Cognitive activity relates to cognitive performance but not to Alzheimer disease biomarkers

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ABSTRACT

Objective: We aimed to determine whether there was a relationship between lifestyle factors and Alzheimer disease biomarkers.

Methods: In a cross-sectional study, we evaluated self-reported histories of recent and past cognitive activity, self-reported history of recent physical activity, and objective recent walking activity in 186 clinically normal individuals with mean age of 74 ± 6 years. Using backward elimination general linear models, we tested the hypotheses that greater cognitive or physical activity would be associated with lower Pittsburgh compound B-PET retention, greater ^{18}F -fluorodeoxyglucose-PET metabolism, and larger hippocampal volume, as well as better cognitive performance on neuropsychological testing.

Results: Linear regression demonstrated that history of greater cognitive activity was correlated with greater estimated IQ and education, as well as better neuropsychological testing performance. Self-reported recent physical activity was related to objective exercise monitoring. However, contrary to hypotheses, we did not find evidence of an association of Pittsburgh compound B retention, ^{18}F -fluorodeoxyglucose uptake, or hippocampal volume with past or current levels of cognitive activity, or with current physical activity.

Conclusions: We conclude that a history of lifelong cognitive activity may support better cognitive performance by a mechanism that is independent of brain β -amyloid burden, brain glucose metabolism, or hippocampal volume. *Neurology*® 2015;85:48–55

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **AMNART** = American version of the National Adult Reading Test; **CA** = cognitive activity; **FDG** = ^{18}F -fluorodeoxyglucose; **FS** = FreeSurfer; **GLM** = general linear model; **mcPiB** = mean cortical Pittsburgh compound B; **MP-RAGE** = magnetization-prepared rapid-acquisition gradient echo; **PiB** = Pittsburgh compound B; **PrecFDG** = precuneus ^{18}F -fluorodeoxyglucose; **RelHippoVol** = relative hippocampal volume; **ROI** = region of interest; **TPA_{Self}** = self-reported total physical activity; **TWA_{Ped}** = pedometer-measured total walking activity; **Walk_{Self}** = self-reported walking activity.

Disproportionate growth of the elderly population has raised the profile of Alzheimer disease (AD) dementia as a major public health concern and motivated intense efforts to identify protective or preventive lifestyle factors. Cognitive and physical activities, that range from recent to lifelong, have positive effects on cognition and may reduce the risk of dementia.^{1–12} While the causal sequence remains to be established, cognitive activities hypothetically build cognitive reserve, which allows an individual to mitigate the effects of age-related brain pathology.^{4,13–15} A neurobiological basis for these hypothetical effects has been sought by relating cognitive^{5,16,17} or physical^{18–20} activity levels to AD biomarkers or postmortem histopathology, and links between a β -amyloid (A β) biomarker and cognitive¹⁶ and physical¹⁸ activity levels have been reported.

A β deposition, one of the defining pathologic constituents of AD, likely begins decades before the onset of dementia symptoms. Pittsburgh compound B (PiB)-PET studies, in line with autopsy data, have shown that 25% to 50% of normal older individuals show evidence of

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A β accumulation, with the frequency depending on the sample composition and choice of PiB binding cutpoint.^{21–26} Because A β deposition appears well established in many clinically normal older individuals, we tested the hypotheses that cognitive or physical activity was associated with A β deposition as well as other AD biomarkers of neurodegeneration. We measured A β burden with PiB-PET, brain metabolism with ¹⁸F-fluorodeoxyglucose (FDG) PET, hippocampal volume with MRI, and cognitive function with neuropsychological tests; in addition, we assessed lifelong cognitive activity⁵ and recent physical activity. We hypothesized that greater cognitive or physical activity would be associated with lower PiB retention, greater FDG metabolism, and larger hippocampal volume, as well as better cognitive performance.

METHODS **Standard protocol approvals, registrations, and participant consents.** This study was performed using protocols in accordance with and approved by the institutional review board of the Partners Human Research Committee, and with the informed consent of all participants.

