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Relation between aerobic fitness and brain structures in amnestic mild cognitive impairment elderly

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Abstract Mild cognitive impairment (aMCI) is a clinical condition, with high risk to develop Alzheimer's disease. Physical exercise may have positive effect on cognition and brain structure in older adults. However, it is still under research whether these influences are true on aMCI subjects with low Ab_42 and high total tau in cerebrospinal fluid (CSF), which is considered a biomarker for AD. Therefore, we aimed to investigate a possible relation between aerobic fitness (AF) and gray matter (GM) volume and AF and white matter (WM) integrity in aMCI with a CSF biomarker. Twenty-two participants with aMCI acquired the images on a 3.0-T MRI. AF was assessed by a graded exercise test on a treadmill. Voxel-based morphometry and tract-based spatial statistic methods were used to analyze the GM volume and WM microstructural integrity, respectively. We correlated AF and GM volume and WM integrity in aMCI ($p < 0.05$, FWE corrected, cluster with at least five voxels). There was a positive relation between AF and GM volume mostly in frontal superior cortex. In WM integrity, AF was positively correlated with fractional anisotropy and negatively correlated with mean diffusivity and radial diffusivity, all in the same tracts that interconnect frontal, temporal, parietal, and occipital areas (longitudinal fasciculus, fronto-occipital fasciculus, and corpus callosum). These results suggest that aerobic fitness may have a positive influence on protection of brain even in aMCI CSF biomarker, a high-risk population to convert to AD.

Keywords Elderly · Mild cognitive impairment · Aerobic fitness · Brain structure · Gray matter · White matter

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Introduction

Amnestic mild cognitive impairment (aMCI) is considered a risk population for developing Alzheimer's disease (AD) and is characterized by a cognitive decline in memory or more domains, but without significant impairment in the social and functional performance (Winblad et al. 2004; Petersen et al. 2006). Unfortunately, the evidence for current pharmacological treatments for older adults with aMCI is not strong (Ballard and O'brien 1999), and the development of potential disease-modifying strategies has become essential worldwide. In this context, the development of nonpharmacological strategies that may influence

disease progression has become increasingly important, and the concomitant application of both pharmacological and nonpharmacological treatments could lead to a differential outcome for the patients. Increasing evidence demonstrates that physical activity is an important modifiable risk factor not only for cardiovascular fitness but also for brain health (Hillman et al. 2008).

Some findings in the neuroimaging field have provided evidence that age-related effects in the brain of nondemented older adults are largely influenced by their aerobic fitness (AF) levels. For example, it has been shown that AF is positively correlated with blood flow in the gray matter (GM) which, in turn, is related to regional measures of brain volume (Zimmerman et al. 2014). Other studies have demonstrated that aerobic training also reduces cerebral volume loss of cognitively normal older adults and attenuate white matter (WM) volume reduction in the corpus callosum (Colcombe et al. 2003, 2006; Erickson et al. 2011; Voss et al. 2013). Furthermore, AF has been related to WM integrity previously (Marks et al. 2007; Johnson et al. 2012), specifically in the left superior and inferior longitudinal fasciculi in the physically fit older adults (Tseng et al. 2013). Studies involving patients, in turn, are scarce. In adults over 80 years old with a range of chronic disease conditions and low physical activity participation, higher AF was associated with WM integrity in the cingulum, hippocampus, and entorhinal cortex (Tian et al. 2014). The only study involving AD patients, in turn, found that higher VO2peak (maximum capacity of an individual's body to transport and metabolize oxygen during incremental exercise) was associated with increased FA in the right inferior fronto-occipital fasciculus (Perea et al. 2015).

