainesville, FL. Send correspondence and reprint requests to Dr. Caterina Rosano, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, 5139 Parran South, Pittsburgh, PA 15261. e-mail: rosanoc@edc.pitt.edu

© 2017 Published by Elsevier Inc. on behalf of American Association for Geriatric Psychiatry.

http://dx.doi.org/10.1016/j.jagp.2016.11.007

There is emerging evidence that well-functioning and healthy older adults participating in exercise interventions for up to one year display increases in hippocampal volume.[1–4] It is not known, however, whether hippocampal remodeling also occurs in older and frailer adults exposed to longer-term moderate regimens of physical activity (PA). For adults older than 70 years presenting with impaired mobility and a range of comorbidities, exposure to higher-intensity PA is not feasible; for these older adults, other moderate intensity and "real world" PA protocols need to be applied. Examining hippocampal remodeling in these vulnerable older adults is of great public health relevance because of their high risk of dementia and the rapid growing rates.

To address this issue, we examined changes in hippocampal volume in a randomized clinical trial of real-world and moderate-intensity PA for 2 years, targeting adults 70 years and older at higher risk of physical disability. Among this population of older adults, exposure to this type of PA was shown to be beneficial for psychomotor speed, with effects lasting up to 2 years after the end of the intervention,[5–7] lending support to the possibility of beneficial brain effects of this type of PA.

In addition to the whole hippocampus, we examine its two subregions, the cornu ammonis and the dentate gyrus, via the use of ultra high field neuroimaging at 7 Tesla. Human studies of PA effects have mostly examined the hippocampus as a whole and have not examined its subregions because of limitations in the resolution of neuroimaging methodology. To date, most of the evidence for a differential effect of PA on these subregions is from animal studies that indicate a preferential effect of PA on volume of the anterior hippocampus, including subfields of dentate gyrus and cornu ammonis.[8] The dentate gyrus and the cornu ammonis display differential vulnerability to aging and disease. For example, the smaller volume of the cornu ammonis has been related to earlier stages of cognitive impairment,[9–11] and precedes volumetric loss in other hippocampal subregions. Cornu ammonis is preferentially susceptible to ischemic damage.[12] On the other hand, the dentate gyrus is the only hippocampal subregion that retains neurogenesis potential late in life. Therefore, examining the associations between PA and changes in hippocampal subregions can further our understanding of the mechanisms underlying the neuroprotective effects of PA in vulnerable older adults.

METHODS

Overview of the Parent Study

The Lifestyle Interventions and Independence for Elders (LIFE, U01 AG022376; http://clinicaltrials.gov/ct2/show/NCT01072500) study was a phase 3 single-masked randomized controlled clinical trial evaluating the effects of a long-term moderate-intensity PA on physical and cognitive function in 1,635 sedentary older adults aged 70–89 years with compromised function (short physical performance battery <10).[13] Other inclusion criteria were ability to complete the 400-m walk test within 15 minutes without sitting or the help of another person; and willingness to be randomized to either intervention group. The exclusion criteria reflect conditions that may interfere with the conduct of the physical activity program.[13]

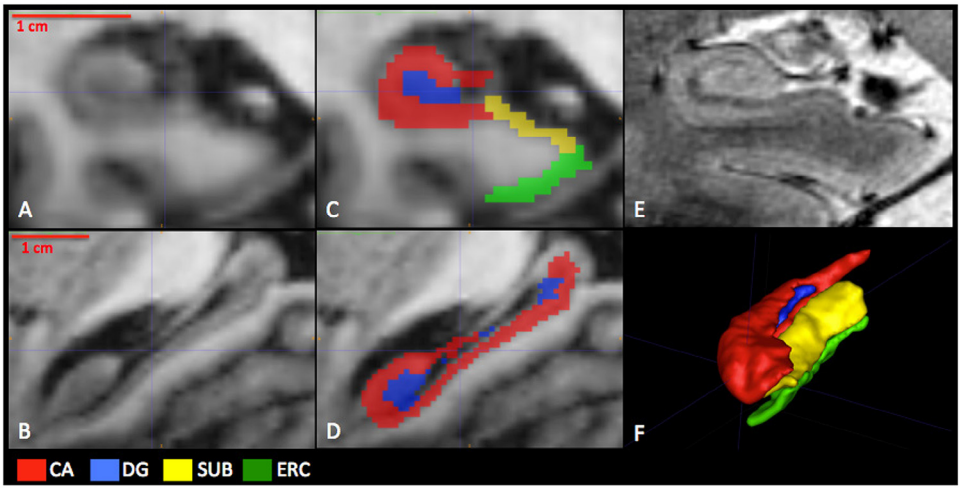
The PA intervention consisted primarily of walking at moderate intensity, lower extremity resistance exercises, balance exercises, stretching, and behavioral counseling. The PA program was compared with a health education (HE) program, consisting of health education seminars regarding health-related matters and upper extremity stretching exercises. The primary outcome was major mobility disability (inability to walk 400-m within 15 minutes), with cognitive function as a secondary outcome over an average of 2.6 years (range: approximately 2–4 years). LIFE participants received concurrent assessments of cognition, mobility, and subclinical vascular conditions. Number of sessions attended was recorded for each group. Percentage sessions attended was computed separately for the two groups by dividing the number attended by the total possible number for that group (187 for the PA and 39 for the HE).

