NeuroImage: Clinical 19 (2018) 616–624

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Aerobic training modulates salience network and default mode network metabolism in subjects with mild cognitive impairment

F.H.G. Porto[a,*], Artur Martins Coutinho[b,e], Fabio Luís de Souza Duran[c], Ana Lucia de Sá Pinto[d], Bruno Gualano[d], Carlos Alberto Buchpiguel[b], Geraldo Busatto[c], Ricardo Nitrini[a], Sonia Maria Dozzi Brucki[a]

[a] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Neurology and Cognitive Disorders Reference Center (CEREDIC), São Paulo, SP, Brazil
[b] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Radiology, Nuclear Medicine Center (LIM43), São Paulo, SP, Brazil
[c] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Psychiatry and LIM21, São Paulo, SP, Brazil
[d] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Laboratory of Assessment and Conditioning in Rheumatology (LACRE), São Paulo, SP, Brazil
[e] Hospital Sírio-Libanês, São Paulo, Brazil

ARTICLE INFO

Keywords:
Mild cognitive impairment
Aerobic training
Salience network
Default mode network
FDG-PET
Non-pharmacological interventions
Structural equation modeling

ABSTRACT

Aerobic training (AT) is a promising intervention to improve cognitive functioning. However, its modulatory effects on brain networks are not yet entirely understood. Sixty-five subjects with mild cognitive impairment performed a moderate intensity, 24-week AT program. Differences in resting regional brain glucose metabolism (rBGM) with FDG-PET were assessed before and after AT on a voxel-by-voxel basis. Structural equation modeling was used to create latent variables based on regions with significant rBGM changes and to test a hypothetical model about the inter-relationships between these changes. There were significant rBGM reductions in both anterior temporal lobes (ATL), left inferior frontal gyrus, left anterior cingulate cortex, right hippocampus, left meddle frontal gyrus and bilateral caudate nuclei. In contrast, there was an increase in rBGM in the right precuneus and left inferior frontal gyrus. Latent variables reflecting the salience network and ATL were created, while the precuneus represented the default mode network. In the model, salience network rBGM was decreased after AT. In contrast, rBGM in the default mode network increased as a final outcome. This result suggested improved salience network efficacy and increased control over other brain functional networks. The ATL network decreased its rBGM and connected to the salience network and default mode network with positive and negative correlations, respectively. The model fit values reached statistical significance, demonstrating that this model explained the variance in the measured data. In mild cognitive impairment subjects, AT modulated rBGM in salience network and default mode network nodes. Such changes were in the direction of the normally expected resting-state metabolic patterns of these networks.

1. Introduction

Physical activity is associated with a decreased risk of dementia in cognitively normal older adults (Ahlskog et al., 2011; Hamer and Chida, 2009; Ngandu et al., 2015). Importantly, studies have demonstrated that aerobic training (AT) (physical activity for aerobic conditioning) may improve cognition in subjects with mild cognitive impairment (MCI). Randomized controlled clinical trials evaluating the effects of AT on subjects with MCI showed improvements in overall cognitive function, memory and executive function (Baker et al., 2010; Lautenschlager et al., 2008; Nagamatsu et al., 2013; Suzuki et al., 2012; van Uffelen et al., 2008). A meta-analysis confirmed the benefits of AT for cognitive function in MCI (Wang et al., 2014). However, the neural mechanisms explaining how AT improves cognition are still not completely understood. Improved knowledge of how AT changes or modulates brain structure and function would be important to the field of cognition and aging.

Positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) measures regional brain glucose metabolism (rBGM), an indirect marker of neuronal synaptic function (Riedl et al., 2016; Rocher et al., 2003), and brain hypometabolism is considered a measure of neuronal dysfunction (Jack et al., 2013). FDG-PET is a promising method to be

* Corresponding author at: CEREDIC - Centro de Referência em Distúrbios Cognitivos (CEREDIC), 206 Arruda Alvim st, Cerqueira César, São Paulo, SP 05419-020, Brazil.
E-mail address: portofhg@gmail.com (F.H.G. Porto).

https://doi.org/10.1016/j.nicl.2018.05.002
Received 12 June 2017; Received in revised form 2 May 2018; Accepted 3 May 2018
Available online 04 May 2018
2213-1582/ © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

used as an endpoint in intervention with physical exercise (Boecker and Drzezga, 2016) because it provides objective data, has high reliability in test and retest situations, and has good correlation with cognitive performance (Drzezga et al., 2003; Herholz et al., 2011; Herholz, 2012).

In addition to identifying key brain regions showing hypometabolic patterns associated with cognitive decline in Alzheimer's disease (AD) and MCI, the data generated using FDG-PET imaging can also be analyzed using a brain network approach. The usefulness of FDG-PET in functional connectivity studies was recently addressed to create "metabolic connectivity" maps (Riedl et al., 2016; Rocher et al., 2003). Additionally, there is a well-known relationship between blood flow at rest and activity in the default mode network (DMN) (Liang et al., 2013; Passow et al., 2015; Pfefferbaum et al., 2011; Zou et al., 2009).

Resting-state FDG-PET and functional connectivity methods such as functional magnetic resonance imaging (MRI) or electroencephalogram provide different sorts of data. While connectivity methods investigate the synchronicity of activity between different areas and thus provide correlation coefficients between regions within networks, FDG-PET provides quantitative information on the magnitude of the metabolism in regions corresponding topographically to hubs or nodes within each of the networks. Therefore, FDG-PET may provide information about which area of a particular network is more or less metabolic during resting-state, which is crucial to the interpretation of the effects of AT on the brain. Connectivity studies would only provide information about the strength of the connection between regions and would not provide information on possible higher metabolism in a network.

In a previous report, our group evaluated the effects of AT on brain metabolism in subjects with MCI (Porto et al., 2015). We showed changes in resting rBGM after AT in brain areas critical for cognitive performance, including a metabolic decrease in the anterior cingulate cortex (ACC) and increased metabolism in the posterior cingulate cortex and precuneus. We additionally found a significant correlation between decrements in the resting rBGM of the ACC with improvements in cognitive performance. Furthermore, AT reduced the metabolic deficit in the precuneus of the MCI group against the cognitively normal elderly.

It is important to note that the regions where we found metabolic changes after AT are nodes of the salience network (SN) and DMN (Buckner, 2012; Seeley et al., 2007). The SN is a task-positive network involved in cognitive control and the dynamic regulation of other brain networks (Dosenbach et al., 2008). This network is composed of the cortices of the anterior cingulate, supplementary premotor area and cortex of the insula (Seeley et al., 2007; Sestieri et al., 2014) and is strongly connected to the ventral portions of the basal ganglia, particularly the caudate nuclei (Robinson et al., 2012). The DMN is a task-negative network (preferentially active when individuals are not focused on the external environment) involved in several internal cognitive aspects, such as autobiographical memory retrieval, envisioning the future, and conceiving the perspectives of others, as well as emotional and cognitive processing (Buckner, 2012). It is composed of the medial prefrontal cortex (both ventromedial and dorsomedial), precuneus and posterior cingulate cortex, heteromodal posterior and inferior parietal lobe (especially temporoparietal junction and the angular gyrus), dorsolateral prefrontal cortex, middle temporal gyrus, and parahippocampal gyrus (Buckner, 2012). In the current study, we used an extended MCI sample ($n = 65$) from our previous report (data from 25 new subjects were added to the 40 previously reported subjects) with the aim of investigating relationships between the rBGM changes induced by AT using statistical methods specifically designed to analyze network models. The main hypothesis of this study is not only that might AT induce neuroplasticity in regions of the SN and DMN but also that these changes might be interconnected and behave as a network. We hypothesized that AT would impact the rBGM in regions of the SN (a task-positive network), decreasing its rBGM, and in regions of the DMN (a task-negative network), increasing its rBGM (a tendency to change resting metabolism towards its physiologic pattern). We proposed and tested a hypothetical model using structural equation modeling to explore the relationships between the brain metabolic changes induced by AT in these networks.

