EXERCISE AMELIORATES AGE-ASSOCIATED HIPPOCAMPAL ATROPHY IN AT-RISK ADULTS: EVIDENCE FROM THE WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION

Erin M. Jonaitis, PhD[1], Ozioma C. Okonkwo, PhD[1,2], Dorothy Edwards, PhD[1], Rebecca L. Koscik, PhD[1], Jennifer Oh[1,2], Asenath La Rue, PhD[1], Barbara B. Bendlin, PhD[1,2], Sterling C. Johnson, PhD[1,2] & Mark A. Sager, MD[1]

[1]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [2]Geriatric Research, Education and Clinical Center (GRECC), William S. Middleton Veteran's Administration Hospital, Madison, Wisconsin, USA

BACKGROUND

Evidence from numerous animal studies and a growing number of clinical investigations with older adults suggests that physical activity has salutary effects on brain health and cognitive function, even within the context of frank cognitive impairments[1-4]. Physical exercise stimulates hippocampal neurogenesis[1], and an inactive lifestyle has been tied to brain changes associated with Alzheimer's disease (AD)[4]. It is presently unknown whether these effects are observable in midlife. Therefore, in this study, we investigated whether exercise moderates the effect of age on hippocampal volume and cognition in a cohort of middle-aged adults at high risk for AD.

METHODS

Participants: The Wisconsin Registry for Alzheimer's Prevention (WRAP) is a longitudinal cohort (n>1500) enriched for positive family history of AD. Participants for the present analyses were 317 WRAP subjects (216 (68%) women; 232 (73%) FH+; 127 (40%) APOE4+) who had undergone T1-weighted MRI and had completed a self-report questionnaire assessing current physical activity[6]. Because WRAP is a family history cohort, our sample included some siblings from the same family. This study used data from 286 unique families (family sizes: 1=92%, 2=6%, 3=1%, 4=1%).

Exercise measure: Beginning at the second wave of the WRAP study, we asked participants to report their frequency and duration of walking and hard, moderate, and mild exercise using a questionnaire[5]. From these data, we computed an estimated hours per week of exercise for each participant (hours per day × days per week) and scaled it by intensity (hard = 7 METs; moderate = 4.5 METs; mild = 4 METs; walking METs estimated based on reported speed)[6]. Based on the derived MET-hours per week metric, we classified participants as High exercisers if they met AHA recommendations of at least 7.5 MET-hours per week (N = 238 (75%)). We also classified participants as Older if they were at least 60 years at the time of imaging (N = 177 (56%)). Characteristics of High and Low exercisers are summarized in **Table 1**.

T1 MRI Parameters: All participants were scanned on a GE 3.0 Tesla x750 scanner (General Electric, Waukesha, WI) using an 8 channel head coil. A T1-weighted brain volume was acquired in the axial plane with a 3D inversion recovery-prepared fast spoiled gradient-echo (3D SPGR) sequence using the following parameters: TI = 450 ms; TR = 8.1 ms; TE = 3.2 ms; flip angle = 12°; acquisition matrix = 256 × 256 × 156 mm, FOV = 256 mm; slice thickness = 1.0 mm. Voxels were 1 mm isotropic. Hippocampal volume was measured from the images using the FreeSurfer image analysis suite (surfer.nmr.mgh.harvard.edu) and standardized ~ N(0,1) for ease of interpretation..The data acquisition protocol also included T2-weighted and FLAIR anatomical scans which were reviewed by a neuroradiologist for exclusionary abnormalities. MRI data for each participant were linked to exercise scores from the WRAP visit nearest in time to image acquisition. The absolute value of the time interval between brain scan and exercise data ranged from 0 to 2.6 years, with a mean (SD) of 6 (5.0) months.

Cognitive measures: Cross-sectional cognitive analyses linked scores from the WRAP cognitive battery to concurrent exercise. Sixteen cognitive outcomes from seven tests were reduced to six factor scores[7], constituted as in **Table 2** and distributed approximately ~ N(0,1). Seven subjects were missing data for the speed & flexibility factor score and were excluded from that analysis only.