Participants. One hundred eighty-six clinically normal older individuals (102 female) participating in the Harvard Aging Brain Study underwent clinical assessments by a study clinician, *APOE* genotyping, extensive neuropsychological testing, PiB- and FDG-PET imaging, and structural MRI at Massachusetts General Hospital. Participants were between the ages of 65 and 90 years (mean $\pm$ SD, 74 $\pm$ 6 years) and were from a wide range of socioeconomic backgrounds that was estimated using the Hollingshead²⁷ index. All participants had a Clinical Dementia Rating²⁸ global score of 0, scored 27 or higher on the Mini-Mental State Examination,²⁹ performed within 1 SD of education-adjusted cutoff scores on the delayed recall portion of one Logical Memory story of the Wechsler Memory Scale–Revised,³⁰ and scored 11 or lower on the Geriatric Depression Scale³¹ long form. In addition, verbal IQ was estimated using the American version of the National Adult Reading Test (AMNART).³² None of the participants met criteria for mild cognitive impairment, had any neurologic or medical illness, or any history of alcoholism, drug abuse, or head trauma.

Cognitive performance. A previously described confirmatory factor analysis³³ was conducted to create cognitive factor scores to reduce the reliance on individual neuropsychological subtests. The variables were organized into 3 primary factors: executive function (Exec), episodic memory (Memory), and processing speed (Speed). Variance in Exec could be further partitioned into that of 3 subfactors: fluency, working memory, and switching.

Cognitive activity. Participants' self-reported history of cognitive activity was assessed using the Cognitive Activities Scale, a previously reported autobiographical questionnaire that has been shown to have high internal consistency and temporal stability.^{4,5,16} Participants subjectively rated their current activity (11 items) as well as retrospectively rated their past activity at ages 6 (3 items), 12 (6 items), 18 (8 items), and 40 years (8 items) using a 5-point scale

(1 = once a year or less; 2 = several times a year; 3 = several times a month; 4 = several times a week; 5 = everyday or almost everyday). The questionnaire contained common activities, such as reading, writing, going to the library, and playing games such as crossword puzzles, which had minimal physical demands and applied to a diversity of ethnic and socioeconomic statuses.

As in previous studies that used the same questionnaire, composite scores were created for analyses by averaging item responses.^{4–6,16} Past cognitive activity (CA_{Past}) was an average of items from ages 6, 12, 18, and 40 years (25 items) and current cognitive activity (CA_{Current}) was an average of the current responses only (11 items).

Physical activity. Participants' physical activity was assessed with an autobiographical questionnaire as well as a pedometer worn by each participant for 7 days. The physical activity questionnaire asked participants to "indicate the number of occasions and average minutes per occasion" that they engaged in 6 different "exercises over the past 2 weeks."⁵ Activities suggested by the questionnaire included (1) walking for exercise, (2) gardening or yard work, (3) calisthenics or general exercise, (4) bicycle riding, (5) swimming or water exercises, and (6) dancing. The total physical activity (TPA_{Self}) and walking activity (Walk_{Self}) in minutes/week were calculated for each participant. Six participants incorrectly completed the physical activity questionnaire and were excluded from these analyses.

To evaluate current physical activity objectively, each participant was fitted with a pedometer (Omron Walking style Pro HJ-720IT-E2; Omron Healthcare Co., Ltd., Kyoto, Japan), which has been shown to accurately measure step count.³⁴ Based on stride length and body weight, each participant's total walking activity (TWA_{Ped}) was calculated in units of steps per day. Five participants were missing pedometer data and were not included in analyses using this variable.

MRI. MRI acquisition and processing have been previously described.²⁶ Briefly, high-resolution, T1-weighted structural images were acquired with a Siemens Trio 3.0T scanner (Siemens Medical Systems, Erlangen, Germany) using 3-dimensional magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequences.

The FreeSurfer (FS) software package was used to determine cortical (i.e., gray matter ribbon) thickness and hippocampal volume.^{35–37} Relative hippocampal volume (RelHippoVol) was calculated by regressing out total intracranial volume from hippocampal volume. FS also yielded for each participant's magnetic resonance dataset a probabilistic, atlas-based parcellation of the cortical surface into a set of cortical regions of interest (ROIs); average thickness associated with each cortical ROI was computed as the mean cortical thickness over all vertices in the ROI.^{37,38}

