

# Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years

Eric D. Vidoni<sup>a</sup>, Robyn A. Honea<sup>a</sup>, Sandra A. Billinger<sup>b</sup>, Russell H. Swerdlow<sup>a</sup>,  
Jeffrey M. Burns<sup>a,\*</sup>

<sup>a</sup> KU Alzheimer and Memory Program, Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

<sup>b</sup> Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, Kansas City, KS, USA

Received 3 November 2010; received in revised form 22 February 2011; accepted 21 March 2011

## Abstract

We sought to describe change in cardiorespiratory (CR) fitness over 2 years in those with early-stage Alzheimer's disease (AD) and nondemented aging and assess the relationship of CR fitness with cognitive decline, brain atrophy, and dementia progression. Individuals with early-stage AD ( $n = 37$ ) and without dementia ( $n = 53$ ) attended clinical evaluations, cognitive and exercise tests, and magnetic resonance imaging (MRI) at baseline and 2 years later. CR fitness was lower in those with AD over the study period. Lower baseline CR fitness was associated with progression of dementia severity in AD. Declining CR fitness over 2 years was associated with brain atrophy in AD, especially in the parahippocampus. In nondemented participants, there was a trend for lower baseline fitness to be related to cognitive decline. Both lower baseline CR fitness and declining CR fitness over 2 years were associated with regional brain atrophy. We conclude that CR fitness is chronically reduced in those with AD. Further, in those with AD, CR fitness is associated with progression of dementia severity and brain atrophy in AD, suggesting a link between progression of dementia severity and cardiorespiratory health.

© 2012 Elsevier Inc. All rights reserved.

**Keywords:** Dementia; DARTEL; Maximal exercise test

## 1. Introduction

The benefits of physical activity for brain health are receiving increased attention (Kramer et al., 2005). In animals, exercise increases neuronal survival and resistance to brain insults (Carro et al., 2001; Stummer et al., 1994), promotes vascularization (Black et al., 1990; Isaacs et al., 1992), stimulates neurogenesis (van Praag et al., 1999), and mobilizes gene expression profiles predicted to benefit brain plasticity (Cotman and Berchtold, 2002). Additionally, running increases brain-derived neurotrophic factor levels in the hippocampus and dentate gyrus and influences long term potentiation (Neeper et al., 1995; van Praag et al., 1999). In

humans, several randomized controlled trials have examined the cognitive effects of increasing activity in healthy, older adults and found a beneficial impact on cognitive performance (Dustman et al., 1984; Hassmen and Koivula, 1997; Hill et al., 1993; Kramer et al., 1999; Williams and Lord, 1997). Several longitudinal studies report a positive relationship between self-reported physical activity and cognitive function (Laurin et al., 2001; Pignatti et al., 2002; Weuve et al., 2004; Yaffe et al., 2001).

There is an increasing interest in assessing the therapeutic role of exercise and physical activity in individuals with Alzheimer's disease (AD). Recently, greater physical activity and exercise in adults without dementia was associated with lower levels of AD biomarkers such as Pittsburgh Compound B binding (Liang et al., 2010). Additionally, a recent report showed that increased physical activity in those with dementia was associated with lower mortality risk (Scarmeas et al., 2010). Epidemiological studies sug-

\* Corresponding author at: Department of Neurology, KU Alzheimer and Memory Program, University of Kansas Medical Center, MS 1063, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA. Tel.: +1 913 588 0555; fax: +1 913 945 5035.

E-mail address: jburns2@kumc.edu (J.M. Burns).

gest regular physical activity may prevent cognitive decline and dementia, and in midlife is associated with a reduced risk of developing mild cognitive impairment and AD (Friedland et al., 2001; Geda et al., 2010). One such study found that dancing, an aerobic activity, was associated with lower risk for developing dementia (Verghese et al., 2003). Others have demonstrated in randomized controlled trials that aerobic fitness training improves cognitive performance in mild cognitive impairment (Baker et al., 2010; Scherder et al., 2005).

Limitations to previous studies include a reliance on reported activity levels and a lack of standard objective measures of physical activity. Physical activity and exercise influence cardiorespiratory (CR) fitness, an objective measure of an individual's peak level of oxygen consumption during a graded exercise test. CR fitness is associated with lower rates of cognitive decline in nondemented older adults (Colcombe and Kramer, 2003) but there is a paucity of data on individuals with AD regarding the relationship of CR fitness with dementia progression and structural brain change (Rolland et al., 2008). We previously reported cross-sectional data suggesting that CR fitness relates to whole brain (Burns et al., 2008) and medial temporal lobe volume (Honea et al., 2009) in individuals with AD. Additionally, we reported that CR fitness levels were lower in those with AD compared with nondemented peers (Burns et al., 2008). We now extend these findings by reporting the results of a 2-year observational study of individuals with early-stage AD and nondemented controls. We hypothesized that individuals with AD would have greater CR fitness decline compared with nondemented control subjects and that CR fitness would be associated with progression of dementia severity and brain atrophy.

## 2. Methods

### 2.1. Sample

Participants were enrolled in the University of Kansas Brain Aging Project for baseline and follow-up evaluations (mean follow-up time 2.1 [SD 0.2] years). Data used in these analyses were from nondemented individuals (Clinical Dementia Rating [CDR] 0,  $n = 53$ ) and individuals with early-stage AD (CDR 0.5 and 1,  $n = 37$ ) aged 60 years and older. Study exclusions at baseline included neurologic disease other than AD with the potential to impair cognition (e.g., Parkinson disease), current or past history of diabetes mellitus (defined as a clinical diagnosis, use of an anti-diabetic agent, or 2-hour postload serum glucose  $>199$ ), recent history of cardiovascular disease (e.g., diagnosis of congestive heart failure, acute coronary artery event, or angina in the 2 years previous to the baseline evaluation), clinically significant depressive symptoms, use of investigational medications, significant visual or auditory impairment, systemic illness that may have impaired completion of the study, current or past history of alcoholism, and

magnetic resonance imaging (MRI) exclusions (e.g., pacemakers). Baseline measures of these individuals have been reported previously as part of a larger cohort (Burns et al., 2008; Honea et al., 2009). Informed consent was obtained from all participants or their legal representative as appropriate before enrollment into the study.