Information on levels of physical activity was collected by self-report using the CHAMPS questionnaire at 6, 12, and 24 months (http://clinicaltrials.gov/ct2/show/NCT01072500).[14,15]

Recruitment

The parent study was conducted at eight sites in the United States; the current analyses focus on participants recruited at the Pittsburgh site. Of the 1,818 adults who were telephone-screened at the Pittsburgh site, 880 were screened in person for eligibility and 216 were enrolled and randomized to the HE or PA group

FIGURE 1. MPRAGE (Magnetization-prepared rapid gradient-echo) image of one subject in [A] coronal view and [B] sagittal view. Segmented subregions in [C] coronal view and [D] sagittal view. Susceptibility weighted image in [E] coronal view. [F] 3D rendering of template subregions. CA: cornus ammonis; DG: dentate gyrus; SUB: subiculum; ERC: entorhinal cortex.



starting from March 2010. In December 2010, this neuroimaging ancillary study began and all participants who entered the study from that time forward (N = 139 and 216, respectively) were screened for MRI interest and eligibility. A total of 65 HE and 139 PA participants were eligible and agreed to undergo brain magnetic resonance imaging (MRI). When participants returned for their 24-month follow-up, they were again screened and interviewed for MRI eligibility; 36 underwent a second MRI within 1 month of their 24-month visit and, of these, 26 had readable hippocampal subfields at both time points. Ineligibility rates were similar in the PA and in the HE group.

Magnetic Resonance Image Acquisition

Magnetic resonance images were acquired at the MR Research Center at the University of Pittsburgh on a 7-Tesla human scanner (Magnetom, Siemens Medical Solutions, Erlangen Germany) using an eight-channel head coil (Rapid Biomedical GmbH, Rimpar, Germany). The high-resolution T1-weighted 3D MPRAGE sequence used for volumetric analyses was acquired in the axial orientation (TR/TE = 3,430/3.54, voxel size: 0.7 × 0.7 × 0.7 mm, 256 slices). The susceptibility-weighted-imaging (SWI)[16] pulse-sequence was acquired in the coronal orientation along the length of hippocampus to facilitate identification of landmarks for hippocampal subregion identification (Figure 1). SWI images were acquired with TR/TE = 1,570/15. Voxels were 0.25 mm × 0.25 mm × 1.5 mm (x, y, z); 50 slices were acquired in the coronal orientation.

Hippocampal Segmentation

Hippocampal segmentation was done using a combination of a shape-based method (FIRST[17]) for defining the entire hippocampus and atlas-based segmentation to segment the subfields within the hippocampus (Figure 1). This was done for each individual at each time point separately, by a rater blinded to group assignment. Three subregions were identified: cornu ammonis 1–3, which represents about 65% of the hippocampal formation in the LIFE-M cohort; dentate gyrus plus cornu ammonis 4 (~30%); and subiculum (~20%) (Figure 1). The atlas based segmentation method for segmenting the subregions is based on warping an individual atlas to fit each individual. For the atlas we used a manual tracing on 7-T images, from an older adult participant who was not part of this study, using MPRAGE and SWI. In particular, the SWI image allows for excellent visualization of the dentate granular zone. Neuroanatomical segmentation landmarks and guidelines[18–20] were used to trace the dentate gyrus,