PET. PiB-PET data were acquired using a Siemens HR+ (Siemens CTI, Knoxville, TN), expressed as the distribution volume ratio with cerebellar gray reference, coregistered to MRI, and sampled according to FS ROIs as previously described.²⁶ Partial volume correction was applied as the 2-component method.³⁹ Mean cortical PiB (mcPiB) retention was calculated in an aggregate cortical ROI and was then pre-log transformed because of a positive skew, violating the assumption of a normal distribution for the dependent variable for significance tests. PiB retention was analyzed as both a continuous and binary variable; a mcPiB distribution volume ratio cutpoint of 1.6 was used to classify individuals into either PiB+ or PiB– groups, as in previous studies.²⁶

FDG was acquired using a Siemens HR+ (Siemens CTI). After a transmission scan, 5 mCi of FDG was injected and followed by a 30-minute uptake period before a 30-minute acquisition (ADNI [Alzheimer's Disease Neuroimaging Initiative] protocol). ROIs were

defined with FS after coregistration of each participant's MP-RAGE volume and FDG volume similar to the process described above for PiB. FDG was expressed as the standard uptake value ratio with cerebellar cortex as the reference tissue. Mean cortical FDG was calculated in the same aggregate of cortical ROIs as described above for PiB. In addition, since the precuneus is frequently associated with hypometabolism in AD dementia and predementia, we examined a precuneus ROI (PrecFDG). Since the 2 ROIs were highly correlated ($r = 0.88$, $p < 0.0001$), only PrecFDG is reported.

Statistical analysis. Statistical analysis was completed with JMP Pro 10.0.0 and SAS 9.4 (SAS Institute, Cary, NC). Two-tailed t tests were used to compare means between groups (M vs F, PiB+ vs PiB-, *APO* $\epsilon 4$ carrier vs noncarrier). Differences in the presence of an *APO* $\epsilon 4$ allele between groups were evaluated using contingency plots and a 2-tail Fisher exact test. Bivariate comparisons of activity variables were expressed with Pearson correlation r values.

For mcPiB, PrecFDG, and RelHippoVol, each as a dependent variable in a separate analysis, we ran a backward elimination general linear model (GLM) ($\alpha = 0.05$ cutoff) with an initial simultaneous predictor set of the following: age, *APO* $\epsilon 4$ dose, AMNART IQ, years of education, TWA_{Ped} , CA_{Past} , and $CA_{Current}$. We then ran the same group of GLMs for mcPiB, PrecFDG, and RelHippoVol, but substituted TPA_{Self} for TWA_{Ped} into the model. For mcPiB, a follow-up backward elimination GLM with the same simultaneous predictor set was again analyzed, but also included interaction terms of *APO* $\epsilon 4$ dose $\times$ CA_{Past} and *APO* $\epsilon 4$ dose $\times$ $CA_{Current}$. Residuals of all models were checked for conformance to assumptions of normality and homoscedasticity. Additional backward elimination multiple logistic regression analyses analogous to the GLMs for mcPiB were run but where binary PiB status, i.e., PiB+ or PiB-, was the predicted dependent variable.

For Exec, Memory, and Speed as dependent variables in separate models, we also ran a backward elimination GLM analysis with an initial predictor set of the following: age, *APO* $\epsilon 4$ dose, AMNART IQ, years of education, TWA_{Ped} , CA_{Past} , $CA_{Current}$, mcPiB, PrecFDG, and RelHippoVol. We then ran the same group of GLMs but substituted TPA_{Self} for TWA_{Ped} into the model. Furthermore, we ran more focused GLMs separately for Exec, Memory, and Speed, in which CA_{Past} , $CA_{Current}$, age, and *APO* $\epsilon 4$ dose were forced simultaneous predictors. Residuals were checked for all models as above.

RESULTS Participants. PiB status. There were 46 PiB+ and 140 PiB- individuals (table 1). PiB+ individuals were more likely to be *APO* $\epsilon 4$ carriers ($p < 0.0001$), were older ($p = 0.006$), and had lower Memory scores ($p = 0.04$) compared with PiB-. There was no $A\beta$ -related difference in AMNART IQ, years of education, socioeconomic status, Speed, Exec, CA measures, or physical activity. There was no difference in PrecFDG between the PiB groups; however, the PiB+ group had smaller RelHippoVol ($p = 0.008$) compared with the PiB- group.