Statistical models: Linear mixed models (SAS PROC MIXED 9.3) were used to analyze the data. A random intercept was included to account for siblingship. Predictors of interest for both hippocampal and cognitive analyses included exercise (High vs Low) and its interactions with age (Older vs Younger) and sex. In addition to age and sex, included as main effects in both models, hippocampal volume analyses controlled for intracranial volume, and cognitive analyses controlled for education level. Substantive models were constructed in backward-elimination fashion, starting with the largest model (all covariates, main effects, and interactions) and removing nonsignificant interaction effects one by one. For both brain and cognitive data, primary analyses were run on the full set of subjects with complete data.

TABLES & FIGURES

TABLE 1. Participant Characteristics by Exerciser Status (Low vs. High)

	Exercise Status	
	Low (< 7.5 MET-hr/wk) (N=79)	High (≥ 7.5 MET-hr/wk) (N=238)
Age, over 60 (%)	**34 (43)**	**143 (60)**
Sex, female (%)	56 (71)	160 (67)
Race, white (%)	76 (96)	234 (98)
Education level, college (%)	49 (62)	163 (68)
APOE, ε4+ (%)	32 (41)	95 (40)
Family history, FH+ (%)	62 (78)	170 (71)
BMI, mean (SD)	**30.6 (6.3)**	**27.1 (4.5)**
Waist-hip ratio, mean (SD)	0.85 (0.1)	0.85 (0.1)
BP: Systolic, mean (SD)	126 (14)	123 (16)
BP: Diastolic, mean (SD)	75 (9)	73 (10)
Total cholesterol, mean (SD)	197 (35)	196 (34)
Insulin, mean (SD)	**11.9 (9.7)**	**8.5 (6.2)**
Glucose, mean (SD)	95 (10.8)	95 (17.6)
HOMA-IR, mean (SD)	**2.7 (2.4)**	**2.0 (1.8)**
IL-6, mean (SD)	2.1 (1.7)	2.0 (2.0)
CRP, mean (SD)	3.0 (3.3)	2.3 (4.4)
Baseline IQ, mean (SD)	**112.4 (8.5)**	**114.8 (8.6)**
Scan-test interval, months, absolute value, mean (SD)	**5.3 (4.6)**	**6.1 (5.2)**

Bold entries represent statistically significant (p < .05) group differences.

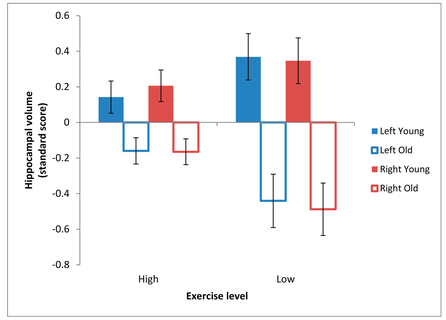
TABLE 2. WRAP Cognitive Factor Scores

Factor Score	Tests Included
Immediate Memory	Rey AVLT (Trials 1, 2)
Verbal Learning & Memory	Rey AVLT (Trials 3, 4, 5, delay)
Working Memory	WAIS-III (Digit Span Forward, Backward, Letter-Number Sequence)
Speed & Flexibility	Stroop (Color-Word), Trail-Making Test (A & B)
Visual Learning & Memory	Brief Visual Memory Test (immediate & delayed)
Story Recall	Logical Memory II (immediate & delayed)

TABLE 3. Regression Coefficients Predicting Cognition from Exercise

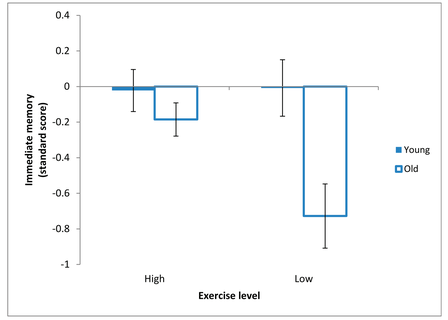
	Immediate memory	Verbal learning & memory	Working memory	Speed & flexibility	Visual learning & memory	Story recall
Age, over 60	-0.719	-0.316	-0.062	-0.777	-0.226	-0.012
Sex, female	0.798	0.883	0.176	0.171	0.398	0.285
Education level						
Some college	0.108	0.056	-0.156	0.043	0.115	0.111
BA/BS	0.212	0.266	0.144	0.063	0.150	0.357
Some postgrad	0.202	0.115	0.407	-0.003	-0.041	0.049
Exercise, High	-0.014	0.099	-0.026	0.344	0.074	0.144
Exercise × age	0.557	--	--	--	--	--
Exercise × sex	--	--	--	--	--	--
Legend: p-values	*>.10*	*<.10*	*<.05*	*<.01*	*<.001*	*<.0001*