### 2.2. Clinical assessment

The clinical assessment included a semistructured interview with the participant and a collateral source knowledgeable about the participant. Medications, past medical history, education, demographic information, and family history were collected from the collateral source. Dementia status of the participant was based on clinical evaluation (Morris et al., 2001). Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and at least 1 other cognitive and functional domain (McKhann et al., 1984). The CDR (Morris, 1993) assesses function in multiple domains and was used to assess dementia severity. The ratings in each of the 6 domains can be summed ("CDR Sum of Boxes") to expand the CDR scale. The range of Sum of Boxes extends from 0 (no impairment) to 18 (maximum impairment). A Global CDR score is derived from individual ratings in each domain such that CDR 0 indicates no dementia, CDR 0.5 indicates very mild, CDR 1 indicates mild, CDR 2 indicates moderate, and CDR 3 indicates severe dementia. Nondemented status was defined as having a Global CDR 0 at both timepoints. Individuals with AD met criteria for very mild or mild dementia and had persistent impairment at follow up (Global CDR 0.5 or greater). These methods have a diagnostic accuracy for AD of 93% and have been shown to be accurate in discriminating those with mild cognitive impairment who have early-stage AD (Berg et al., 1998; Morris et al., 2001).

### 2.3. Cognitive assessment

A trained psychometrician administered a psychometric battery including standard measures of memory, language, working memory, executive function, and visuospatial ability as described previously (Burns et al., 2008). All cognitive performance scores were standardized (Z-score) to a larger set ( $n = 82$ ) of nondemented subjects (positive scores represent better performance). The mean of each participant's Z-scores was calculated to create an index of global cognition, a composite measure of performance on the battery. The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was also administered to facilitate comparison across the literature.

### 2.4. Cardiorespiratory fitness assessment

CR fitness was assessed as peak oxygen consumption ( $\text{VO}_2$  peak; mL/kg/minute) during a symptom-limited, graded treadmill test using a modified Bruce protocol (Burns et al., 2008; Hollenberg et al., 1998) and metabolic cart (Parvomedics, Sandy, UT, USA) to measure the con-

centration of oxygen and carbon dioxide in expired air as described previously (Burns et al., 2008). Oxygen consumption was averaged over 15-second intervals.  $\text{VO}_2$  peak was considered the highest observed value during the exercise test. Individuals included in these analyses terminated the test at voluntary exhaustion and met criteria for peak exercise (respiratory exchange ratio (RER) of 1.0 or greater during the test) (Gibbons et al., 1997).

### 2.5. Neuroimaging

Baseline and follow-up whole brain structural MRI data were obtained using a Siemens 3.0 Tesla Allegra MRI Scanner. High-resolution T1 weighted anatomical images were acquired (magnetization-prepared rapid gradient echo [MPRAGE];  $1 \times 1 \times 1 \text{ mm}^3$  voxels, repetition time [TR] = 2500, echo time [TE] = 4.38 ms, inversion time [TI] = 1100 ms, field of view =  $256 \times 256$ , flip angle = 8 degrees) and processed for voxel-based morphometric (VBM) analysis. Every scan was checked for image artifacts and gross anatomical abnormalities; 18 data sets (9 from each group) were excluded.

We examined regional brain atrophy over the 2-year study period using SPM8 algorithms (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB 7.2 (The MathWorks, Natick, MA, USA) on Linux. VBM was used to compare changes over time in regional tissue volume. In this technique, a deformation field characterizes the high dimensional warp required to approximate baseline and follow-up T1 images within subject. First, the follow-up MRI of a subject was rigidly registered onto the subject's baseline image to remove position differences. Then we used a high dimensional deformation field to warp the follow-up T1 image to the baseline T1 image (Ashburner et al., 2000). The result of this deformation was a field map describing changes that occurred between baseline and follow-up. The local volume change was measured in each voxel by computing the determinant of the Jacobian matrix of the deformation field. The baseline gray matter segment and Jacobian determinants (containing information about the follow-up image) were multiplied, voxel-by-voxel, to form a product image, or gray matter volume change image (GM Change).

The baseline and follow-up images were segmented using the unified segmentation ("New Segment") model in SPM8 (Ashburner and Friston, 2005). To compare regional volume change between groups it was necessary to spatially normalize the baseline segmentation images to a common stereotactic space to ensure that the same voxel in different subjects sampled an approximately corresponding neuro-anatomic structure. To do this we used Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL), which is a suite of tools for achieving more accurate intersubject registration of brain images (Ashburner, 2007), increasing localization as well as sensitivity for VBM studies.

All subjects' gray matter volume segmentations were imported into DARTEL and used to create a customized template. This is a nonlinear image registration procedure, which involves iteratively matching all the selected images to a template generated from their own mean. This DARTEL template, as well as the estimated spatial normalization parameters, or flow fields from the template creation, were normalized to Montreal Neurological Institute (MNI) standard space. The flow fields from the template creation, as well as parameters from normalization to MNI space were then applied to the GM Change images. To preserve the original tissue volumes, the normalized GM Change images were modulated and smoothed with an 8 mm isotropic Gaussian kernel to accommodate inexact spatial normalization. The normalized, modulated, and smoothed GM Change maps for each individual were used in the statistical analysis outlined in the next section.

### 2.6. Statistical analysis

Group differences in demographic measures (age, gender, race, and education) were tested with Student's *t* or chi square tests as appropriate. To test for differences between groups and over the study period, group (AD, nondemented) and time (baseline, follow-up) effects were examined using repeated measures analysis of variance (ANOVA) across the study for CR fitness ( $\text{VO}_2$  peak), cognition (Global Cognition score), and dementia severity (CDR Sum of Boxes) corrected for age and gender.

To assess the relationship of baseline CR fitness ( $\text{VO}_2$  peak) with cognitive change (change in Global Cognition score) and progression of dementia severity (change in CDR Sum of Boxes; AD group only) we used a multistep, hierarchical linear regression with CR fitness as the predictor variable, separately for AD and nondemented groups. We adjusted all analyses for age and gender. In AD analyses we also controlled for baseline CDR Sum of Boxes ( $F = 3.94$ ;  $p < 0.05$  to retain). Using the same multistep hierarchical approach, we then explored the relationship of change in  $\text{VO}_2$  peak (follow-up, baseline) with CDR Sum of Boxes change and Global Cognition change as response variables.