The physiological aspects that underlie the benefits of AF in the human brain are, however, little known. Previous research with rats has shown that chronic aerobic exercise can lead to the growth of new capillaries in the brain (Black et al. 1990), increase the length and number of the dendritic interconnections between neurons (Cotman and Berchtold 2002), and even increase cell production in the hippocampus (Van Praag et al. 1999). These effects likely result from increases in growth factors such as brain-derived neurotrophic factor (Neeper et al. 1995; Cotman and Berchtold 2002) and insulin-like growth factor (Carro et al. 2001). That said, the macrostructural changes that have been reported to occur in the brain—such as volume loss and cortical thinning— are likely a result from subtler microscopic changes in the cerebral tissue (Douaud et al. 2011). In this context, some neuroimaging techniques like voxel-based morphology (VBM) and diffusion tensor imaging (DTI) can detect microstructural alterations in the GM and WM, respectively. By using DTI, specifically, it is possible to measure the behavior of diffusing water molecules as indicators of tissue microarchitectural properties, detecting alterations before gross anatomical changes become apparent on conventional MRI.

Given that physical exercise may be considered a preventive tool that attenuates age-related decline and influence the development of neurodegenerative diseases such as AD (Rovio et al. 2005), and also a nonpharmacological intervention for patients with aMCI (Cyarto et al. 2012; Teixeira et al. 2012; Suzuki et al. 2013; Nascimento et al. 2014), studying the relation between cerebral GM volume and WM integrity changes with AF could bring potential insights into future prevention/intervention strategies. However, to our knowledge, there are no studies showing the relationship between these subtler brain alterations with AF in the population with aMCI, despite the great importance of physical exercise on brain structures seen in nondemented older adults. Therefore, in the present cross-sectional study, we aimed to investigate the possible relationship between brain GM morphology and WM integrity and measures of aerobic fitness in older adults with aMCI.

Methods

Subjects

The study was approved by our local ethics committee, and all patients signed an informed consent form prior to any procedure. We studied 22 individuals with aMCI single and multiple domains. The participants were diagnosed aMCI using the core criteria of the NIA/AA for MCI (Albert et al. 2011). All participants with aMCI had a CDR (Morris 1993) score of 0.5 (with an obligatory memory score of 0.5), performed using a semistructured interview. All the participants had physiopathological evidence of AD (which consisted in low $A\beta_{42}$ and high tau protein in CSF), memory cognitive complaint confirmed by poor performance on episodic memory test (Rey auditory-verbal learning test (RAVLT)), and absence of dementia. Patients underwent a full range of neuropsychological testing, as described below.

We excluded individuals with other neurological or psychiatric diseases, Hachinski ischemic score >4 (Hachinski et al. 2006), Fazekas scale ≥1 (Fazekas et al. 1987), head injury with loss of consciousness, use of sedative drugs 24 h prior to neuropsychological testing, history of drug or alcohol addiction, and prior chronic exposure to neurotoxic substances.

Neuropsychological evaluation

Global cognitive status were measured using the Mini Mental Status Examination (MMSE) (Folstein et al. 1975), and episodic memory was evaluated by the RAVLT (subitems encoding, delayed recall and recognition) (Malloy-Diniz et al. 2007). Visuospatial perception was assessed with the following tests: subtests of Luria's Neuropsychological Investigation (Christensen 1975), mental rotation of figures (Ratcliff 1979), and clock drawing (Sunderland et al. 1989). Constructive praxis was evaluated by the copy of the Rey-Osterrieth complex figure test (Osterrieth 1944). Executive function was assessed by Trail Making Test A and B (Reitan 1958) and Stroop test, with time and number of errors in congruent and incongruent conditions (Stroop 1935). Language tests included the Boston Naming Test (Kaplan et al. 1983), verbal fluency for category (animals), and phonological fluency for letters (Christensen and Guilford 1959). Working memory and attention were assessed by the forward and backward digit span subtest of the WAIS-R (Wechsler 1987).

CSF sample

For the CSF biomarkers, the samples were centrifuged at 800×*g* for 5 min to remove cells and were stored frozen for protein analysis. $A\beta_{42}$ and total tau were measured using Inno-Bia Alzbio3 kit (Innogenetics, Gent, Belgium) and the cutoff values as previously described (Olsson et al. 2005).