2. Methods

2.1. Patient recruitment and selection

Volunteers of at least 60 years of age with cognitive complaints were recruited into the study. Recruitment was undertaken by an active search for older adults in the community. Only volunteers with more than four years of formal education (corresponding to the basic education in Brazil) were included, from January 2011 to July 2014. The active search phase was carried out by one of the authors (FHGP) in meeting groups of older adults in the city of São Paulo, Brazil. Additionally, volunteers interested in participating could directly contact the Reference Center for Cognitive Disorders of the University of São Paulo. An interview was then scheduled after the voluntary registration of individuals by telephone. After the registration and initial consultation, these individuals initiated the study procedures.

In the screening evaluation, all participants had a medical evaluation where clinical and neurological examinations were performed, along with a screening test for cognitive changes (Mini-mental State Examination (MMSE) (Folstein et al., 1975) validated for the Portuguese language in the Brazilian population (Brucki et al., 2003) and brief cognitive battery (BCB) (Nitrini et al., 2005). Later, the volunteers suspected of mild cognitive impairment (MCI) who fulfilled the inclusion criteria of the study were invited to undergo a standard neuropsychological assessment for the study (full description of the neuropsychological evaluation is provided in Supplementary Text 1). The final clinical diagnosis was established by consensus with the participation of a multidisciplinary team with expertise in cognitive neurology composed of at least two neurologists. Neuropsychological assessment was considered the gold standard for diagnosis in this study.

Included participants were administered the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-Cog) (primary cognitive outcome of the study) (Mohs et al., 1997; Rosen et al., 1984) and then later sent to perform and undergo an ergospirometry test and imaging exams (MRI and FDG-PET).

All subjects agreed to participate in the study and underwent an informed consent process approved by our local Human Research Ethics Committee (No 0064/11). The study was registered under the Universal Trial Number (UTN) U1111-1149-2365 and Brazilian Clinical Trials Registry (ReBec) number RBR-5tv5vt.

2.2. Clinical diagnosis and inclusion and exclusion criteria

MCI was defined according to standard criteria (Petersen et al., 1999; Winblad et al., 2004). A cognitive domain (function) was considered compromised if one of the neuropsychological tests pertinent to that function had a *Z*-score of less than -1.5 (standard values for age and education) or if two or more tests pertinent to the same function had a Z-score between -1.0 and -1.5 (Clark et al., 2013). This criterion was used in an attempt to balance the sensitivity and specificity of the neuropsychological assessment.

The exclusion criteria were as follows: a) clinically relevant psychiatric symptoms that met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association (DSM-IV-TR) (American Psychiatric Association, 2000), and depressive symptoms as assessed with the short version of the Geriatric Depression Scale (Almeida and Almeida, 1999; Sheikh and Yesavage, 1986), with a cutoff score of $> 5/15$ used to exclude subjects; b) any decompensated clinical comorbidity; c) history or signs of neurological disease (such as Parkinson's disease, epilepsy, inflammatory diseases or stroke), with the exception of migraine; 4) presence of any drug abuse (especially alcohol use); d) orthopedic problems that could

prevent the subjects from participating in AT (e.g., knee osteoarthritis); e) presence of cardiovascular disease that contraindicates performing aerobic exercise (e.g., coronary artery disease, congestive heart failure, or atrial fibrillation); f) brain lesions detected by MRI that could have significant clinical repercussions, including stroke and vascular lesions, and white matter hyperintensities analyzed in their intensity by a qualified neuroradiologist and in their clinical repercussion by a neurologist who searched for the presence of focal neurologic signs in neurological examination; g) claustrophobia or any other reason for refusal to undergo the MRI and/or FDG-PET examinations; h) diabetic patients without adequate glycemic control (for risk of interference in the quality of the FDG-PET); or i) sufficiently intense functional decline to meet the criteria for dementia, as assessed by the questionnaire of functional activities (Pfeffer et al., 1982) using a cutoff score of 5.

None of the participants were using acetylcholinesterase inhibitors or memantine. Antidepressants (as maintenance treatment in cases of remitted depression) were only allowed if they had been administered with stable doses for at least three months. The participants were not necessarily sedentary. Volunteers were not included if they were doing supervised physical activity or an AT program before the beginning of the study.

2.3. Ergospirometric test and aerobic training program

The ergospirometric test and the exercise program were conducted in the evaluation and conditioning laboratory in rheumatology of our University. The ergospirometric test protocol and the AT program have been detailed elsewhere (Porto et al., 2015) and are shown as supplementary data (Supplementary Text 2). AT consisted of a 24-week supervised program of walking on a treadmill that was conducted twice per week and was of moderate intensity. Subjects were excluded from the study if they had < 70% adherence to training (minimum of 33 sessions in 24 weeks). The number of mean trained days was 39.6 (4.3), representing approximately 80% adherence (range from 33 to 48).

2.4. Reassessment

After the completion of the 24-week AT program, subjects performed the ergospirometric test, ADAS-Cog, neuropsychological battery, and FDG-PET. The sequence was as follows: first the ergospirometric test, followed by ADAS-Cog, performed within the first week after the last training session. PET-FDG was repeated within the second week after the last training session, followed by the neuropsychological evaluation.

2.5. Acquisition and processing of imaging exams

The acquisition of MRIs was intended to exclude possible clinically relevant structural changes (tumors, malformations, vascular disease, etc.) and co-registration with FDG-PET images for later quantification. All patients underwent a 3.0 Tesla MRI acquired in the following sequence: sagittal 3D T1, axial T2 FSE, axial FLAIR, coronal T2 SPIR and diffusion SENSE. All images were acquired on the same equipment (Philips ACHIEVA 3.0 Tesla). Sagittal T1-weighted 3D volumetric sequence was used to perform voxel-based morphometry and co-registration of the PET images, consisting of 180 images with a slice thickness of 1 mm and pixel size of 1 mm (RT = 7 ms, ET = 3.2 ms, FOV 24 cm^2, matrix 240 × 240). A full description of the MRI sequence parameters is provided in Supplementary Text 3.

All PET-FDG studies were acquired with Siemens Biograph equipment (CTI/Siemens, Knoxville, TN, USA), composed of sets of BGO detectors coupled to a helical computed tomography (CT) scan. Acquisition was made 60 min after intravenous injection of approximately 370 MBq (10 mCi) of FDG, during which subjects were kept under standard resting conditions (absence of audiovisual stimuli). All participants fasted for at least 6 h. Prior to the administration of FDG, fasting blood glucose was measured systemically according to standard protocol in the institution.