cornu ammonis, subiculum, and the entorhinal cortex on the individual 7-T atlas (Figure 1). For defining the anterior border of the hippocampus we used guidelines described by Convit et al.[18] The method for warping to each individual involves a semi-automated skull stripping of each MPRAGE image, followed by a linear, hierarchical, and demons-based registration, as previously described.[21] The segmented hippocampus from the automated labeling pathway is then masked with the hippocampus boundaries identified with FIRST, which uses intensity-based tissue segmentation to correct the outer boundaries. The resulting segmented images were then visually inspected for accuracy of the segmentation. For 10% of the images the initial alignment appeared inaccurate, in that it did not follow the hippocampal–cerebrospinal fluid boundaries. For these cases, we noted that the original semi-automated skull strip had left a small amount of non-brain tissue around the temporal lobe. When this was further restripped, and the warp rerun, the alignment looked good for all but one image. That one image was excluded from the analysis. Raters were blinded to any information about the participants including time point and treatment group. Volumes of the subregions were computed using FSLSTATS[22] separately for baseline and follow-up. Number of gray matter voxels of each region was divided by number of gray matter voxels of total brain. Atrophy of total brain was computed as the ratio of gray matter volume of total brain by intracranial volume. Intracranial volume was calculated using BET,[23] as the volume contained within the "inner skull".

White Matter Hyperintensities

White matter hyperintensity (WMH) burden was imaged using a T2-weighted sequence (TR = 12500 msec; TE = 55 msec; voxel size = 0.5 mm × 0.5 mm × 6.0 mm) and T1-weighted MPRAGE (TR = 3430 msec; TE = 3.54 msec; voxel size = 0.7 mm × 0.7 mm × 0.7 mm). It was rated by consensus of two raters (CR, HJA) using a 0–3 visual scale based on Fazekas ratings.[24] Ratings consisted of the following: 0 = none, if no punctate hyperintense areas or periventricular rims; 1 = mild, if few punctate hyperintense areas and/or limited amount of hyperintense rims around the ventricular horns; 2 = moderate, if multiple punctate hyperintense areas and/or larger rims around the ventricular horns; or 3 = severe, if confluent subcortical hyperintense areas and/or rims all around the ventricles, including horns and sides. Because few individuals had a WMH rating of 0 (N = 4), we combined the 0 and 1 category to create a "none/mild" WMH burden category. We did not differentiate between periventricular and deep WMH.

Other Variables of Interest

Baseline weekly walking and strength training, demographic variables, and medical history were based on self-report.[13] Trained clinic staff measured body mass index based on weight in kilograms divided by height in meters squared. Gait speed was assessed with the 400-m walking test. Presence of at least one APOE e4 allele was determined based on blood draw. Modified Mini-Mental State Examination was administered by trained certified technicians.

Statistical Analyses

Median with interquartile ranges (IQRs) are presented for all continuous variables because of the small sample size, and sample sizes and percentages are reported for categorical variables. Between-group comparisons at baseline were tested using nonparametric tests. Specifically, Spearman's test was used to test correlations between continuous variables; Wilcoxon-Mann Whitney tests (Z-statistic, two-sided p value) or Fisher's Exact χ^2 tests were used to compare medians or proportions between groups, respectively. Linear regression models were used to test the associations between group assignment and neuroimaging markers measured at 24 months, adjusted for percent of sessions attended first, and subsequently adjusted for the baseline value of that neuroimaging marker. Adjustment for percent of sessions attended was added to the model to capture actual engagement in the intervention. The Benjamini-Hochberg false discovery rate (FDR) was applied to correct for multiple comparisons with an alpha of 5%. The associations between risk factors for dementia (age, race, education, APOE e4 allele, and prevalence of cardiovascular and cerebrovascular disease) and regional volume at 24-month follow-up were also tested, adjusted for baseline volume. To further confirm the strength of the associations between group assignment and the outcomes, these variables were added to regression models one at a time and the change in

the coefficient of arm predicting the neuroimaging measure at 24 months was explored. In exploratory analyses, the variables modifying the association between group assignment and neuroimaging greater than 10% were tested for potential interaction with arm assignment.