Aerobic fitness assessment

Measures of oxygen utilization during a graded treadmill test provide a direct index of cardiorespiratory fitness (VO2max) and are considered the gold standard. After obtaining their individual physician's approval to engage in cardiorespiratory fitness testing, the participants performed a graded maximal exercise test, which protocols consisted of starting walking at speed of 3 mph without slope, then both increased 2 % every 2-min intervals. Measures of oxygen uptake, heart rate, and blood pressure were continuously monitored by a cardiologist. Relevant measures include VO2peak (highest volume of oxygen value attained on a graded exercise test) and VO2max (value at which VO2 plateaus or increases minimally despite increased workload on graded exercise test). The aerobic test was finished when the subject reached volitional exhaustion and/or symptom limitation. VO2max was defined as the highest recorded VO2 value after two of the three criteria were met: (1) a plateau in the peak VO2 between two or more workloads, (2) a respiratory exchange ratio >1.00, and (3) a heart rate equivalent to their age-predicted maximum.

MRI acquisition

All patients underwent high-resolution MRI on a 3-T Achieva-Intera PHILLIPS® scanner. Routine T1- and T2-weighted sequences were performed for all subjects to exclude unrelated abnormalities. For VBM analyses, we used volumetric T1 images of the brain acquired using a standard eight-channel head coil: sagittal orientation, voxel matrix 240 × 240 × 180, voxel size 1 × 1 × 1 mm^3, TR/TE 7/3.201 ms, and flip angle 8°. For the DTI analyses, we used a spin echo DTI sequence: 2 × 2 × 2 mm^3 acquiring voxel size, interpolated to 1 × 1 × 2 mm^3, reconstructed matrix 256 × 256, 70 slices, TE/TR 61/8500 ms, flip angle 90°, 32 gradient directions, no averages, and max b-factor = 1000 s/mm^2.

MRI analysis

GM morphology

We used VBM8 plus DARTEL toolbox for the GM morphology analysis. All T1-weighted images were preprocessed using SPM12/VBM8 routines. The images were normalized into the same stereotaxic space (DARTEL algorithm, MNI 152), segmented into WM, GM, and CSF, modulated (a step that preserves tissue volumes after being spatially normalized), and smoothed with isotropic Gaussian kernel of 10 mm.

WM integrity

Maps of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AxD) were created using FMRIB toolbox on FSL

v.4.1.4 [51]. The following tract-based spatial statistic (TBSS) steps preceded the statistical analyses: a FA skeleton was generated from the FA images that were aligned to each other using nonlinear registration. Then, the preprocessed FA image of each patient was projected onto the mean FA skeleton. To visualize the statistical maps of MD, AxD, and RD, we applied these parameters over the mean FA skeleton. We did not put ROIs in any brain region, because we wanted to check what brain areas would relate to AF in the participants.

Statistical analysis

Demographic, clinical, and neuropsychological data We performed a nonimaging statistical data analysis using the Statistical Package for the Social Sciences (SPSS, version 22; SPSS Inc., Chicago, IL, USA). A χ^2 test was used to compare frequency distribution of sex and *t* tests to compare other demographic and neuropsychological data. The significant *p* level was <0.05.

GM morphology In order to verify the relationship between AF and GM from our participants with aMCI, we performed correlation tests between both variables ($p < 0.001$, uncorrected, cluster with at least 30 continuous voxels).

WM integrity For the WM statistical analysis, the general linear model was performed in order to investigate for possible correlations between the TBSS results and AF. Johns Hopkins white matter DTI-based atlas, available in the FSL software (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), was used to identify WM tracts with abnormal findings. The results were corrected for multiple comparisons (cluster-based correction, $p < 0.05$).

Results

Demographic and neuropsychological data

Characteristics and neuropsychological data are shown in Table 1.

AF assessment

The mean maximal oxygen consumption (VO2max) was 21.4 (3.26) ml/kg/min, being the minimum and maximum values of 16 and 29 ml/kg/min, respectively.