Initially, the acquired CT scans were used for anatomical co-registration and attenuation corrections of PET-FDG tomographic images. CT images were also used for diagnostic purposes to possibly evaluate the presence of parenchymal calcifications or other abnormalities eventually not detected in the MRI scans. PET images were acquired for 15 min with a 256 × 256 matrix, 2.5 zoom, resulting in a 1.04 mm pixel size (voxel of 1.04 mm^3) in 2D mode. The images were reconstructed by iterative method ordered subset expectation maximization (OSEM) with six iterations and 16 “subsets” and smoothed with a Gaussian filter of 5 mm. The data were corrected for scatter, attenuation and decay. No correction method for partial volume effects was applied at this time.

All procedures related to the processing and quantification of FDG-PET and were performed using the Statistical Parametric Mapping software (SPM8) (Wellcome Department of Cognitive Neurology, Functional Imaging Laboratory, London, UK - http://www.fil.ion.ucl.ac.uk/spm/), implemented on the MATLAB platform R2009a (the Mathworks Inc., Sherborn, MA, USA). Processing steps and quantification followed standard procedures. After collection and quality-checking of the images looking for errors related to movement, co-registration, attenuation correction and reconstruction issues, all images were transformed into Digital Imaging and Communications in Medicine (DICOM) standard format (.dcm extension) and then to the NIFTI format (extension.nii), which is the default format for processing in SPM8. At this time, the images were converted from what is called “radiologic orientation” (left side of image is the patient's right side), into so-called “neurological orientation,” in which the left side of the image is the patient's left side. After this, the images underwent spatial normalization and smoothing processes, followed by different processing methods.

FDG-PET images of each patient were initially co-registered with their own MRI images (T1-weighted sequence). After co-registration, images were spatially normalized in SPM8 in a stereotaxic map based on the standard space coordinates (x, y, z) of the Montreal Neurological Institute (MNI). Each image was individually smoothed with a Gaussian filter of 8 mm to reduce the impact of possible co-registration error in space and to improve signal-to-noise ratio. To ensure that the analysis contained only voxels mapping brain tissue, a cutoff value (threshold) of 0.8 of the mean radiotracer uptake in brain tissue was selected. The differences between the global capture of images were adjusted by using the proportional scaling option of SPM8, which is normalization by averaging the brain counts for each group (normalization by global means). The resulting tomographic cuts were resampled using trilinear interpolation, producing voxels of 2 × 2 × 2 mm.

The above processes are taken as the standard analysis for functional metabolic images and are procedures that have been previously validated (Signorini et al., 1999) and used in several previous clinical studies involving FDG-PET and MCI (Clerici et al., 2009; Drzezga et al., 2003; Jagust et al., 2006; Perneczky et al., 2007; Salmon et al., 2008).

To analyze brain metabolic differences in the same cohort of individuals before and after the AT with FDG-PET, voxel-by-voxel comparisons were undertaken using the SPM8 software to identify differences in regional radiotracer uptake, a marker of rBGM. For statistical analysis in the SPM8 program, we performed a within-subjects (paired comparison) pre- and post-AT comparison. Thus, p values < 0.001 (uncorrected for multiple comparisons) were considered statistically significant at the voxel level, with a minimum of 50 voxels grouped in each area of significance (called “cluster”). Numerical values of the mean radioactive counts of voxels that reached statistical significance between groups (pre- versus post-AT) were obtained through the MarsBar toolbox for SPM (http://marsbar.sourceforge.net/) using the option “explore design/files and factors”. Such values were obtained after performing all processing of the images and are related to the amount of radioactivity in a specific brain region normalized by radioactive counts of whole brain (normalization by global counts).

Such radioactive counts indicate the glucose consumption in that area, which is an indirect measure of synaptic neuronal activity (Lundgaard et al., 2015; Riedl et al., 2016). These counts were used in the structural equation modeling analysis.

Statistically relevant voxels were automatically identified in the SPM8 program in terms of numerical coordinates (x, y, z) according to the Montreal Neurologic Institute (MNI) map coordinates. After identifying the MNI coordinates, these were converted to coordinates according to the atlas of Talairach and Tournoux in a specific open source software (http://bioimagesuite.yale.edu/ - noodle.med.yale.edu) (Lacadie et al., 2008) and subsequently confirmed with the help of Talairach Client software (Lancaster et al. 1997 and 2000). When the coordinates did not automatically match a specific gray matter area in both programs, we used the "nearest gray matter" function in the Talairach Client software within a cube of 4 mm range. This procedure can be performed to find Broadmann areas anatomically close to that specific voxel within the limits of the ideal spatial resolution of the PET technology.

2.6. Statistical analysis

Analyses of clinical data, including principal component analysis (PCA), were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) with different statistical tests according to the variable used. Structural equation modeling was used to explore hypotheses of how AT would influence resting rBGM, especially if these metabolic changes would follow a network behavior. This technique involves a set of statistical methods (i.e., regression, path analysis, confirmation of factors model) and was conducted using the program SPSS AMOS version 24.0 (SPSS Inc., Chicago, IL, USA). To test the hypothesis that some metabolic abnormalities could be connected to each other and represent a latent (non-measured) variable, a confirmation factor analysis was initially used to create latent variables based on measured data. Subsequently, a theory based on previous and current analyses was tested by a path model analysis, where statistical values of model fit were determined. According to statistical recommendations (Blunch, 2008), a combination of model fit ratios was used, each with a suggested minimum fit value: chi-square with $p > 0.05$; comparative fit index (CFI) > 0.93; normed fit index (NFI) > 0.9; and root mean square error of approximation (RMSEA) < 0.08.

3. Results

3.1. Baseline demographic data

Sixty-five subjects completed the 24-week program of AT. The mean (M) and standard deviation (SD) in years were 69.2 (5.5) for age and 11.1 (4) for years of education. There was a predominance of women in this sample (male-to-female ratio of 14/51, $\chi^2 < 0.001$). The initial MMSE was 28 (1.6). Demographic characteristics and scores on the tests used for screening are shown in Table 1.

3.2. Results related to physical conditioning and cognition after aerobic training

The data confirmed the previous results showing statistically significant improvements in aerobic fitness (respiratory compensation point and VO2max) and cognition (ADAS-cog, visual memory and processing speed). Detailed results can be found in the supplementary data (Supplementary Tables 1 and 2).