Sex. There were 102 women and 84 men in the sample (table e-1 on the *Neurology*[®] Web site at Neurology.org). There were no sex differences in age, AMNART IQ, years of education, socioeconomic status, *APO* $\epsilon 4$ carrier status, Speed, or Exec; Memory scores trended nonsignificantly higher in

women ($p = 0.06$). Women reported greater CA_{Past} ($p = 0.007$) and $CA_{Current}$ ($p = 0.03$). There were no sex differences in TPA_{Self} or $Walk_{Self}$, but the TWA_{Ped} measure was lower in women ($p = 0.03$). Women had lower PrecFDG ($p = 0.01$), but there were no sex differences in mcPiB retention or RelHippoVol.

APOE genotype status. *APOE* genotype data were not available in 9 participants (all of whom were PiB-). Of the remaining 177 participants, 54 were *APO* $\epsilon 4$ carriers (2/4 in 6, 3/4 in 45, 4/4 in 3) while 123 were *APO* $\epsilon 4$ noncarriers (2/2 in 1, 2/3 in 13, 3/3 in 109). There was no difference in age, years of education, socioeconomic status, AMNART IQ, or any cognitive factor score between carriers and noncarriers. There were no differences in cognitive activity or self-reported physical activity measures between carriers and noncarriers. Noncarriers had greater TWA_{Ped} ($p = 0.04$). There were no differences in RelHippoVol or PrecFDG uptake. *APO* $\epsilon 4$ carriers had greater mcPiB retention than noncarriers ($p < 0.0001$).

Cognitive activity. Bivariate comparisons showed that greater CA_{Past} and $CA_{Current}$ were correlated ($r = 0.49$, $p < 0.0001$) and each was associated with higher education (CA_{Past} $r = 0.30$, $p < 0.0001$; $CA_{Current}$ $r = 0.29$, $p < 0.0001$) and higher AMNART IQ (CA_{Past} $r = 0.29$, $p < 0.0001$; $CA_{Current}$ $r = 0.26$, $p = 0.0004$). Education and AMNART IQ were correlated with each other ($r = 0.38$, $p < 0.0001$). No measure of CA was related to age.

Physical activity. Bivariate comparisons showed that greater self-reported recent physical activity (TPA_{Self} or $Walk_{Self}$) correlated with greater TWA_{Ped} ($r > 0.23$, $p < 0.005$). Age was not related to either TPA_{Self} or $Walk_{Self}$; however, increasing age was significantly associated with reduced TWA_{Ped} ($r = -0.30$, $p < 0.0001$).

Prediction of biomarkers. Relations of activity variables to AD biomarkers are demonstrated in figure 1. For the GLM analyses, PiB was significantly (all significant findings were at $p < 0.01$ except where noted) predicted only by age and *APO* $\epsilon 4$ dose, both in the expected positive direction. *APO* $\epsilon 4$ dose and CA interactions were nonsignificant. The logistic regression predicting PiB status (+/-) showed the same significant predictors. Higher PrecFDG was significantly predicted by older age and marginally by higher current physical activity (TPA_{Self} $p = 0.068$, and TWA_{Ped} $p = 0.064$ in separate GLM analyses). RelHippoVol was significantly predicted only by age, with older age predicting smaller volume. Except for the marginal relation of TPA_{Self} and TWA_{Ped} to PrecFDG, no measure of cognitive or physical activity was significantly related to any of the biomarkers. In