Table 1 Demographic and neuropsychological information for patients with aMCI ($n = 22$)

	Mean (SD)	Range
Sex (female)	12 (54 %)	
Age (years)	68.5 (5.3)	57–80
Education (in years)	7.6 (4.8)	0–16
CDR	0	0–0.5
CSF sample (pg/μl)		
$A\beta_{42}$	310.6 (96.6)	178.1–446.7
Total tau	88.4 (55.3)	2187–17.6
MMSE	26.2 (3.2)	24–30
Episodic memory tests		
RAVLT encoding	31.4 (10.9)	9–53
RAVLT A7	4.2 (3.5)	0–11
RAVLT RC-FP	6.2 (6.5)	−8-13
Working memory/attention tests		
FDS	4.3 (0.9)	3–6
BDS	3.1 (1.1)	2–5
Language tests		
SVF	14.4 (3.9)	7–28
FAZ	27.6 (8.4)	15–39
BNT	51.6 (8.1)	34–59
Executive function tests		
Stroop C (s)	50.7 (23.6)	29–148
Stroop C (errors)	0.2 (0.6)	0–2
Stroop I (s)	129.9 (48.3)	84–237
Stroop I (errors)	7.7 (8.4)	0–36
TMT-A (s)	103.4 (61.6)	39–300
TMT-B (s)	135 (90.9)	0–300
Visuospatial skill tests		
Rey figure copy	29 (7.8)	9.5–36
Clock drawing	8.9 (4.3)	5–29
LNI	16 (2.2)	13–18

Data presented as average (standard deviation)

CSF cerebral spinal fluid, $A\beta_{42}$ amyloid beta, *CDR* clinical dementia rating, *MMSE* Mini Mental Status Examination, *RAVLT encoding* encoding of Rey auditory-verbal learning test, *RAVLT A7* delayed recall of Rey auditory-verbal learning test, *RAVLT RC-FP* Rey auditory-verbal learning test true recognition (i.e., recognition minus false positives), *FDS* forward digit span, *BDS* backward digit span, *SVF* semantic verbal fluency, *FAS* phonological fluency for letters, *BNT* Boston Naming Test, *Stroop C* Stroop test congruent, *Stroop I* Stroop test incongruent, *TMT-A* Trail Making Test A, *TMT-B* Trail Making Test B, *Rey figure copy* copy of the Rey-Osterrieth complex figure test, *LNI* visuospatial perception item of Luria's Neuropsychological Investigation

Relationship between GM morphology and aerobic fitness

Voxelwise multiple regression analysis revealed a significant and positive relationship between AF and GM morphology in the left inferior parietal cortex, left frontal superior cortex, left frontal middle cortex, medial frontal superior cortex, right frontal superior cortex, and right frontal superior orbital cortex (Table 2, Fig. 1).

Relationship between WM microstructural integrity and aerobic fitness

TBSS showed a positive correlation between the participants with aMCI FA values and AF in the following regions: major and minor right forceps, right inferior and superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, and genu of corpus callosum. Also, a negative correlation between MD and RD values and AF could be seen in the same regions described for FA. A negative correlation could be seen in genu of corpus callosum and right superior longitudinal fasciculus between AxD and AF (Fig. 2).

Discussion

The present study presents a comprehensive approach of the relationship between AF and GM morphology and WM integrity in older adults with aMCI with physiopathological evidence of AD. According to our findings, we can conclude that in older adults with aMCI, (1) AF positively correlated with GM morphology, especially in frontal areas, and (2) AF levels had a positive correlation with FA and negative correlation with MD, RD, and AxD in multiple tracts.

Voxelwise GM analysis across the participants' brains showed correlation between AF and frontal areas mainly (such as left and right frontal superior cortex, left frontal middle cortex, medial frontal superior cortex and right frontal superior orbital cortex), which are known to be related to executive functions, attention tasks, decision making, working memory, mental flexibility, problem solving, planning, and task execution (Alvarez and Emory 2006; Chan et al. 2008). Memory and executive functions, indeed, are the first affected cognitive domains in the aging process, in which prefrontal cortex and hippocampus have a shrinking rate of 1–2 % per year after the age of 55 (Olsson et al. 2005). The benefits of AF in the frontal-mediated functions, however, have been demonstrated previously in the healthy population. For example, healthy controls with higher fitness level had a better performance on executive function tests and greater GM volume in several frontal areas including the dorsal lateral prefrontal cortex, even after controlling for several potentially confounding variables including age (Weinstein et al. 2012). In fact, the largest fitness-induced benefits occur selectively in executive control processes (Colcombe and Kramer 2003).