To assess the relationship of CR fitness with brain atrophy, we used a full-factorial multiple regression model in SPM8 within each group (nondemented and AD separately). Baseline and change in  $\text{VO}_2$  peak served as the variables of interest, and age and gender (and baseline CDR Sum of Boxes in the AD group only) served as covariates of no interest, similar to the clinical model. The relationship between CR fitness and gray matter atrophy was considered significant at  $p \leq 0.05$  corrected for multiple comparisons (family wise error [FWE], and cluster size  $k > 100$ ), with trends presented at  $p < 0.001$ , uncorrected.

We also examined the relationship of change in CR fitness with medial temporal cortex atrophy in both the AD and nondemented groups. The medial temporal region of interest was selected a priori as it is affected early in AD

Table 1  
Demographics and baseline and change at follow-up measures

	Nondemented (n = 53)		Alzheimer's disease (n = 37)		Significance		
Age at enrollment	73.2 (6.7)		73.8 (5.8)		0.69	—	—
Gender (% female)	54.7		54.1		0.95	—	—
Education (years)	16.6 (2.7)		15.4 (3.2)		0.04	—	—
	Baseline	Δ At follow-up	Baseline	Δ At follow-up	Group effect	Time effect	Group × time interaction
Baseline MMSE	29.5 (0.8)	−0.3 (1.1)	26.7 (2.6)	−3.1 (5.2)	<0.001	0.102	<0.001
CDR Sum of Boxes	0 (0)	0 (0.1)	2.7 (1.1)	1.8 (2.7)	<0.001	0.042	<0.001
Global cognition	0.2 (0.5)	0 (0.4)	−1.3 (0.9)	−0.6 (0.7)	<0.001	0.142	<0.001
Peak oxygen consumption; VO <sub>2</sub> peak (mL/kg/minute)	23 (6.2)	−1.8 (2)	20.6 (3.6)	−2.4 (2.1)	0.003	0.831	0.214

Baseline group differences and change at the 2-year follow-up are presented along with the results of a repeated measures ANOVA of group and time. Key: ANOVA, analysis of variance; CDR, Clinical Dementia Rating; MMSE, Mini Mental State Examination.

(Braak and Braak, 1991), is considered a valid biomarker of AD neuropathology (Jack et al., 2002), and may be related to CR fitness (Honea et al., 2009; Tong et al., 2001). A mask of the region was created by combining bilateral hippocampus and parahippocampus, derived from the Wake Forest University Pickatlas ([www.fmri.wfubmc.edu](http://www.fmri.wfubmc.edu)) (Maldjian et al., 2003). To correct for multiple comparisons in this restricted region of interest, small volume correction (SVC) was employed and results were considered significant at  $p \leq 0.05$  FWE. Voxels are reported with reference to the MNI standard space and anatomic labels are reported with reference to the computerized Talairach Daemon (Lancaster et al., 1997) within the Pickatlas (Maldjian et al., 2003).

### 3. Results

#### 3.1. Demographics and cognition

AD and nondemented groups were not significantly different in age, gender, or race ( $p > 0.2$ , Table 1). All nondemented participants identified as white, with 1 reporting Hispanic ethnicity. Thirty-five participants with AD identified as white, 1 as African-American, and 1 as Native American. Individuals with AD had approximately 1 year less of formal education ( $p = 0.04$ ). At baseline evaluation 34 participants with AD had Global CDR of 0.5 and 3 had a Global CDR of 1. At follow-up, 23 participants with AD had a Global CDR of 0.5, 11 had a Global CDR of 1, and 3 individuals had a Global CDR of 2. Dementia severity (CDR Sum of Boxes) progressed over the 2-year study period by an average of 1.8 points. As expected, cognitive performance was lower in AD (Global Cognition, group main effect  $F = 117.9$ ,  $p < 0.001$ ) and significantly declined over 2 years compared with the nondemented group (group × time interaction,  $F = 21.2$ ,  $p < 0.001$ ). The results of the MMSE score analysis paralleled the results of the Global Cognition analysis (group × time interaction,  $F = 16.9$ ,  $p < 0.001$ ).

#### 3.2. Relationship of CR fitness with dementia

We then assessed between group differences in CR fitness (VO<sub>2</sub> peak) over the course of the 2-year study period. CR fitness was lower in the AD group compared with the nondemented group (group main effect,  $F = 9.2$ ,  $p = 0.003$ , Table 1). There was no time × group interaction ( $p > 0.2$ ).

We next assessed the relationship of baseline CR fitness to cognitive change and progression of dementia severity. In the AD group, lower baseline levels of CR fitness were associated with greater progression of dementia severity over the study (increase in CDR Sum of Boxes,  $\beta = -0.42$ ,  $p = 0.03$ , Table 2), controlling for age, gender, and baseline CDR Sum of Boxes. Fig. 1 depicts the relationship of baseline VO<sub>2</sub> peak and change in CDR Sum of Boxes. Baseline fitness was not associated with decline in Global Cognition in the AD group. We also examined the relationship of change in CR fitness over the study period with cognitive change and progression of dementia severity, again controlling for age, gender, and baseline CDR Sum of Boxes. CR fitness change was not associated with progression of dementia severity or change in Global Cognition in the AD group.

In the nondemented group there was a trend for baseline CR fitness to be associated with change Global Cognition ( $\beta = 0.36$ ,  $p = 0.06$ ), with lower CR fitness associated with a decline in Global Cognition after controlling for age and

Table 2  
Standardized coefficients ( $\beta$ ) predicting progression of dementia severity and change in global cognition after controlling for age, sex, and baseline dementia severity

	Dementia progression	Change in global cognition
Baseline VO <sub>2</sub> peak	−0.42 <sup>a</sup>	0.27
Change in VO <sub>2</sub> peak	−0.15	0.02
Baseline VO <sub>2</sub> peak	—	0.36 <sup>b</sup>
Change in VO <sub>2</sub> peak	—	0.19

Key: VO<sub>2</sub> peak, peak oxygen consumption.