Table 1 Participant characteristics by PiB status

Characteristic	PiB–	PiB+	All
No.	140	46	186
Sex, no. F (%)	74 (53)	28 (61)	102 (55)
APO ε4 carrier, yes/no/NA	28/103/9 ^a	26/20/0 ^a	54/123/9
Age at PiB, y	73.7 ± 5.9 ^a (65.8–86.8)	76.6 ± 6.1 ^a (66.5–90.5)	74.4 ± 6.0 (65.8–90.5)
Education, y	16.2 ± 2.7 (8–20)	16.3 ± 2.8 (8–20)	16.2 ± 2.7 (8–20)
Hollingshead index	26.7 ± 14.3 (4–69)	28.1 ± 14.5 (11–61)	27.1 ± 14.4 (4–69)
AMNART IQ	121.0 ± 8.6 (95–132)	122.2 ± 9.2 (90–131)	121.3 ± 8.7 (90–132)
CA _{Past} (0–5)	3.04 ± 0.58 (1.52–4.32)	3.15 ± 0.55 (1.52–4.32)	3.07 ± 0.57 (1.52–4.32)
CA _{Current} (0–5)	3.32 ± 0.48 (1.82–4.45)	3.35 ± 0.56 (2.00–4.30)	3.33 ± 0.50 (1.82–4.45)
TPA _{Self} , min/wk	306.6 ± 288.4 (0–1,530)	296.6 ± 381.1 (0–1,565)	304.1 ± 312.5 (0–1,565)
Walk _{Self} , min/wk	109.5 ± 127.8 (0–540)	107.8 ± 165.0 (0–840)	109.1 ± 137.3 (0–840)
TWA _{Pedr} , steps/d	5,657 ± 2,792 (702–14,545)	5,180 ± 2,724 (1,055–11,899)	5,538 ± 2,776 (702–14,545)
mcPiB DVR	1.34 ± 0.09 ^a (1.11–1.58)	1.96 ± 0.24 ^a (1.62–2.44)	1.49 ± 0.31 (1.11–2.44)
PrecFDG SUVR	1.46 ± 0.15 (1.20–2.02)	1.45 ± 1.6 (1.18–1.83)	1.46 ± 0.15 (1.18–2.02)
RelHippoVol	105 ± 851 (–2,232 to 1,984)	–319 ± 934 (–2,222 to 2,306)	0 ± 889 (–2,232 to 2,305)

Abbreviations: AMNART = American National Adult Reading Test; CA_{Current} = current cognitive activity; CA_{Past} = past cognitive activity; DVR = distribution volume ratio; mcPiB = mean cortical Pittsburgh compound B retention; NA = not available; PiB = Pittsburgh compound B; PrecFDG = precuneus ¹⁸F-fluorodeoxyglucose; RelHippoVol = relative hippocampal volume; SUVR = standard uptake volume ratio; TPA_{Self} = self-reported total physical activity; TWA_{Pedr} = pedometer-measured total walking activity; Walk_{Self} = self-reported walking activity.

Values are mean ± SD (min–max) unless otherwise indicated. PiB– = mcPiB DVR <1.6; PiB+ = mcPiB DVR >1.6.

^a*p* < 0.05.

all GLM models, residuals were reasonably normally distributed and homoscedastic in conformance with test assumptions.

Prediction of current cognitive performance. Relations of activity variables to cognitive performance are demonstrated in figure 2. When age and APO ε4 dose were forced simultaneous predictors in the GLM along with CA_{Past} and CA_{Current}, greater CA_{Current} was significantly associated with better Exec and Speed, but not Memory (*p* = 0.12). CA_{Past} was not significantly related to any of the cognitive factor scores. When all relevant covariates were included with CA_{Past} and CA_{Current} in backward elimination GLMs, age and AMNART IQ had robust significant (*p* < 0.03) effects in the expected directions for all 3 cognitive factor scores (Exec, Memory, and Speed), while Education had a robust significant (*p* < 0.005) positive effect for Exec and Speed but not Memory. TWA_{Pedr} was marginally positively related to Exec (*p* = 0.07). CA_{Current} and CA_{Past} were not significant when AMNART IQ and education were covaried, with which they were moderately positively correlated. RelHippoVol had a significant positive effect on Memory (*p* = 0.01) and borderline significant (0.05 < *p* < 0.1) positive effect on Exec and Speed; mcPiB had a marginal (*p* = 0.056) negative relation to Memory, and PrecFDG did not have any significant effects on any of the cognitive factor scores. In all

GLM models above, residuals were reasonably normally distributed and homoscedastic.

DISCUSSION We did not find evidence of a protective effect of either cognitive activity, past or current, or recent physical activity on AD biomarkers. However, greater cognitive activity was associated with greater premorbid IQ and better performance on neuropsychological tests. A previous study in a subset of these participants³³ also reported a direct correlation between reduced cognitive performance using the neuropsychological factor scores with AD pathology biomarkers. These findings suggest that while a history of lifelong cognitive activity may support better cognitive performance, this relation is mediated by a mechanism independent of Aβ burden and markers of neurodegeneration (glucose metabolism and hippocampal volume) in cognitively normal older individuals.