Analyzing the correlation between cardiorespiratory fitness and WM integrity, there was a positive correlation between AF and FA measures in right major and minor forceps, right inferior and superior longitudinal fasciculus, right inferior fronto-occipital fasciculus, and genu of corpus callosum. A positive correlation between anisotrophy levels and cardiorespiratory fitness in the right inferior fronto-occipital fasciculus has been reported to occur in AD patients in a study using a tract-of-

Table 2 VBM results for correlations between GM morphology and AF ($p < 0.001$, familywise error corrected)

	Stereotaxic coordinates (mm)						Cluster size
Region	X	Y	Z	T value	Z value	*p*	Voxels
L parietal inferior	−33	−45	52	4.46	3.50	<0.00022	75
L frontal superior	−17	56	21	4.34	3.44	<0.00006	135
L frontal middle	−27	54	25	4.08	3.30	<0.00017	782
Medial frontal superior	−12	63	12	2.77	3.11	<0.00022	174
R frontal superior	23	59	03	4.35	3.45	<0.00006	135
R frontal superior orbital	20	69	−3	4.57	3.56	<0.00017	782

Cluster size >30 voxels

L left, *R* right

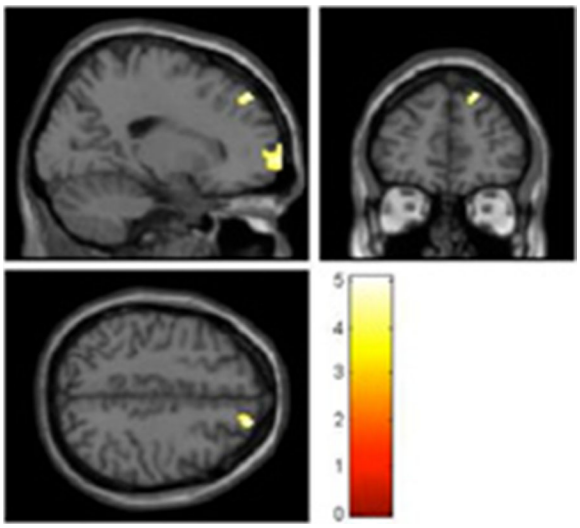

Fig. 1 SPM representation of VBM results ($p < 0.05$, familywise error corrected, cluster > five voxels) showing positive correlation between gray matter morphology and aerobic fitness in aMCI subjects

interest approach (Perea et al. 2015). Similarly, AF and WM microstructural integrity positively correlated in the corpus callosum in cognitively healthy subjects (Johnson et al. 2012), in which the authors report that each portion of the corpus callosum related to AF is interconnected to the frontal regions—known to be associated with high-level motor planning. Indeed, the largest age-associated reduction in FA occurs mainly in the frontal regions of the brain (Nusbaum et al. 2001; Abe et al. 2002) and has been interpreted as an increased axonal dispersion rather than a demyelination process (Billiet et al. 2015).

Likewise, FA, mean, and radial diffusivity values correlated with the level of AF throughout the brain, whereas AxD measures correlated to AF in more specific areas. Although the biological underpinnings of DTI are still not fully understood and are mostly based on animal models, diffusivity abnormalities have been related to axonal damage in previous reports (Tyszka et al. 2006). Axonal defects such as impaired axonal transport and swellings have been confirmed even at early stages of AD in both animal models and humans (Stokin et al. 2005) and was associated with the origin and development of Aβ plaques and hyperphosphorylated tau in the brains of AD patients (Xiao et al. 2011).