3.3. Comparison of brain metabolism before and after aerobic training

The results of exploratory analyses evaluating the changes in rBGM are shown in Table 2 and in Fig. 1. Significant increases in rBGM were observed in two brain areas, described herein by their respective Brodmann area (BA): the right precuneus ($p < 0.001$, BA = 7) and the right inferior frontal gyrus (IFG) ($p < 0.001$, BA = 47). In contrast, there were decreases in rBGM in a large bilateral cluster in the superior temporal gyrus (STG) very close in proximity to the insula on both sides with four-voxel peaks, two on BA 22 (left and right) and two on BA 38 (both right) ($p < 0.001$ for all); the left IFG ($p < 0.001$, BA = 47); a cluster encompassing the bilateral caudate nucleus and left ACC ($p < 0.001$, BA 33); the right hippocampus ($p < 0.001$, BA = 28); and the middle frontal gyrus ($p < 0.001$, BA = 9). The peak voxel in the right superior temporal gyrus (BA 22) remained significant after correction for multiple comparisons at the peak level (p-FWE_{corr} = 0.009) and showed a non-significant trend at the cluster level (p-FWE_{corr} = 0.053). No other voxels survived correction for multiple comparisons at the peak and cluster levels. After repeating the statistical analysis with age, sex, education, number of trained days and mini-mental state examination scores as covariates, the results remained essentially the same (Supplementary Table 3).

Table 1
- Results of demographic variables and screening tests in subjects with MCI participating in the study.

Variable	Mean (SD)	Variable	Mean (SD)
Age (Y)	69.2 (5.5)	CVF	16.5 (3.7)
Gender (F)	51 (78%)[a,†]	PVF	11.1 (3.8)
Educ (Y)	11.1 (4.2)	GDS	1.3 (1.5)
AH	29 (44%)[a]	HAS	5.1 (4.5)
DM	9 (13%)[a,†]	FAQ	0.6 (1.6)
DLP	26 (40%)[a]		
MMSE	28 (1.6)		
BCBdr	8.3 (1.3)		

AH: arterial hypertension; BCBdr: delayed recall of Brief Cognitive Battery – maximum of 10 figures to be remembered; DLP: dyslipidemia; CVF: categorical verbal fluency (animals/1 min); DM: diabetes mellitus; Educ: education; F: female; FAQ: Functional Activities Questionnaire; GDS: Geriatric Depression Scale (15 items); HAS Hamilton anxiety scale; MMSE: Mini Mental State Examination; PVF: phonemic verbal fluency (words with the letter "P"/1 min); SD: standard deviation; Y: years.

[a] Number of cases and percentage of total.

[†] p = 0,001 (Chi-squared distribution).

3.4. Principal component analysis and structural equation modeling

We extracted the numerical values representing rBGM in the areas with statistically significant metabolism increases or decreases (listed in the previous section) using the MarsBar toolbox for SPM8. The values from the second scans were then subtracted from the values of the first scans for each patient and recorded as areas with increased (positive values) or decreased (negative values) rBGM. We used these values as inputs for the following statistical analyses.

A PCA with varimax rotation was conducted to assess how the changes in mean radioactive counts after the AT in each area were grouped. Sample adequacy measurements were tested and shown to be adequate (Kaiser-Meyer-Olkin measurement = 0.81 and Bartlett sphericity test < 0.001). Two components were identified after rotation based on the eigenvalue criterion of values > 1. The first component accounted for 49.3% of the variance and the second component for 12.9%, amounting to a total of 62.2% of the total variance of the variables. Table 3 shows the areas with metabolic changes that were loaded in each component and the correlation coefficient values of each of these areas with the corresponding component. The PCA simply derived fewer variables without the influence of a previous hypothesis stating that measured variables could reflect an underlying or latent variable, such as brain networks. However, it is noteworthy that the ACC cluster and left caudate were present in both components, with correlation coefficients > 0.5, indicating that these areas may have a central modulatory role in the metabolic response induced by AT.

Table 2
Regions with reduction and increased rBGM after aerobic training. The results were obtained at peak voxel level (global analysis, minimum of 50 voxels) ($N = 65$).

Metabolic reduction	Z-score	CS	Voxel peak coordinates[a]
Superior temporal gyrus, BA 22 R	4.94	451	52 5 0
Superior temporal gyrus, BA 38 R_1[b]	3.73	451	49 12–12
Superior temporal gyrus, BA 38 R_2[b]	3.91	100	48 20–19
Superior temporal gyrus, BA 22 L	3.65	59	−50 8 0
Inferior frontal gyrus, BA 47 L	4.58	163	−43 21–15
Caudate nucleus L_1[b]	3.91	228	−8 11 7
Caudate nucleus L_2[b]	3.82	228	−11 2 20
Caudate nucleus R	3.39	65	16–6 24
Anterior cingulate gyrus, BA 33 L	3.14	228	−8 14 22
Middle Frontal Gyrus , BA 9 L	3.48	74	−29 13 27
Hippocampus R, BA 28	3.69	61	29–16 −8
Metabolic increase			
Precuneus, BA 7 R	4.27	326	18–45 41
Inferior frontal gyrus, BA 47 L	3.79	79	−18 23–13

BA: Brodmann area; CS: cluster size (number of voxels); L: left; R: Right, rBGM: regional brain glucose metabolism.
[a] Talairach coordinates (x,y,z).
[b] Different peak voxels within the same cluster region.

Structural equation modeling was used to test the main hypothesis of this paper. Fig. 2 shows the model, the correlation coefficient between factors and the model fit values. First, a confirmatory factor analysis was used to create latent variables based on measured numerical values of the mean radioactive counts of voxels that reached statistical significance between groups (pre- versus post-AT). Two latent variables were created. The first represented the metabolic changes in brain areas corresponding topographically to the SN, consisting of regions of the ACC, supplementary premotor area and caudate nuclei. The second latent variable included brain areas corresponding topographically to the network formed by the anterior portion of the temporal lobe, composed of regions of the STG and IFG adjacent to the temporal pole, designated as “ATL”. All regions used in the creation of the respective latent variables were highly correlated with them ($p < 0.01$).

After the generation of latent variables representing these two networks, a path model analysis was used to study the relationships between these variables and the metabolic changes induced by AT in the precuneus (a node of the DMN). In this hypothetical model, the metabolic changes induced after the AT in the latent variable representing the SN were chosen as the first step. This variable is highly correlated ($r = 0.78$, $p < 0.01$) with the latent variable representing the ATL, indicating that metabolic changes in these regions are going in the same direction (both decreasing after the AT).

Finally, the ATL variable was linked and inversely correlated with the precuneus ($r = -0.49$, $p < 0.01$). The precuneus is an important component of the DMN, and changes in this node went in the opposite direction of the areas with decreased metabolism after AT (increasing its resting rBGM). As the DMN is a task-negative brain network, this may possibly represent a better function in the area. This theoretical model about the relationship of areas with rBGM changes after AT was tested using statistical values of model fit and was shown to be statistically significant, meaning that the model was able to explain the variance of the measured data.

4. Discussion

Our results confirmed the predicted hypothesis that AT may induce changes in rBGM in anatomical coincident areas of the SN and DMN, and these changes may have a network behavior. Based on previous results from our group (Porto et al., 2015), the current PCA results and published data on the effects of AT on brain function (Voss et al., 2010a; Voss et al., 2010b; Voss et al., 2016), we were able to formulate a model that predicted the behavior of metabolic changes using a path model. This hypothetical model reached statistically significant levels of mathematical adequacy (model fit), i.e., this model provided a good explanation for the variance of the measured data.