A prior study¹⁶ compared PiB-PET data in 65 cognitively normal participants with self-reported current and past activity using the same cognitive activities scale as the current study. In contrast to our findings, they reported a direct association between greater cognitive activity and less PiB uptake. Past cognitive activity drove the relation with PiB uptake, and therefore they divided their sample into tertiles based on past cognitive activity. They found that cognitively normal older individuals who

Figure 1 Unadjusted data of cognitive and physical activity vs Alzheimer disease biomarkers

CAcurrent = self-reported current cognitive activity; CApast = self-reported past cognitive activity; mcPiB = mean cortical Pittsburgh compound B retention; PiB = Pittsburgh compound B; PrecFDG = precuneus ^{18}F -fluorodeoxyglucose; RelHippoVol = relative hippocampal volume; TPAself = self-reported total physical activity; TWaped = pedometer-measured total walking activity. Red diamonds = PiB- participants; blue crosses = PiB+ participants.

reported greater past cognitive activity had lower A β burden that was similar to a sample of 11 young controls, whereas cognitively normal older individuals who reported less past cognitive activity had greater A β burden that was similar to a sample of 10 individuals with AD dementia. In agreement with the current findings, they found no relation of self-reported physical activity to PiB-PET. The different findings between these 2 studies may be attributable to our larger sample size, lower levels of activity reported in our participants, and our backward elimination statistical approach.

Another study⁴⁰ of 118 cognitively normal individuals, which included all 65 individuals from the previously mentioned study,¹⁶ used hierarchical regression models adjusted for age, sex, and years of education to examine effects of *APO* $\epsilon 4$ carrier status, lifetime cognitive activity,

and the interaction of *APO* $\epsilon 4$ and cognitive activity with PiB retention. They found that lifetime cognitive activity moderated the effect of *APOE* genotype, such that PiB retention was lower in $\epsilon 4$ carriers who reported higher lifetime cognitive activity. They suggest that greater lifetime cognitive activity may prevent AD pathology, specifically in genetically susceptible individuals. In contrast, we found no interaction of *APO* $\epsilon 4$ dose with cognitive activity in relation to PiB retention.

Using PiB-PET, FDG-PET, and hippocampal volume as biomarkers in a sample of 515 clinically normal individuals, another study¹⁷ found that biomarker data were not correlated with lifetime intellectual, current intellectual, or current physical activities. As in the current study, cognitive activity and biomarkers, but not physical activity, were related to cognitive testing performance.

Figure 2 Unadjusted data of cognitive and physical activity vs cognitive performance

CAcurrent = self-reported current cognitive activity; CApast = self-reported past cognitive activity; Exec = executive function; Memory = episodic memory; PiB = Pittsburgh compound B; Speed = processing speed; TPAself = self-reported total physical activity; TWAped = pedometer-measured total walking activity. Red diamonds = PiB⁻ participants; blue crosses = PiB⁺ participants.

A neuropathologic study⁶ used the same retrospective cognitive activity questionnaire at baseline as the current study, and participants also underwent longitudinal cognitive testing to estimate rate of cognitive decline. Postmortem evaluations on 294 participants included measures of A β plaque burden, neurofibrillary tangle density, gross and microscopic cerebral infarcts, and neocortical Lewy bodies. In agreement with the current findings, greater cognitive activity across the lifespan was associated with slower late-life cognitive decline that was independent of common neuropathologic measures.

Strengths of the current study include the use of multiple neuroimaging modalities to measure multiple biomarkers of AD, as well as the examination of multiple cognitive domains using sensitive tests that yield a wide range of scores in clinically normal

elderly. Another strength is the use of pedometers to record an objective measure of physical activity not available in previous studies, although the measure relied on participant compliance and was limited to only 1-week duration. The study is limited, similar to previous studies, in that it was a cross-sectional association study. Measurement of lifelong cognitive and recent physical activity relied on a retrospective self-reported questionnaire, which is not free from participants' bias. Objective measures of lifelong cognitive and physical activity could possibly enable a better test of these hypotheses. Nonetheless, these results add to the current literature and align well with the results of other studies with large sample sizes,^{6,17} finding a relationship between lifelong cognitive activity and current neuropsychological testing performance without a direct relationship

between cognitive or physical activity and biomarkers of AD.

AUTHOR CONTRIBUTIONS

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DISCLOSURE

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