<sup>a</sup>  $p < 0.05$ .

<sup>b</sup>  $p = 0.06$ .

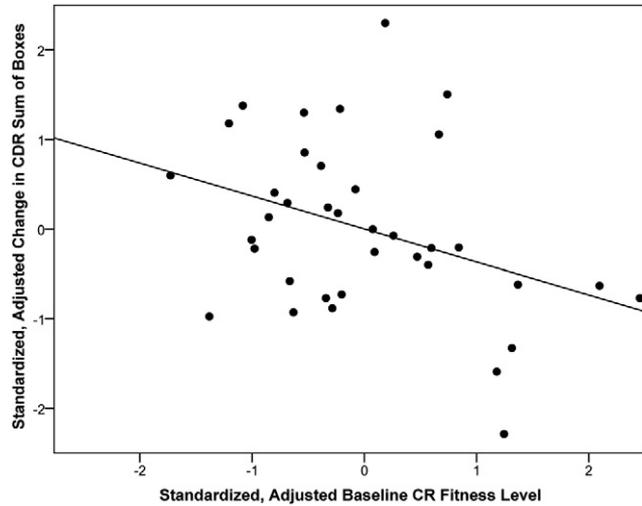


Fig. 1. Scatter plot of baseline cardiorespiratory (CR) fitness (peak oxygen consumption;  $\text{VO}_2$ ) plotted against progression of dementia severity (Change in Clinical Dementia Rating [CDR] Sum of Boxes), full model adjusted  $r^2 = 0.356$ ,  $p = 0.001$ . Higher CR fitness level (positive values along the x-axis) are associated with less progression in dementia severity over the course of the study (negative values along the y-axis),  $\beta = -0.42$ ,  $p = 0.03$ . Variables are adjusted for age, gender, and baseline CDR Sum of Boxes.

sex. Two-year change in CR fitness was not associated with decline in Global Cognition.

### 3.3. CR fitness and regional brain atrophy

We then assessed the relationship of baseline and 2-year change in CR fitness with atrophy patterns in AD. Though baseline CR fitness was not significantly related to regional gray matter atrophy in AD, we observed several trends ( $p < 0.001$ , uncorrected,  $k > 100$ ) where decline in CR fitness over the 2-year study period was associated with atrophy in the left parahippocampus, bilateral insular lobes, right lingual gyrus, right putamen, and right inferior temporal gyrus (Fig. 2, Table 3A). When our analysis was restricted to our

a priori region of interest, the medial temporal lobe, there was a significant relationship of change in CR fitness and atrophy in left parahippocampus (small volume correction,  $p < 0.05$  FWE), with 2-year decline in CR fitness associated with greater atrophy, controlling for age, gender, and baseline CDR Sum of Boxes.

In the nondemented group, there was a trend for lower baseline CR fitness to be associated with regional atrophy in bilateral occipital and temporal cortices and right uncus ( $p < 0.001$ , uncorrected,  $k > 100$ , Fig. 3A, Table 3B). There was also a trend for an association between decline in CR fitness and atrophy in the left frontal cortex and putamen and right caudate nucleus (Fig. 3B, Table 3C). Neither baseline CR fitness nor change in CR fitness was associated with significant atrophy in the medial temporal region of interest in the nondemented group.

## 4. Discussion

Our data show that higher baseline CR fitness in individuals with AD was associated with attenuated progression of dementia severity, independent of age, gender, and baseline dementia severity. Additionally, decline in CR fitness over 2 years was most notably associated with greater rates of medial temporal atrophy. In nondemented older adults, lower baseline levels of CR fitness were marginally associated with cognitive decline ( $p = 0.06$ ) and atrophy in temporal and posterior regions, whereas declining fitness was associated with frontal and subcortical atrophy.

### 4.1. CR fitness change over Time

Our first aim was to characterize CR fitness change in a population with early-stage AD. The AD group demonstrated consistently lower CR fitness levels than the nondemented group over the course of the study, extending our previously reported cross-sectional findings (Burns et al., 2008). However, our data do not demonstrate exacerbated decline in CR fitness in the AD group compared with the

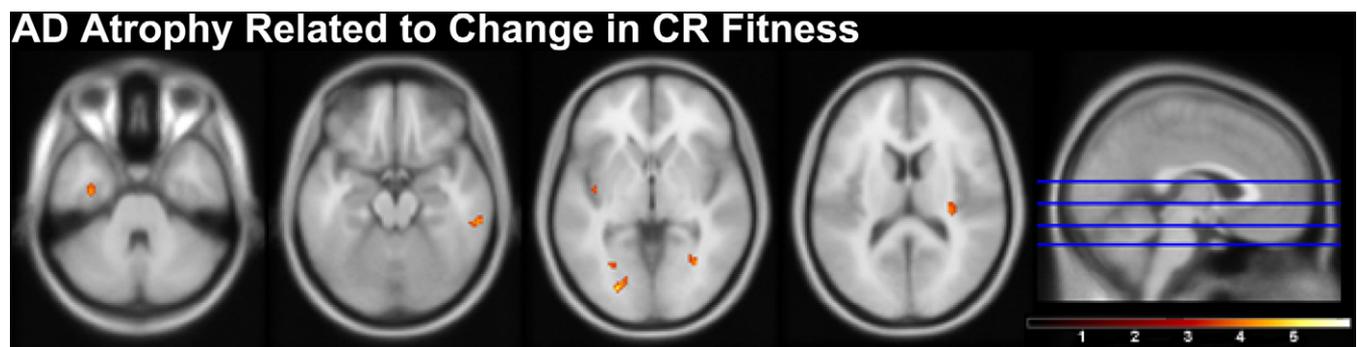


Fig. 2. Statistical parametric maps showing regions of brain atrophy associated with decline in cardiorespiratory (CR) fitness in the Alzheimer's disease (AD) group over 2 years. Anatomic locations are in Table 3A. Color bar represents T-statistics, with voxels presented at  $p < 0.001$  uncorrected, cluster size ( $k$ )  $> 100$ . Slices are presented inferior to superior at the location identified by the blue lines on the sagittal image on the right. The cluster in the right parahippocampal gyrus is significant (family wise error [FWE],  $p < 0.05$ ) under small volume corrected analysis of the medial temporal lobe.