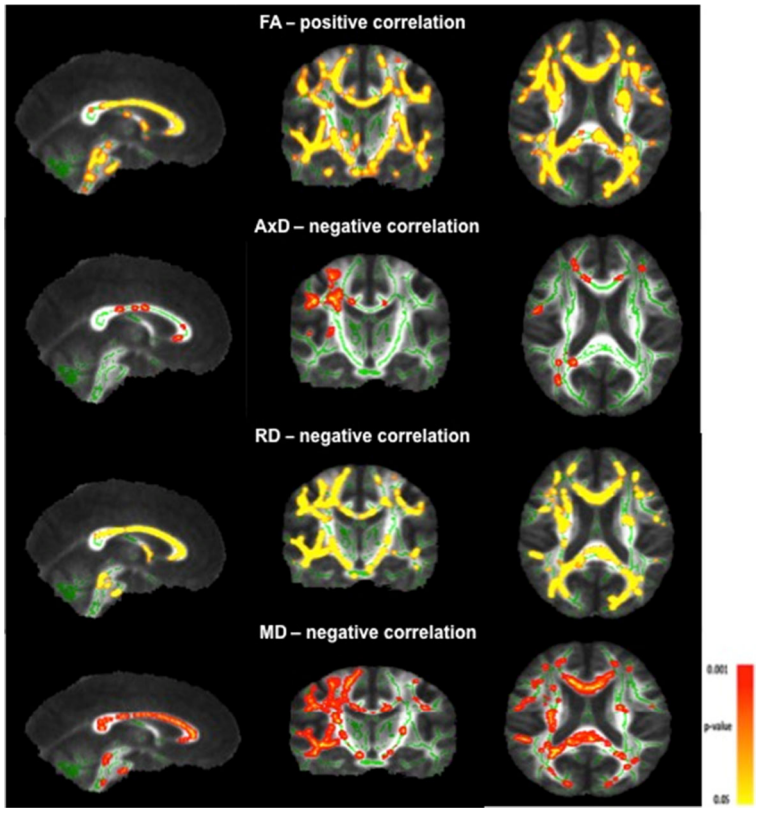

Fig. 2 TBSS analysis showing correlation between aerobic fitness and white matter in aMCI subjects. Significant related areas are shown in *yellow-red* and represent cluster-based corrected values ($p < 0.05$). *FA* fractional anisotropy, *AxD* axial diffusivity, *RD* radial diffusivity, *MD* mean diffusivity

There are evidences in the literature that physical exercise affects some of the biological mechanisms that contribute to improve neurocognitive function, such as enhanced cerebral blood flow, synthesis of neurotransmitters, vascular brain neurogenesis, and regulation of neurotrophic factors (Colcombe et al. 2006; Etnier et al. 2006; Davenport et al. 2012). The increase in brain-derived neurotrophic factor (BDNF) has been described as favorable to brain neuroplasticity (Ding et al. 2006; Gomez-Pinilla et al. 2008) and seems to be highly concentrated in hippocampus and cortex, promoting cell proliferation and signaling through several pathways (Lessman and Brigadski 2009). In addition, physical exercise practice seems to reduce pro-inflammatory cytokines such as TNF-α and IL-6 (Baker et al. 2010; Nascimento et al. 2014), which in turn are in higher levels in MCI subjects when compared to healthy controls (Magaki et al. 2007; Trollor et al. 2012; Saleem et al. 2015).

There are some limitations in this work that must be acknowledged. Because of the cross-sectional nature of our study, we are unable to claim that physical exercises in fact have a beneficial effect on both WM and GM of older adults with aMCI. Longitudinal studies controlling for other confounding factors would be necessary to confirm our suggestion of a protective role of physical exercise in WM and GM. Even so, our work brings new and robust findings involving population with aMCI with a CSF biomarker for AD, showing that the subjects with higher levels of AF present greater microstructural integrity in multiple WM tracts and higher density in GM frontal.

We have to bear in mind that most of the studies have used cognitively normal older adults to analyze the effect of physical exercise on the brain's structure. In this study, we demonstrated that AF might have a beneficial impact even in the older adults with high risk of developing AD.

Considering that older adults with aMCI, and a biological biomarker, is a high risk population for developing dementia, the findings from the present study should encourage future longitudinal studies designed to analyze the real effect of physical exercise in this population and the use of this nonpharmacological strategy as a resource of health improvement.

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