Previous data from our group allowed us to create the hypothesis that the SN and the DMN could be “modulated”, as some of their main components, the ACC and the precuneus, showed metabolic changes after AT (Porto et al., 2015). The creation of the latent variable representing the SN was also based on previous reports demonstrating that the ACC may be an important region of neuroplasticity after AT (Burdette et al., 2010; Chapman et al., 2013; Colcombe et al., 2004; Kemppainen et al., 2005). A decrease in rBGM in the SN variable may possibly represent an improved function in this network, as it is a task-positive network and the metabolism was measured at rest. As one possible function of the SN is to regulate other networks, improved SN efficiency may facilitate the functioning of the connected networks (Jilka et al., 2014; Menon and Uddin, 2010).

The ATL latent variable was considered to be a link between the SN and the precuneus in the path model because it is strongly connected at rest with components of both the SN and DMN networks, especially in its anterior and dorsal portions (portions with metabolic changes in the present study) (Pascual et al., 2015). In addition, several studies have shown connections of the ATL with DMN and SN, though less robustly (Buckner, 2012; Seeley et al., 2007). Additionally, in the PCA, areas of the ATL had correlation with components of the two networks (DMN and SN) and there is an anatomical connectivity with both components of the SN and DMN via the anteromedial branch of the uncinate fasciculus and the cingulum fasciculus, respectively (Agrawal et al., 2011; Catani and Thiebaut de Schotten, 2008; Wu et al., 2016).

The precuneus is the region of the DMN with more interaction with other networks, as it is the region with the highest connection to “task-positive” networks, the most recruited subcomponent when other networks become active (Leech and Sharp, 2014). It is important to note that precuneus hypometabolism is a marker for the progression of MCI to dementia and has been considered part of the “metabolic signature” of AD (Drzezga et al., 2003; Winblad et al., 2004). The changes in rBGM found after AT approach the normalization of the expected metabolic pattern in the precuneus, as we had already shown that subjects had hypometabolism in comparison with an age- and education-matched control group before the AT and that the metabolic deficit decreased to non-significant levels after the AT (Porto et al., 2015). Additionally, accelerometer-measured physical activity intensity was demonstrated to be positively correlated with precuneus metabolism in cognitively normal late-middle-aged adults with risk factors for AD (Dougherty et al., 2017), a finding in agreement with the current results.

Metabolic reductions in several brain regions after aerobic exercise have been shown in the literature. A widespread decrease in metabolism after acute aerobic physical activity in young, healthy adults was seen in several brain areas, particularly in the dorsal ACC (Kemppainen et al., 2005), especially in more trained subjects, suggesting some form of neuroplasticity in the dorsal ACC. In addition, other studies using functional neuroimaging showed changes in the ACC after AT (Burdette

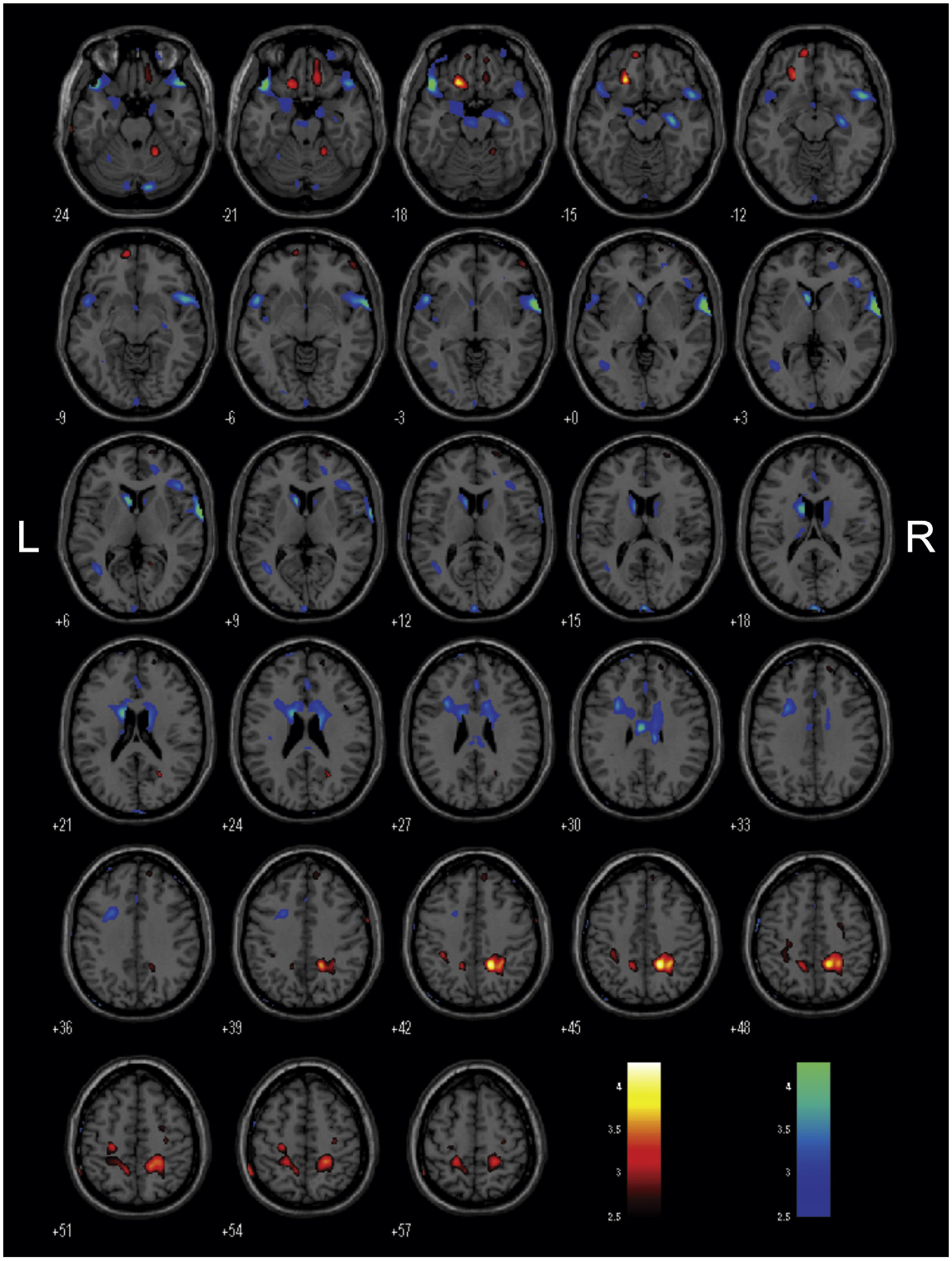

Fig. 1. Illustrative view of the main areas with reductions (blue) and increases (red) in regional glucose metabolism after the aerobic training program plotted on a magnetic resonance model. Images were made with visualization thresholds at p values < 0.001, uncorrected for multiple comparisons and using an extent threshold of 50 voxels. Color scale according to SPM T-value.
R: right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2010; Chapman et al., 2013; Colcombe et al., 2004). These findings might indicate that neuroplasticity in the ACC may be of crucial importance in the link between physical fitness and improved cognitive performance. Our current findings add to this literature, showing that AT may modulate not only the ACC as a key target, but possibly the SN as a whole. The neuroplasticity induced in the SN after AT may improve its function (decreasing resting-state metabolism, as the SN is a task-positive network), consequently promoting better dynamic regulation of other brain networks. The outcome would be an increased resting-state metabolism in the precuneus, an important node of the DMN (a task-negative network).