RESULTS

The PA and HE groups had similar characteristics at baseline (Table 1). Participants in the PA group attended a median of 66.74% of the maximum number of 187 sessions from baseline to the 24-month follow-up. Participants in the HE group attended 90.6% of the maximum number of 39 sessions by the 24 month follow-up.

The PA group reported higher physical activity levels during the prior week as compared with the HE group at each of the follow-up time points (Figure 2). Between-group differences in self-reported physical activity levels from baseline to the 24-month follow-up were statistically significant (median [IQR] for HE and PA over the 24-month period: 88.13 [132.19] and 148.13[123.75], Wilcoxon-Mann Whitney Z-test statistic: 2.23, df = 1, p = 0.023).

Baseline characteristics of the participants with baseline and 24-month follow-up MRI were similar to those of the participants at the Pittsburgh site with baseline MRI only (Supplemental Table S1) and also similar to those of the participants of the parent study, with the exception of age (3 years younger) and race (more likely to be white).[13,25]

Larger hippocampal volume at the 24-month follow-up was associated with higher percent sessions attended for the PA group, but not for the HE group (Figure 3); Spearman partial correlation coefficients and p values adjusted for baseline hippocampal volume were −0.693 (p = 0.039) for the PA group (N = 10) and 0.201 (p = 0.473) for the HE group (N = 16).

TABLE 1. Baseline Characteristics of Participants in the LIFE Study

Characteristic	Physical Activity (N = 10)	Health Education (N = 16)	Test Statistic	p
Age at randomization, years	73.8 (5.6)	76.4 (9.8)	−0.55	0.58
Women	7 (70.0%)	14 (87.5%)	0.22	0.34
Education, high school or less	12 (75%)	5 (50%)	2.77	0.24
White race	6 (60.0%)	9 (43.8%)	0.31	0.99
Body mass index	32.8 (9.0)	32.6 (5.9)	0.37	0.71
Gait speed, m/sec	0.84 (0.2)	0.82 (0.2)	−0.11	0.92
Walking and strength training, minutes/week	15.00 (127.5)	15.00 (105.0)	−0.28	0.78
Modified Mini-Mental State Examination score	93.0 (7.0)	91.5 (10.0)	0.29	0.77
Digit Symbol Substitution Test	49.5 (16.4)	44.0 (13.7)	0.55	0.59
Cardiovascular conditions				
Prevalence of diabetes	3 (30.0%)	3 (18.8%)	0.29	0.64
History of cardiovascular disease	3 (30.0%)	5 (31.3%)	0.34	0.99
Apolipoprotein E e4 allele, ≥1 allele	2 (20.0%)	5 (35.7%)	0.26	0.65
Neuroimaging markers				
White matter hyperintensities =2 or 3	6 (37.5%)	3 (30.0%)	0.31	0.99
Intracranial volume[a]	4833.03 (625.44)	4715.40 (607.78)	0.82	0.41
Total brain volume[a]	1329.68 (102.63)	1292.19 (162.36)	0.50	0.62
Hippocampus,[b] left	3.58 (0.97)	3.46 (0.53)	1.08	0.28
Hippocampus,[b] right	3.84 (0.45)	3.39 (1.01)	1.58	0.11
Cornu ammonis,[b] left	2.61 (0.53)	2.39 (0.43)	1.45	0.15
Cornu ammonis,[b] right	3.07 (0.44)	2.64 (0.75)	1.58	0.11
Dentate gyrus,[b] left	0.94 (0.20)	0.95 (0.23)	−0.03	0.98
Dentate gyrus,[b] right	0.73 (0.15)	0.62 (016)	1.38	0.17

Notes: Values are median (IQR) or N (%), unless otherwise noted. Test statistics and p values are from Wilcoxon-Mann Whitney tests (Z-statistic, 2-sided p values) or Fisher's exact χ^2 tests for comparisons of medians or proportions, respectively. All tests reported have 1 degree of freedom.

[a]Median (interquartile range) of number of voxels.

[b]Median (interquartile range) of normalized gray matter volumes of each region, computed as: number of voxels from the gray matter of that region, divided by number of voxels from the gray matter of total brain; ratios are multiplied by 1,000 for ease of presentation.