Table 3

Regional atrophy associated with decline in VO<sub>2</sub> peak in AD (A) and with baseline (B) and decline (C) in VO<sub>2</sub> peak in nondemented participants

	k	T	Z	x	y	z
(A) Decline in VO <sub>2</sub> peak, AD group						
Left insula	191	4.35	3.65	−39	−10	0
Left fusiform/parahippocampal gyrus <sup>a</sup>	235	4.72	3.88	−35	−13	−30
Left lingual gyrus	176	4.34	3.65	−28	−61	−4
Left middle occipital cortex	153	5.32	4.22	−25	−82	−2
Right caudate	109	3.82	3.31	23	4	20
Right insula	327	4.24	3.58	30	−24	15
Right occipital cortex	101	4.50	3.75	33	−64	−2
Right inferior temporal gyrus	476	4.55	3.78	60	−32	−21
(B) Baseline VO <sub>2</sub> peak, nondemented group						
Left inferior temporal cortex	332	3.90	3.58	−69	−25	−20
Left middle occipital	345	3.67	3.39	−49	−84	10
Left superior occipital cortex	480	4.14	3.76	−34	−86	23
Right uncus	160	4.31	3.89	20	14	−33
Right middle temporal pole	with above	3.63	3.36	21	12	−43
Right middle occipital	309	3.75	3.46	49	−81	−19
(C) Decline in VO <sub>2</sub> peak, nondemented group						
Left inferior frontal gyrus	227	4.71	4.18	−48	20	6
Left middle frontal	128	3.88	3.56	−25	47	−13
Left putamen	319	3.91	3.59	−20	15	−7
Right caudate	138	3.83	3.52	14	27	5

Regions are listed left to right. x, y, and z coordinates refer to the MNI brain atlas. A minimum cluster size ( $k = 100$ ) was set as a threshold for uncorrected analyses.

Key: AD, Alzheimer's disease; MNI, Montreal Neurological Institute; VO<sub>2</sub> peak, peak oxygen consumption.

<sup>a</sup> Region is significant with small volume analysis in the medial temporal lobe with family-wise error correction ( $p < 0.05$ ).

nondemented group. These results suggest preclinical AD may impact physical activity and CR fitness levels before the clinical recognition of the disease. Early disease-related changes in physical activity may influence a cycle of decline that includes reduced CR fitness, brain and body changes, and functional decline that may exacerbate the AD syndrome. Alternatively, individuals with a lifetime history of physical inactivity may be at increased risk of developing the disease and thus are overrepresented in our AD cohort. This is consistent with prior reports linking low levels of physical activity, even in midlife, with mild cognitive impairment and dementia (Geda et al., 2010; Larson et al., 2006; Podewils et al., 2005; Rovio et al., 2005).

#### 4.2. Cardiorespiratory fitness, physical activity, and dementia progression

Our second aim was to explore the relationship of fitness with dementia progression. In the AD group we found that higher baseline CR fitness was associated with less progression of dementia severity (change in CDR Sum of Boxes) over the 2-year study period, independent of age, gender, and baseline dementia severity. This is consistent with the hypothesis that higher CR fitness may be associated with slower disease progression. CR fitness was not related to decline in cognitive performance despite the relationship with dementia severity. We suspect that CR fitness more closely reflects the functional domains assessed in the CDR. It is possible that individuals with higher CR fitness have greater physical function reserve that may reduce the functional impact of disease. Future studies may wish to use

more robust statistical techniques to accurately assess the relationship of CDR constructs to physical and cognitive measures.

When assessing change in CR fitness over the 2-year study period, we found that declining CR fitness was associated with brain atrophy in several regions in the AD group, including those most affected by AD neuropathology. The findings extend our prior cross-sectional report and suggest a relationship between a validated neuroimaging marker of AD neuropathological burden, atrophy in the medial temporal lobes (Barnes et al., 2004; Jack et al., 1998; Wang et al., 2003), and maintenance of CR fitness. We found specific regional brain volume associations with CR fitness in the left parahippocampus. This is interesting as this region is recruited to a greater degree during verbal memory tasks in those with mild AD and mild cognitive impairment than nondemented controls (Hamalainen et al., 2007; Peters et al., 2009). If the parahippocampal areas provide compensatory activity for task execution, CR fitness may further support sustained cognitive function in early AD, although it is important to note these data do not establish a causal relationship between physical activity and parahippocampal function.

While the observational nature of this study is unable to assess causal relationships, these data are consistent with the possibility that interventions to maintain CR fitness, such as exercise, may slow brain atrophy related to AD. This hypothesis is supported by data from animals that suggest exercise enhances neurogenesis, is anti-apoptotic, and promotes angiogenesis (Kim et al., 2010; Pereira et al., 2007).