Cardiorespiratory fitness has been found to slow down aging-related

Table 3
Brain regions with rBGM changes after the AT and their weighted values in the components after rotation. Values < 0.4 were removed to facilitate viewing, ($N = 65$).

Metabolic Reduction	Components 1	2
Superior temporal gyrus, BA 22 R		0.66
Superior temporal gyrus, BA 38 R_1[a]		0.66
Superior temporal gyrus, BA 38 R_2[a]		0.74
Superior temporal gyrus, BA 22 L		0.52
Inferior frontal gyrus, BA 47 L		0.84
Caudate nucleus L_1[a]	0.73	0.51
Caudate nucleus L_2[a]	0.73	0.51
Anterior cingulate gyrus, BA 33 L	0.73	0.51
Medium Frontal Gyrus L, BA8	0.67	
Hippocampus R	0.69	
Caudate nucleus R	0.76	
Metabolic increase		
Precuneus, BA 7 R		−0.72
Inferior frontal gyrus, BA 47 L	−0.80	
Eigenvalues	4.9	1.2
Variance percentage	49.3%	12.9%

AT: aerobic training, BA: Brodmann area; L: left, R: Right, rBGM: regional brain glucose metabolism.
[a] Different peak voxels within the same cluster region.

impairment in the functional connectivity of associative networks (DMN, SN, executive control network and dorsal attention network) in resting state fMRI (Voss et al., 2016). Additionally, the DMN and SN were shown to be sensitive to age-related decline (Voss et al., 2010a) and to increase functional connectivity after AT (Voss et al., 2010b). Recently, Chirles et al., 2017 demonstrated increased functional connectivity of the precuneus and posterior cingulate cortex with several brain regions after a 12-week AT program in subjects with MCI (Chirles et al., 2017). The authors argued that the enhancement of neural recruitment mechanisms may increase the cognitive reserve and be related to the cognitive benefits of physical exercise. The current findings using resting rBGM changes are in agreement with resting state fMRI data demonstrating that AT may moderate the deleterious effects of brain aging, even in the MCI clinical phase.

It is important to note that studies comparing cognitively normal agers with “super agers” (older adults with cognitive functioning at a youthful level) showed increased brain volume in nodes of both DMN and SN (Rogalski et al., 2013; Sun et al., 2016). As physical activity is associated with healthier cognitive aging (Gajewski and Falkenstein, 2016) and neuroplasticity in similar associative networks, the relationship between them needs to be further explored. It is possible that long-term exposure to aerobic activity produces functional and structural changes in cognitive networks such as the DMN and SN and may be associated with less age-related cognitive decline.

4.1. Limitations

The current study has some limitations. A control group of subjects with MCI without an intervention was not included. This design may raise questions about whether the results were caused by the intervention or by other factors. However, naturalist data with MCI showed that the ADAS-Cog scale did not improve over time (mean baseline: 10.6 (4), after 6 months: 11.5 (4.6) (Herholz et al., 2011). Additionally, the FDG-PET data demonstrated progressive reduction in the metabolism of the precuneus (Herholz et al., 2011; Herholz, 2012). Moreover, the learning effect is minimal in MCI or mild dementia (Machulda et al., 2013). Our discussion on brain networks using FDG-PET can be considered somewhat inferential because it is based on resting metabolism. However, our data are supported by previous functional connectivity data and by our statistically significant values of model fit; ours may be considered a reasonable new approach in studies investigating the effects of AT on brain function. Finally, we aggregate a region of the IFG that clustered together with areas of the anterior part of the superior temporal gyrus as “ATL”. This is a limitation of the spatial resolution capacity of the method (4–6 mm). Adjacent regions may cluster together, and as most voxels were in the temporal pole, we labeled the latent variable as ATL. Additionally, the existing literature about ATL connectivity is quite limited, and further research is needed to clarify the role of this region in terms of connectivity.

5. Conclusion

In conclusion, a moderate-intensity AT program not only improved aerobic performance and cognition but also induced rBGM changes in subjects with MCI. A model where AT induced rBGM changes in regions of the SN and DMN was tested using structural equation modeling analysis and proved to be statistically significant. These findings suggest that AT may be an important strategy to induce neuroplasticity and could impact the dynamic interaction and function of brain networks in older adults with MCI.

Finally, investigating the metabolic effects of AT on brain networks is crucial to understanding the neural underpinnings of the protective effects of physical activity on cognition. Thus, our study can be considered a “proof of concept” study. Our research provides a model for future studies focusing on changes in rBGM induced by AT.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.05.002.

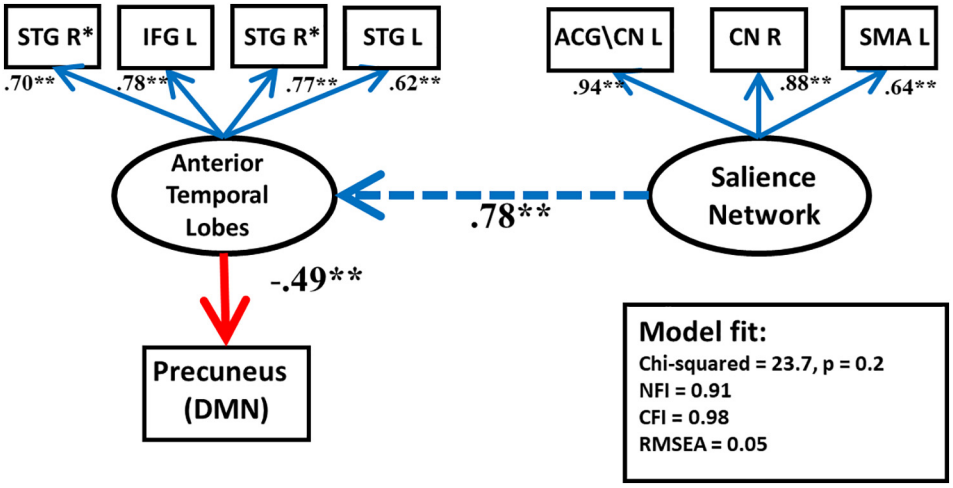

Fig. 2. - Illustrative view of the structural equation modeling. Circles represent latent variables, rectangles manifest variables, blue arrows show positive correlations, red arrow shows negative correlation, dashed arrow links latent variables, continuous arrows link latent to a measured variable.
ACG: anterior cingulate gyrus; CFI: comparative fit index; IFG: inferior frontal gyrus; L: left; NFI: normed fit index; R: right; RMSEA: root mean square error of approximation; SMA: supplementary motor area; STG: superior temporal gyrus; CN: caudate nucleus. * different peak voxels within the same cluster region ** $P < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Acknowledgments

This study was funded by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (numbers 2011/18245-4). The first author (FHGP) was also sponsored by the Coordination for the Improvement of Higher Education Personnel (CAPES)/Brazil as part of his PhD research in the program Science without Borders (number 99999.003029/2014-00).