FIGURE 2. **Physical activity related to walking and strength exercise, measured by self-report using the CHAMPS questionnaire at four time points from study entry to 24-month follow-up, presented separately for the physical activity (PA, red) and health education (HE, black) groups. Dashed lines indicate that activity was not measured at 18 months. Median values and standard errors of the median in minutes/week are presented.**

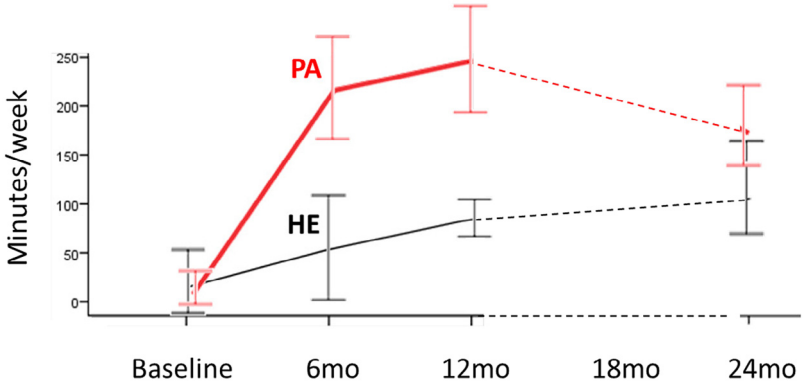
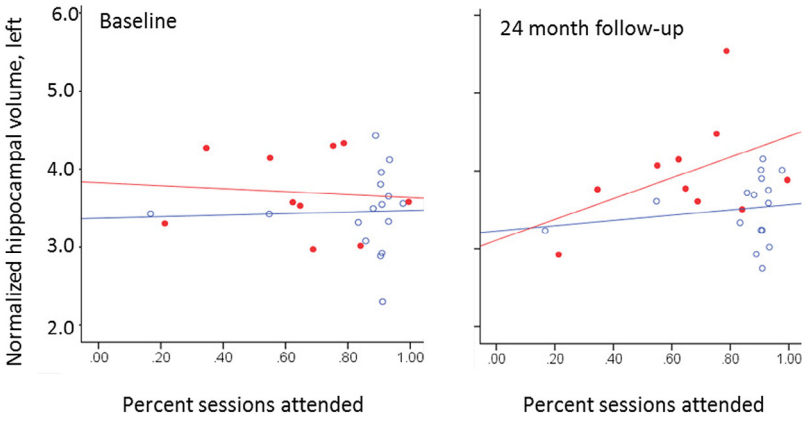


FIGURE 3. **Percent of sessions attended from study entry to 24-month follow-up (X axis) and left hippocampal normalized volume (Y axis) at baseline (left panel) and at 24 month follow-up (right panel).**
LEGEND: Values are presented for the Physical activity (PA) and Health Education (HE) groups (red and blue, respectively). Normalized hippocampal volumes were computed as: number of voxels from that region, divided by number of voxels from the gray matter of total brain; ratios are multiplied by 1000.



Between-group differences in the volumes of the hippocampus and its subregions at the 24-month follow-up were in the expected direction, with values larger in PA as compared with the HE group (Table 2). In linear regression models adjusted for percent sessions attended, between-group differences were significant after FDR correction for the whole hippocampus bilaterally (Table 2). After further adjustment for regional baseline volume, associations remained statistically significant only for the left hippocampus (standardized β[95% confidence interval]:1.002[0.135, 1.870], t = 2.40, df = 2, p = 0.026); these adjustments attenuated results for the right hippocampal volume (0.628 [–0.135, 1.392], t = 1.71, df = 2, p = 0.10) and the left cornu ammonis (0.875 [0.020, 1.730], t = 2.12, df = 2, p = 0.045). Associations for the right cornu ammonis and dentate gyrus bilaterally were not statistically significant. Results were similar with adjustment for

TABLE 2. Gray Matter Volume of Total Brain and Normalized Gray Matter Volume of Hippocampus and Hippocampal Subregions at 24-month Follow-up