FIG 1. MRI and Exercise: Interaction with Age



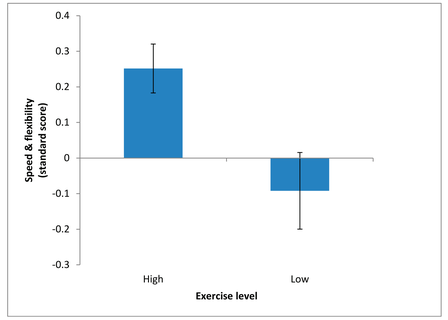
Bars represent least-squares means (±SE) adjusted for age, sex and intracranial volume.

FIG 2. Immediate Memory and Exercise: Interaction with Age



Bars represent least-squares means (±SE) adjusted for age, sex and education level.

FIG 3. Speed & Flexibility and Exercise: Main Effect



Bars represent least-squares means (±SE) adjusted for age, sex and education level.

RESULTS

Hippocampal volume: We constructed separate linear models for left (LH) and right (RH) hippocampal volumes. Adjusting for intracranial volume and sex, we found a significant exercise by age interaction (LH, $F(1,311) = 4.84$, $p = .029$; RH, $F(1,311) = 4.15$, $p = .042$). Simple main effects tests indicated a negative effect of age on hippocampal volume that was weaker in the High exercise group (**Fig. 1**; LH, Low: $\beta_{OLDER} = -0.81$, $F(1,311) = 16.67$, $p < .0001$; LH, High: $\beta_{OLDER} = -0.30$, $F(1,311) = 6.64$, $p = .01$; RH, Low: $\beta_{OLDER} = -0.83$, $F(1,311) = 18.21$, $p < .0001$; RH, High: $\beta_{OLDER} = -0.37$, $F(1,311) = 10.30$, $p = .002$). The exercise by sex interaction was nonsignificant in both hemispheres ($p > .10$) and was removed. Supplementary analyses indicated that Older participants were significantly more likely to report frequent engagement in exercise ($X^2_1 = 6.99$; $p = .008$).

Cognitive measures: We constructed separate linear models for six factor outcomes, adjusting for age, sex, and education level. For Immediate Memory, we observed a significant exercise by age interaction ($F(1,311) = 4.53$, $p = .034$). Simple main effects tests indicated a negative effect of age on memory performance in Low exercisers, but not High exercisers (**Fig. 2**; Low: $\beta_{OLDER} = -0.72$, $F(1,306) = 10.14$, $p = .0016$; High: $\beta_{OLDER} = -0.16$, $F(1,308) = 1.51$, $p = .22$). We also observed a significant effect of exercise on speed and flexibility with no interactions (**Fig. 3**; $\beta_{EXER} = 0.34$, $F(1,296) = 9.20$, $p = 0.0026$). The exercise by sex interaction was nonsignificant in all models ($p > .10$) and was removed. Other exercise effects were also nonsignificant in all other models. Betas from final models are presented in **Table 3**. Since cognitive data were collected at multiple sites, we reran final models adding site as a covariate; no meaningful changes to effects of interest were observed.

CONCLUSIONS

This study revealed that engagement in physical activities is associated with an attenuation of the deleterious influence of age on hippocampal volume and memory test scores, suggesting potential mechanisms for the influence of physical activity on AD risk reduction. Longitudinal analyses would help clarify whether these effects hold prospectively, as well as provide information on the extent to which midlife participation in physical activities protects against the development of AD and related disorders in later life.

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Erin Jonaitis, PhD, Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine & Public Health, Madison, Wisconsin USA Phone: 608-829-3300 Email: jonaitis@wisc.edu Web: www.wai.wisc.edu