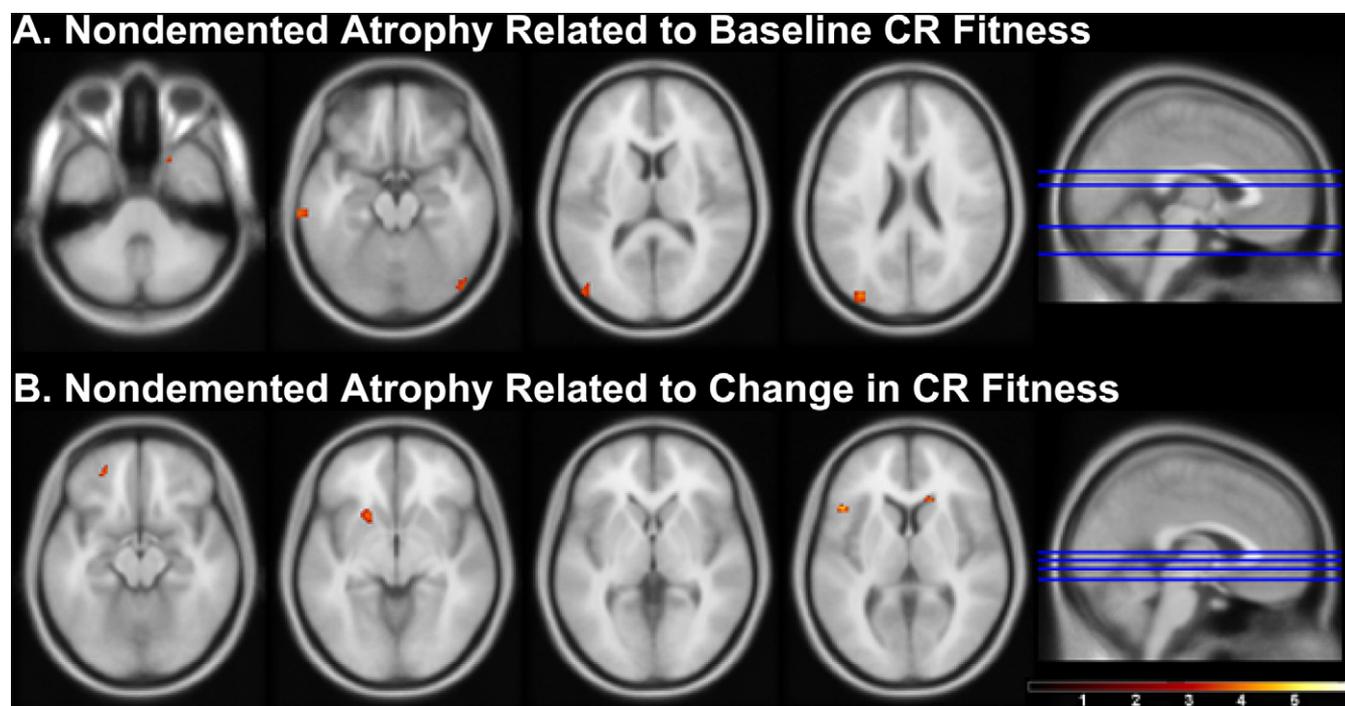


Fig. 3. Statistical parametric maps showing regions of brain atrophy associated with cardiorespiratory (CR) fitness in the nondemented group. Anatomic locations are in Table 3B and C. Regional atrophy is related to lower baseline (A) and decline (B) in CR fitness in the nondemented group. Color bar represents T-statistics, with voxels presented at  $p < 0.001$  uncorrected, cluster size ( $k$ )  $> 100$ . Slices are presented inferior to superior at the location identified by the blue lines on the sagittal image on the right.

Exercise has also been reported to influence imaging markers of neurogenesis in human hippocampus (Pereira et al., 2007).

The relationship of CR fitness and brain health is also moderately supported in our nondemented group, where greater baseline CR fitness was associated with less cognitive decline ( $p = 0.06$ ) and lower rates of brain atrophy in the occipital and temporal lobes, supporting previous reports (Colcombe et al., 2003; Erickson et al., 2010; Yaffe et al., 2001). Additionally, worse decline in CR fitness over 2 years was associated with atrophy in frontal and subcortical regions in our nondemented group. Some frontal and temporal atrophy is common in aging (Colcombe et al., 2003; Fjell et al., 2009), and moderate exercise has previously been shown to attenuate this change (Colcombe et al., 2006) and result in improvements in executive cognitive function (Colcombe et al., 2004; Kramer et al., 1999).

An alternative possibility to explain our observed relationship between CR fitness and disease progression is that an underlying effect of AD pathology concomitantly drives decline in cognition, brain atrophy, and CR fitness. For example, muscle mitochondria are responsible for a substantial degree of muscle oxygen consumption, and AD subjects have systemically reduced mitochondrial function (Swerdlow and Khan, 2009; Swerdlow et al., 1997). Over the course of the 2-year study period, AD subjects whose oxygen uptake capacity ( $VO_2$  peak) declined the most had

the greatest degree of brain atrophy suggesting these factors may be interrelated. It is important to note that our cohort is composed only of those individuals capable of satisfactorily completing an exercise test ( $RER > 1.0$ ) and reasonably reflects near maximal physiological capacity for oxygen consumption rather than motivation during the test. Thus, our findings suggest the possibility that declining respiratory function is a manifestation of the AD process, and emphasizes an emerging recognition of systemic biochemical dysfunction in AD.

In conclusion, we report that lower CR fitness seen early in AD persists over 2 years. Those with the lowest CR fitness in the earliest stages of AD experienced more severe AD progression. Further, declining fitness over 2 years was associated with greater brain atrophy in regions affected by AD neuropathology. The results support prior findings of a link between fitness and brain health in AD and indicate the need to further investigate the interaction of CR health and function and mechanistic links between CR fitness and brain change in AD.

#### Disclosure statement

The authors have no actual or potential conflicts of interest to disclose.

Informed consent was obtained from all participants or their legal representative as appropriate before enrollment into the study.

### Acknowledgements

This study was supported by grant R03AG026374-01 from the National Institutes of Aging, grant K23NS058252 from the National Institute on Neurological Disorders and Stroke, and generous support from the University of Kansas Endowment Association, William and Carolie Hougland, and the Fraternal Order of Eagles. The University of Kansas General Clinical Research Center (M01RR023940) provided essential space, expertise, and nursing support. The Hogle Brain Imaging Center is supported by grant C76 HF00201. E.D.V. is supported in part by a fellowship from the Foundation for Physical Therapy.

We thank Natalia Loskutova for her insight into early versions of the manuscript. We also appreciate the dedication of the Brain Aging Project team and participants.