	Normalized Gray Matter Volume, Median (IQR)		Results of Linear Regression Models for the Group Assignment Variable, Predicting Normalized Gray Matter Volume		
	Physical Activity (N = 10)	Health Education (N = 16)	Standardized Beta	t	p[a]
Total brain	1,317.738 (385.721)	1,312.158 (522.511)	0.19	0.42	0.68
Hippocampus, left	3.828 (0.649)	3.599 (0.521)	1.06	2.62	0.015
Hippocampus, right	4.141 (1.061)	3.694 (1.054)	1.01	2.51	0.020
Cornu ammonis, left	3.028 (0.560)	2.780 (0.441)	1.05	2.58	0.020
Cornu ammonis, right	2.665 (0.665)	2.435 (0.783)	0.84	1.97	0.060
Dentate gyrus, left	1.023 (0.298)	1.012 (0.208)	0.79	1.86	0.080
Dentate gyrus, right	0.815 (0.261)	0.695 (0.232)	0.68	1.58	0.130

Notes: Standardized betas, t test statistics, and p values of between-group differences are for the group assignment variable (physical activity = 1 and health education = 0) predicting gray matter volume in linear regression models adjusted for percent session attended. t tests all had 2 degrees of freedom. Normalized gray matter volumes of each region were computed as: number of voxels from the gray matter of that region, divided by number of voxels from the gray matter of total brain; ratios are multiplied by 1,000. IQR: interquartile range.

[a]Between-group comparisons significant after correction for False Discovery Rate (see text for details).

self-reported physical activity in lieu of percent sessions attended.

The associations between left hippocampal volume at the 24-month follow-up and other risk factors for dementia risk were not statistically significant; adjustment for these variables did not modify the main effect of intervention on left hippocampal volume (not shown). The interaction of baseline volume by arm assignment predicting follow-up volume was statistically significant for the left hippocampus and left cornu ammonis (β[95% confidence interval]: 1.182 [0.547, 1.81], t = 3.87, df = 2, p = 0.002 and 0.956 [0.277, 1.635], t = 2.93, df = 2, p = 0.008, respectively), but not for the right hippocampal volume (0.072 [–0.937, 1.082], t statistic = 0.15, df = 2, p = 0.88).

The mean (SD) values of left hippocampal volume normalized by intracranial volume followed a similar trend, and are as follows for the health education arm: at baseline 0.98 (0.15) and at 24 months 0.97 (0.13); and for the physical activity arm: at baseline 1.03 (0.10) and at 24 months 1.10 (0.19).

DISCUSSION

In this group of sedentary older adults at risk for mobility disability, participation in a 24-month PA program (relative to an education control) was associated with larger hippocampal volumes, independently of many known contributors of dementia risk. Our findings extend prior findings in younger and healthier elderly and indicate that the hippocampus may respond to moderate-intensity levels of PA even among older and frailer adults. The interaction of arm assignment with baseline hippocampal and cornu ammonis volume indicates that the post-intervention volume differences we observe in these regions were likely influenced by the baseline volumes; in other words, those with a higher baseline volume were more likely to experience change in hippocampal volume. Our observation suggests that a certain level of hippocampal volume (or integrity) may be necessary for PA to affect hippocampal response to PA. Further work is necessary to replicate this exploratory finding in a larger sample. Hippocampal volume may potentially act as a marker for personalizing intervention strategies for older adults.

Our use of ultra-high field imaging (7-T) allowed for segmentation of hippocampal subfields, to localize those subfields most strongly associated with PA-related effect. After controlling for baseline volume, the subfield analysis found results suggesting a PA-related effect in the left cornu ammonis. The fields of the cornu ammonis are known to be particularly

sensitive to environmental stress and aging.[26] Contrary to our hypothesis, we did not find significant associations with the dentate gyrus. Limited significant subfield findings are likely due to small sample size and limited power. Future studies in larger samples are warranted to examine the beneficial effects of this lifestyle intervention on hippocampal subregions. With the increased reliability of hippocampal subfield analyses even at 3-T (e.g., Yushkevich et al.[27]), future studies with larger samples will likely clarify the subfield specificity of hippocampal volume changes with exercise.

Associations appeared overall stronger for the left as compared with the right hemisphere. Previous reports of PA interventions have not shown a consistent pattern of hemispheric lateralization of PA effects on hippocampal volume. A greater susceptibility of the left hemisphere versus the right hemisphere to the process of aging is known,[28] but the reasons for this are still under investigation. Future studies with larger samples should examine potential for selected beneficial effects for one as compared with the other hemisphere, as well as the clinical implications of such differences.