References

Agrawal, A., Kapfhammer, J.P., Kress, A., Wichers, H., Deep, A., Feindel, W., Sonntag, V.K., Spetzler, R.F., Preul, M.C., 2011. Josef Klingler's models of white matter tracts: influences on neuroanatomy, neurosurgery, and neuroimaging. Neurosurgery 69, 238–252. http://dx.doi.org/10.1227/NEU.0b013e318214ab79.

Ahlskog, J.E., Geda, Y.E., Graff-Radford, N.R., Petersen, R.C., 2011. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin. Proc. 869, 876–884. http://dx.doi.org/10.4065/mcp.2011.0252.

Almeida, O.P., Almeida, S.A., 1999. Reliability of the Brazilian version of the abbreviated form of geriatric depression scale (GDS) short form. Arq. Neuropsiquiatr. 57, 421–426. http://dx.doi.org/10.1590/S0004-282X1999000300013.

American Psychiatric Association, 2000. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. http://dsm.psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890420249.dsm-iv-tr, Accessed date: 1 December 2017.

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. 671, 71–79. http://dx.doi.org/10.1001/archneurol.2009.307.

Blunch, N.J., 2008. Introduction to Structural Equation Modelling Using SPSS and AMOS. http://dx.doi.org/10.4135/9781446249345.

Boecker, H., Drzezga, A., 2016. A perspective on the future role of brain pet imaging in exercise science. NeuroImage 131, 73–80. http://dx.doi.org/10.1016/j.neuroimage.2015.10.021.

Brucki, S.M.D., Nitrin, R., Caramelli, P., Bertolucci, P.H.F., Okamoto, I.H., 2003. Sugestões para o uso do mini-exame do estado mental no Brasil. Arq. Neuropsiquiatr. 61, 777–781. http://dx.doi.org/10.1590/S0004-282X2003000500014.

Buckner, R.L., 2012. The serendipitous discovery of the brain's default network. NeuroImage 62, 1137–1145. http://dx.doi.org/10.1016/j.neuroimage.2011.10.035.

Burdette, J.H., Laurienti, P.J., Espeland, M.A., Morgan, A., Telesford, Q., Vechlekar, C.D., Hayasaka, S., Jennings, J.M., Katula, J.A., Kraft, R.A., Rejeski, W.J., 2010. Using network science to evaluate exercise-associated brain changes in older adults. Front. Aging Neurosci. 2, 23. http://dx.doi.org/10.3389/fnagi.2010.00023.

Catani, M., Thiebaut de Schotten, M., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44, 1105–1132. http://dx.doi.org/10.1016/j.cortex.2008.05.004.

Chapman, S.B., Aslan, S., Spence, J.S., DeFina, L.F., Keebler, M.W., Didehbani, N., Lu, H., 2013. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front. Aging Neurosci. 5 (75). http://dx.doi.org/10.3389/fnagi.2013.00075.

Chirles, T.J., Reiter, K., Weiss, L.R., Alfini, A.J., Nielson, K.A., Smith, J.C., 2017. Exercise training and functional connectivity changes in mild cognitive impairment and healthy elders. J. Alzheimers Dis. 57, 845–856. http://dx.doi.org/10.3233/JAD-161151.

Clark, L.R., Delano-Wood, L., Libon, D.J., McDonald, C.R., Nation, D.A., Bangen, K.J., Jak, A.J., Au, R., Salmon, D.P., Bondi, M.W., 2013. Are empirically-derived subtypes of mild cognitive impairment consistent with conventional subtypes? J. Int. Neuropsychol. Soc. 19, 635–645. http://dx.doi.org/10.1017/S1355617713000313.

Clerici, F., Del Sole, A., Chiti, A., Maggiore, L., Lecchi, M., Pomati, S., Mosconi, L., Lucignani, G., Mariani, C., 2009. Differences in hippocampal metabolism between amnestic and non-amnestic MCI subjects: automated FDG-PET image analysis. Q. J. Nucl. Med. Mol. Imaging 53, 646–657.

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. http://dx.doi.org/10.1073/pnas.0400266101.

Dosenbach, N.U.F., Fair, D.A., Cohen, A.L., Schlaggar, B.L., Petersen, S.E., 2008. A dual-networks architecture of top-down control. Trends Cogn. Sci. 12, 99–105. http://dx.doi.org/10.1016/j.tics.2008.01.001.

Dougherty, R.J., Schultz, S.A., Kirby, T.K., Boots, E.A., Oh, J.M., Edwards, D., Gallagher, C.L., Carlsson, C.M., Bendlin, B.B., Asthana, S., Sager, M.A., Hermann, B.P., Christian, B.T., Johnson, S.C., Cook, D.B., Okonkwo, O.C., 2017. Moderate physical activity is associated with cerebral glucose metabolism in adults at risk for Alzheimer's disease. J. Alzheimers Dis. 58, 1089–1097. http://dx.doi.org/10.3233/JAD-161067.

Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., Kurz, A., 2003. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into alzheimer's disease: a PET follow-up study. Eur. J. Nucl. Med. Mol. Imaging 30, 1104–1113. http://dx.doi.org/10.1007/s00259-003-1194-1.

Folstein, M.F., Folstein, S.E., McHugh, P.R., Roth, M., Shapiro, M.B., Post, F., Lofving, B., Ingles, J., Withers, E., Hinton, J., Halstead, H., Post, F., Kiloh, L.G., 1975. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198. http://dx.doi.org/10.1016/0022-3956(75)90026-6.

Gajewski, P.D., Falkenstein, M., 2016. Physical activity and neurocognitive functioning in aging - a condensed updated review. Eur. Rev. Aging Phys. Act. 13 (1). http://dx.doi.org/10.1186/s11556-016-0161-3.

Hamer, M., Chida, Y., 2009. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol. Med. 391, 3–11. http://dx.doi.org/10.1017/S0033291708003681.

Herholz, K., 2012. Use of FDG PET as an imaging biomarker in clinical trials of Alzheimer's disease. Biomark. Med 6, 431–439. http://dx.doi.org/10.2217/bmm.12.51.

Herholz, K., Westwood, S., Haense, C., Dunn, G., 2011. Evaluation of a calibrated 18F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. J. Nucl. Med. 52, 1218–1226. http://dx.doi.org/10.2967/jnumed.111.090902.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216. http://dx.doi.org/10.1016/S1474-4422(12)70291-0.

Jagust, W., Gitcho, A., Sun, F., Kuczynski, B., Mungas, D., Haan, M., 2006. Brain imaging evidence of preclinical Alzheimer's disease in normal aging. Ann. Neurol. 59, 673–681. http://dx.doi.org/10.1002/ana.20799.

Jilka, S.R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R.M., Leech, R., Sharp, D.J., 2014. Damage to the salience network and interactions with the default mode network. J. Neurosci. 34, 10798–10807. http://dx.doi.org/10.1523/JNEUROSCI.0518-14.2014.

Kemppainen, J., Aalto, S., Fujimoto, T., Kalliokoski, K.K., Långsjö, J., Oikonen, V., Rinne, J., Nuutila, P., Knuuti, J., 2005. High intensity exercise decreases global brain glucose uptake in humans. J. Physiol. 568, 323–332. http://dx.doi.org/10.1113/jphysiol.2005.091355.