### References

- Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113.
- Ashburner, J., Andersson, J.L., Friston, K.J., 2000. Image registration using a symmetric prior—in three dimensions. *Hum. Brain Mapp.* 9, 212–225.
- Ashburner, J., Friston, K.J., 2005. Unified segmentation. *Neuroimage* 26, 839–851.
- Baker, L.D., Frank, L.L., Foster-Schubert, K., Green, P.S., Wilkinson, C.W., McTiernan, A., Plymate, S.R., Fishel, M.A., Watson, G.S., Cholerton, B.A., Duncan, G.E., Mehta, P.D., Craft, S., 2010. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch. Neurol.* 67, 71–79.
- Barnes, J., Scahill, R.I., Boyes, R.G., Frost, C., Lewis, E.B., Rossor, C.L., Rossor, M.N., Fox, N.C., 2004. Differentiating AD from aging using semiautomated measurement of hippocampal atrophy rates. *Neuroimage* 23, 574–581.
- Berg, L., McKeel, D.W., Jr, Miller, J.P., Storandt, M., Rubin, E.H., Morris, J.C., Baty, J., Coats, M., Norton, J., Goate, A.M., Price, J.L., Gearing, M., Mirra, S.S., Saunders, A.M., 1998. Clinicopathologic Studies in Cognitively Healthy Aging and Alzheimer Disease: Relation of Histologic Markers to Dementia Severity, Age, Sex, and Apolipoprotein E Genotype. *Arch. Neurol.* 55, 326–335.
- Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A., Greenough, W.T., 1990. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc. Natl. Acad. Sci. U. S. A.* 87, 5568–5572.
- Braak, H., Braak, E., 1991. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol. [Berl]* 82, 239–259.
- Burns, J.M., Cronk, B.B., Anderson, H.S., Donnelly, J.E., Thomas, G.P., Harsha, A., Brooks, W.M., Swerdlow, R.H., 2008. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology* 71, 210–216.
- Burns, J.M., Mayo, M.S., Anderson, H.S., Smith, H.J., Donnelly, J.E., 2008. Cardiorespiratory fitness in early-stage Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 22, 39–46.
- Carro, E., Trejo, J.L., Busiguina, S., Torres-Aleman, I., 2001. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J. Neurosci.* 21, 5678–5684.
- Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol. Sci.* 14, 125–130.
- Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J., McAuley, E., Kramer, A.F., 2003. Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 58, M176–MM80.
- Colcombe, S.J., Erickson, K.I., Scalf, P.E., Kim, J.S., Prakash, R., McAuley, E., Elavsky, S., Marquez, D.X., Hu, L., Kramer, A.F., 2006. Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* 61, 1166–1170.
- Colcombe, S.J., Kramer, A.F., Erickson, K.I., Scalf, P., McAuley, E., Cohen, N.J., Webb, A., Jerome, G.J., Marquez, D.X., Elavsky, S., 2004. Cardiovascular fitness, cortical plasticity, and aging. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3316–3321.
- Cotman, C.W., Berchtold, N.C., 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 25, 295–301.
- Dustman, R.E., Ruhling, R.O., Russell, E.M., Shearer, D.E., Bonekat, H.W., Shigeoka, J.W., Wood, J.S., Bradford, D.C., 1984. Aerobic Exercise Training and Improved Neuropsychological Function of Older Individuals. *Neurobiol. Aging* 5, 35–42.
- Erickson, K.I., Raji, C.A., Lopez, O.L., Becker, J.T., Rosano, C., Newman, A.B., Gach, H.M., Thompson, P.M., Ho, A.J., Kuller, L.H., 2010. Physical activity predicts gray matter volume in late adulthood: The Cardiovascular Health Study. *Neurology* 75, 1415–1422.
- Fjell, A.M., Walhovd, K.B., Fennema-Notestine, C., McEvoy, L.K., Hagler, D.J., Holland, D., Brewer, J.B., Dale, A.M., 2009. One-year brain atrophy evident in healthy aging. *J. Neurosci.* 29, 15223–15231.
- Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental State: A practical method for grading the cognitive state of patients for the clinicians. *J. Psychiatr. Res.* 12, 189–198.
- Friedland, R.P., Fritsch, T., Smyth, K.A., Koss, E., Lerner, A.J., Chen, C.H., Petot, G.J., Debanne, S.M., 2001. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3440–3445.
- Geda, Y.E., Roberts, R.O., Knopman, D.S., Christianson, T.J., Pankratz, V.S., Ivnik, R.J., Boeve, B.F., Tangalos, E.G., Petersen, R.C., Rocca, W.A., 2010. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch. Neurol.* 67, 80–86.
- Gibbons, R.J., Balady, G.J., Beasley, J.W., Bricker, J.T., Duvernoy, W.F., Froelicher, V.F., Mark, D.B., Marwick, T.H., McCallister, B.D., Thompson, P.D., Jr, Winters, W.L., Yanowitz, F.G., Ritchie, J.L., Cheitlin, M.D., Eagle, K.A., Gardner, T.J., Garson, A., Jr, Lewis, R.P., O'Rourke, R.A., Ryan, T.J., 1997. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J. Am. Coll. Cardiol.* 30, 260–311.
- Hamalainen, A., Pihlajamaki, M., Tanila, H., Hanninen, T., Niskanen, E., Tervo, S., Karjalainen, P.A., Vanninen, R.L., Soininen, H., 2007. Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol. Aging* 28, 1889–1903.
- Hassmen, P., Koivula, N., 1997. Mood, physical working capacity and cognitive performance in the elderly as related to physical activity. *Aging* 9, 136–142.
- Hill, R.D., Storandt, M., Malley, M., 1993. The impact of long-term exercise training on psychological function in older adults. *J. Gerontol.* 48, 12–17.
- Hollenberg, M., Ngo, L.H., Turner, D., Tager, I.B., 1998. Treadmill Exercise Testing in an Epidemiologic Study of Elderly Subjects. *J. Gerontol. A Biol. Sci. Med. Sci.* 53A, 259–267.
- Honea, R.A., Thomas, G.P., Harsha, A., Anderson, H.S., Donnelly, J.E., Brooks, W.M., Burns, J.M., 2009. Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* 23, 188–197.
- Isaacs, K.R., Anderson, B.J., Alcantara, A.A., Black, J.E., Greenough, W.T., 1992. Exercise and the brain: angiogenesis in the adult rat