Of interest is the association between percent of sessions attended and larger follow-up hippocampal volume in the PA group but not in the HE group. This finding suggests the presence of a dose-response effect (perhaps from the exercise and/or social stimulation) and needs to be further tested in a larger sample. Alternatively, it could be that the participants with low engagement may have had apathy, which would interfere with intervention engagement and also reflects preclinical disease.

A strength of the current study is its integration into the parent LIFE study,[14] which is one of the largest and longest studies of moderate-intensity PA in older adults to date, and focused on sedentary older adults at greater risk for mobility disability who may not be willing or may not be eligible to participate in higher intensity PA regimens. Secondary analyses of the parent LIFE study found that among the oldest and most frail individuals, PA had significant beneficial effects on executive control functions.[7] An association between this type of intervention and tests of executive function was also found at the end of a 1-year exposure in a prior study,[6] and up to 2 years after the end of the intervention.[5] These benefits on cognitive function are particularly relevant to our brain imaging findings. The hippocampus plays a role in cognitive flexibility, a component of executive function,[29] and is also the region most amenable to behavioral interventions.[30,31] We could speculate that the beneficial effects of PA on executive function would be mediated by hippocampal volumes responses. Although our study was not powered to test mediation effects, it underscores the relevance of further examining the beneficial effects of physical activity on the hippocampus in older and frailer adults.

There are several limitations in the current study. As in all MRI studies of older adults, magnetic resonance eligibility tends to introduce a bias toward healthier and younger participation. Such bias does not appear to be related to the strength of the magnet, however, and these rates are similar to what we have previously observed in our 3-Tesla studies. Unlike other PA clinical trials with neuroimaging, our study has the unique advantage of being able to quantify the bias introduced by scanning by comparing our cohort with the larger parent cohort. Indeed, we found little difference between our subsample and the parent cohort. Additionally, the number of participants is small (only 26), thus, our conclusions and power to estimate true effect sizes are limited. It is likely that a larger sample is required to better localize where in the hippocampus these changes are most prominent. Nevertheless, even with this minimal sample size we were able to demonstrate an effect of PA on hippocampal volume.

This work reinforces the potentially beneficial effects of moderate-intensity physical activity programs, by showing that among older and frail adults there is a positive effect on hippocampal volume post-intervention. This is important, as these older and frail adults are those at the highest risk for cognitive impairment. It is important for future studies to investigate these associations further in a larger sample size, especially in subregions of the hippocampus, and particularly the dentate gyrus, to gain a better understanding of the mechanisms underlying the neuroprotective effects of physical activity.

The Lifestyle Interventions and Independence for Elders Study is funded by a National Institutes of Health/National Institute on Aging Cooperative Agreement (UO1 AG22376) and a supplement from the National Heart, Lung, and Blood Institute (3U01AG022376-05A2S), and sponsored in part by the Intramural Research Program, National Institute on Aging, NIH. Support for this manuscript is also from grant

1R01AG044474-02: "Ultra-high-field neuroimaging in elderly after a two-year exercise intervention"; grant P30 AG024827; and the Claude D. Pepper Older Americans Independence Centers at the University of Florida.

The authors have no disclosures to declare.

APPENDIX: SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at doi:10.1016/j.jagp.2016.11.007.

References

1. Pereira AC, Huddleston DE, Brickman AM, et al: An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 2007; 104:5638–5643
2. Pajonk FG, Wobrock T, Gruber O, et al: Hippocampal plasticity in response to exercise in schizophrenia. Arch Gen Psychiatry 2010; 67:133–143
3. Rovio S, Spulber G, Nieminen LJ, et al: The effect of midlife physical activity on structural brain changes in the elderly. Neurobiol Aging 2010; 31:1927–1936
4. Erickson KI, Miller DL, Weinstein AM, et al: Physical activity and brain plasticity in late adulthood: a conceptual review. Ageing Res 2012; 4:e6
5. Rosano C, Venkatraman VK, Guralnik J, et al: Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J Gerontol A Biol Sci Med Sci 2010; 65: 639–647
6. Williamson JD, Espeland M, Kritchevsky SB, et al: Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. J Gerontol A Biol Sci Med Sci 2009; 64: 688–694
7. Sink KM, Espeland MA, Castro CM: Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults: the LIFE randomized trial. JAMA 2015; 314:781–790
8. Erickson KI, Voss MW, Prakash RS, et al: Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 2011; 108:3017–3022
9. Wisse LE, Biessels GJ, Heringa SM, et al: Hippocampal subfield volumes at 7T in early Alzheimer's disease and normal aging. Neurobiol Aging 2014; 35:2039–2045
10. La Joie R, Perrotin A, de La Sayette V, et al: Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia. Neuroimage Clin 2013; 3:155–162
11. Li YD, Dong HB, Xie GM, et al: Discriminative analysis of mild Alzheimer's disease and normal aging using volume of hippocampal subfields and hippocampal mean diffusivity: an in vivo magnetic resonance imaging study. Am J Alzheimers Dis Other Demen 2013; 28:627–633
12. Kawasaki K, Traynelis SF, Dingledine R: Different responses of CA1 and CA3 regions to hypoxia in rat hippocampal slice. J Neurophysiol 1990; 63:385–394
13. Pahor M, Guralnik JM, Ambrosius WT: Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE study randomized clinical trial. JAMA 2014; 311:2387–2396
14. Rejeski WJ, Axtell R, Fielding R, et al: Promoting physical activity for elders with compromised function: the lifestyle interventions and independence for elders (LIFE) study physical activity intervention. Clin Interv Aging 2013; 8:1119–1131
15. Stewart AL, Mills KM, King AC, et al: CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Med Sci Sports Exerc 2001; 33:1126–1141
16. Geerlings MI, Ruitenberg A, Witteman JC, et al: Reproductive period and risk of dementia in postmenopausal women. JAMA 2001; 285:1475–1481
17. Patenaude B, Smith SM, Kennedy D, et al: A Bayesian model of shape and appearance for subcortical brain. Neuroimage 2011; 56:907–922
18. Convit A, McHugh P, Wolf OT, et al: MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. Psychiatry Res 1999; 90:113–123
19. Pluta J, Mueller S, Craige C, et al: Hippocampal subfield segmentation protocol at 4T. Available at: http://www.itksnap.org/pmwiki/uploads/ExternalLinks/plutaprotocol.pdf
20. Yushkevich P, Wang H, Pluta J, et al: Nearly automatic segmentation of hippocampal subfields in in vivo focal T2-weighted MRI. Neuroimage 2010; 53:1208–1224
21. Wu M, Carmichael O, Lopez-Garcia P, et al: Quantitative comparison of AIR, SPM, and the fully deformable model for atlas-based segmentation of functional and structural MR images. Hum Brain Mapp 2006; 27:747–754
22. Yushkevich PA, Piven J, Hazlett HC, et al: User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006; 31: 1116–1128
23. Smith SM: Fast robust automated brain extraction. Hum Brain Mapp 2002; 17:143–155
24. Fazekas F, Chawluk JB, Alavi A, et al: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987; 149:351–356
25. Fielding RA, Katula J, Miller ME, et al: Activity adherence and physical function in older adults with functional limitations. Med Sci Sports Exerc 2007; 39:1997–2004
26. McEwen BS: Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol Aging 2002; 23:921–939
27. Yushkevich PA, Pluta JB, Wang H, et al: Automated volumetry and regional thickness analysis of hippocampal subfields and medial temporal cortical structures in mild cognitive impairment. Hum Brain Mapp 2015; 36:258–287
28. Taki Y, Thyreau B, Kinomura S, et al: Correlations among brain gray matter volumes, age, gender, and hemisphere in healthy individuals. PLoS ONE 2011; 6:e22734
29. Rubin RD, Watson PD, Duff MC, et al: The role of the hippocampus in flexible cognition and social behavior. Front Hum Neurosci 2014; 8:742
30. McEwen BS: Stress and hippocampal plasticity. Annu Rev Neurosci 1999; 22:105–122
31. Erickson KI, Leckie RL, Weinstein AM: Physical activity, fitness, and gray matter volume. Neurobiol Aging 2014; 35:S20–S28