- cerebellum after vigorous physical activity and motor skill learning. *J. Cereb. Blood Flow Metab.* 12, 110–119.
- Jack, C.R., Jr, Dickson, D.W., Parisi, J.E., Xu, Y.C., Cha, R.H., O'Brien, P.C., Edland, S.D., Smith, G.E., Boeve, B.F., Tangalos, E.G., Kokmen, E., Petersen, R.C., 2002. Ante mortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology* 58, 750–757.
- Jack, C.R., Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1998. Rate of medial temporal lobe atrophy in typical aging and Alzheimer's disease. *Neurology* 51, 993–999.
- Kim, S.E., Ko, I.G., Kim, B.K., Shin, M.S., Cho, S., Kim, C.J., Kim, S.H., Baek, S.S., Lee, E.K., Jee, Y.S., 2010. Treadmill exercise prevents aging-induced failure of memory through an increase in neurogenesis and suppression of apoptosis in rat hippocampus. *Exp. Gerontol.* 45, 357–365.
- Kramer, A.F., Colcombe, S.J., McAuley, E., Scalf, P.E., Erickson, K.I., 2005. Fitness, aging and neurocognitive function. *Neurobiol. Aging* 26 Suppl 1, 124–127.
- Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M.T., McAuley, E., Harrison, C.R., Chason, J., Vakil, E., Bardell, L., Boileau, R.A., Colcombe, A., 1999. Ageing, fitness and neurocognitive function. *Nature* 400, 418–419.
- Lancaster, J.L., Rainey, L.H., Summerlin, J.L., Freitas, C.S., Fox, P.T., Evans, A.C., Toga, A.W., Mazziotta, J.C., 1997. Automated labeling of the human brain: A preliminary report on the development and evaluation of a forward-transform method. *Hum. Brain Mapp.* 5, 238–242.
- Larson, E.B., Wang, L., Bowen, J.D., McCormick, W.C., Teri, L., Crane, P., Kukull, W., 2006. Exercise Is Associated with Reduced Risk for Incident Dementia among Persons 65 Years of Age and Older. *Ann. Intern. Med.* 144, 73–81.
- Laurin, D., Verreault, R., Lindsay, J., MacPherson, K., Rockwood, K., 2001. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch. Neurol.* 58, 498–504.
- Liang, K.Y., Mintun, M.A., Fagan, A.M., Goate, A.M., Bugg, J.M., Holtzman, D.M., Morris, J.C., Head, D., 2010. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann. Neurol.* 68, 311–318.
- Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19, 1233–1239.
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 34, 939–944.
- Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43, 2412–2414.
- Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. *Arch. Neurol.* 58, 397–405.
- Neeper, S.A., Gómez-Pinilla, F., Choi, J., Cotman, C., 1995. Exercise and brain neurotrophins. *Nature* 373, 109.
- Pereira, A., Ribeiro, S., Wiest, M., Moore, L.C., Pantoja, J., Lin, S.C., Nicoletti, M.A., 2007. Processing of tactile information by the hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 104, 18286–18291.
- Peters, F., Collette, F., Degueldre, C., Sterpenich, V., Majerus, S., Salmon, E., 2009. The neural correlates of verbal short-term memory in Alzheimer's disease: an fMRI study. *Brain* 132, 1833–1846.
- Pignatti, F., Rozzini, R., Trabucchi, M., Yaffe, K., 2002. Physical Activity and Cognitive Decline in Elderly Persons. *Arch. Intern. Med.* 162, 361–362.
- Podewils, L.J., Guallar, E., Kuller, L.H., Fried, L.P., Lopez, O.L., Carlson, M., Lyketsos, C.G., 2005. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *Am. J. Epidemiol.* 161, 639–651.
- Rolland, Y., Abellan van Kan, G., Vellas, B., 2008. Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives. *J. Am. Med. Dir. Assoc.* 9, 390–405.
- Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomilehto, J., Soininen, H., Nissinen, A., Kivipelto, M., 2005. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol.* 4, 705–711.
- Scarmeas, N., Luchsinger, J.A., Brickman, A.M., Cosentino, S., Schupf, N., Xin-Tang, M., Gu, Y., Stern, Y., 2010. Physical activity and Alzheimer disease course. *Am. J. Geriatr. Psychiatry*, epub ahead of print. DOI: 10.1097/JGP.0b013e3181eb00a9.
- Scherder, E.J.A., Van Paasschen, J., Deijen, J.B., Van Der Knokke, S., Orlebeke, J.F.K., Burgers, I., Devriese, P.P., Swaab, D.F., Sergeant, J.A., 2005. Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging Ment. Health* 9, 272–280.
- Stummer, W., Weber, K., Tranmer, B., Baethmann, A., Kempfski, O., 1994. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. *Stroke* 25, 1862–1869.
- Swerdlow, R.H., Khan, S.M., 2009. The Alzheimer's disease mitochondrial cascade hypothesis: an update. *Exp. Neurol.* 218, 308–315.
- Swerdlow, R.H., Parks, J.K., Cassarino, D.S., Maguire, D.J., Maguire, R.S., Bennett, J.P., Jr, Davis, R.E., Parker, W.D., Jr, 1997. Cybrids in Alzheimer's disease: a cellular model of the disease? *Neurology* 49, 918–925.
- Tong, L., Shen, H., Perreau, V.M., Balazs, R., Cotman, C.W., 2001. Effects of exercise on gene-expression profile in the rat hippocampus. *Neurobiol. Dis.* 8, 1046–1056.
- van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 13427–13431.
- Verghese, J., Lipton, R.B., Katz, M.J., Hall, C.B., 2003. Leisure activities and the risk of dementia in the elderly. *N. Engl. J. Med.* 348, 2508.
- Wang, L., Swank, J.S., Glick, I.E., Gado, M.H., Miller, M.I., Morris, J.C., Csernansky, J.G., 2003. Changes in hippocampal volume and shape across time distinguish dementia of the Alzheimer type from healthy aging. *Neuroimage* 20, 667–682.
- Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M.B., Ware, J.H., Grodstein, F., 2004. Physical Activity, Including Walking, and Cognitive Function in Older Women. *JAMA* 292, 1454–1461.
- Williams, P., Lord, S.R., 1997. Effects of group exercise on cognitive functioning and mood in older women. *Aust. N. Z. J. Public Health* 21, 45–52.
- Yaffe, K., Barnes, D., Nevitt, M., Lui, L.Y., Covinsky, K., 2001. A Prospective Study of Physical Activity and Cognitive Decline in Elderly Women: Women Who Walk. *Arch. Intern. Med.* 161, 1703–1708.