Lacadie, C.M., Fulbright, R.K., Constable, R.T., Papademetris, X., 2008. More accurate talairach coordinates for neuroimaging using nonlinear registration. NeuroImage 42, 717–725.

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.
Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated talairach atlas labels for functional brain mapping. Hum. Brain Mapp. (3), 120–131.
Lautenschlager, N.T., Cox, K.L., Flicker, L., Foster, J.K., van Bockxmeer, F.M., Xiao, J., Greenop, K.R., Almeida, O.P., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 3009, 1027–1037. http://dx.doi.org/10.1001/jama.300.9.1027.
Leech, R., Sharp, D.J., 2014. The role of the posterior cingulate cortex in cognition and disease. Brain 137, 12–32. http://dx.doi.org/10.1093/brain/awt162.
Liang, X., Zou, Q., He, Y., Yang, Y., 2013. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. Proc. Natl. Acad. Sci. 110, 1929–1934. http://dx.doi.org/10.1073/pnas.1214900110.
Lundgaard, I., Li, B., Xie, L., Kang, H., Sanggaard, S., Haswell, J.D., Sun, W., Goldman, S., Blekot, S., Nielsen, M., Takano, T., Deane, R., Nedergaard, M., 2015. Direct neuronal glucose uptake heralds activity-dependent increases in cerebral metabolism. Nat. Commun. 6 (6807). http://dx.doi.org/10.1038/ncomms7807.
Machulda, M.M., Pankratz, V.S., Christianson, T.J., Ivnik, R.J., Mielke, M.M., Roberts, R.O., Knopman, D.S., Boeve, B.F., Petersen, R.C., 2013. Practice effects and longitudinal cognitive change in normal aging vs. incident mild cognitive impairment and dementia in the Mayo Clinic study of aging. Clin. Neuropsychol. 27, 1247–1264. http://dx.doi.org/10.1080/13854046.2013.836567.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667. http://dx.doi.org/10.1007/s00429-010-0262-0.
Mohs, R.C., Knopman, D., Petersen, R.C., Ferris, S.H., Ernesto, C., Grundman, M., Sano, M., Bieliauskas, L., Geldmacher, D., Clark, C., Thai, L.J., 1997. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's disease assessment scale that broaden its scope. The Alzheimer's disease cooperative study. Alzheimer Dis. Assoc. Disord. 11, S13–S21. 9236948.
Nagamatsu, L.S., Chan, A., Davis, J.C., Beattie, B.L., Graf, P., Voss, M.W., Sharma, D., Liu-Ambrose, T., 2013. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-month randomized controlled trial. J. Aging Res. 2013, 861893. http://dx.doi.org/10.1155/2013/861893.
Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., Bäckman, L., Hänninen, T., Jula, A., Laatikainen, T., Lindström, J., Mangialasche, F., Paajanen, T., Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T., Tuomilehto, J., Soininen, H., Kivipelto, M., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385, 2255–2263. http://dx.doi.org/10.1016/S0140-6736(15)60461-5.
Nitrini, R., Caramelli, P., Bottino, C.M.C., Damasceno, B.P., Brucki, S.M.D., Anghinah, R., 2005. Diagnóstico de doença de Alzheimer no Brasil: avaliação cognitiva e funcional. Arq. Neuropsiquiatr. 63, 713–719. http://dx.doi.org/10.1590/S0004-282X2005000400034.
Pascual, B., Masdeu, J.C., Hollenbeck, M., Makris, N., Insausti, R., Ding, S.L., Dickerson, B.C., 2015. Large-scale brain networks of the human left temporal pole: a functional connectivity MRI study. Cereb. Cortex 25, 680–702. http://dx.doi.org/10.1093/cercor/bht260.
Passow, S., Specht, K., Adamsen, T.C., Biermann, M., Brekke, N., Craven, A.R., Ersland, L., Grüner, R., Kleven-Madsen, N., Kvernenes, O.H., Schwarzlmüller, T., Olesen, R.A., Hugdahl, K., 2015. Default-mode network functional connectivity is closely related to metabolic activity. Hum. Brain Mapp. 36, 2027–2038. http://dx.doi.org/10.1002/hbm.22753.
Perneczky, R., Hartmann, J., Grimmer, T., Drzezga, A., Kurz, A., 2007. Cerebral metabolic correlates of the clinical dementia rating scale in mild cognitive impairment. J. Geriatr. Psychiatry Neurol. 20, 84–88.
Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56, 303–308. http://dx.doi.org/10.1001/archneur.56.3.303.
Pfeffer, R.I., Kurosaki, T.T., Harrah Jr., C.H., Chance, J.M., Filos, S., 1982. Measurement of functional activities in older adults in the community. J. Gerontol. 37, 323–329.
Pfefferbaum, A., Chanraud, S., Pitel, A.L., Muller-Oehring, E., Shankaranarayanan, A., Alsop, D.C., Rohlfing, T., Sullivan, E.V., 2011. Cerebral blood flow in posterior cortical nodes of the default mode network decreases with task engagement but remains higher than in most brain regions. Cereb. Cortex 21, 233–244. http://dx.doi.org/10.1093/cercor/bhq090.
Porto, F.H., Coutinho, A.M., Pinto, A.L., Gualano, B., Duran, F.L., Prando, S., Ono, C.R., Spíndola, L., de Oliveira, M.O., do Vale, P.H., Nitrini, R., Buchpiguel, C.A., Brucki, S.M., 2015. Effects of aerobic training on cognition and brain glucose metabolism in subjects with mild cognitive impairment. J. Alzheimers Dis. 46, 747–760. http://dx.doi.org/10.3233/JAD-150033.
Riedl, V., Utz, L., Castrillón, G., Grimmer, T., Rauschecker, J.P., Ploner, M., Friston, K.J., Drzezga, A., Sorg, C., 2016. Metabolic connectivity mapping reveals effective connectivity in the resting human brain. Proc. Natl. Acad. Sci. U. S. A. 113, 428–433. http://dx.doi.org/10.1073/pnas.1513752113.
Robinson, J.L., Laird, A.R., Glahn, D.C., Blangero, J., Sanghera, M.K., Pessoa, L., Fox, P.M., Uecker, A., Friehs, G., Young, K.A., Griffin, J.L., Lovallo, W.R., Fox, P.T., 2012. The functional connectivity of the human caudate: an application of meta-analytic connectivity modeling with behavioral filtering. NeuroImage 60, 117–129. http://dx.doi.org/10.1016/j.neuroimage.2011.12.010.
Rocher, A.B., Chapon, F., Blaizot, X., Baron, J.C., Chavoix, C., 2003. Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. NeuroImage 20, 1894–1898. http://dx.doi.org/10.1016/j.neuroimage.2003.07.002.
Rogalski, E.J., Gefen, T., Shi, J., Samimi, M., Bigio, E., Weintraub, S., Geula, C., Mesulam, M.M., 2013. Youthful memory capacity in old brains: anatomic and genetic clues from the northwestern SuperAging project. J. Cogn. Neurosci. 25, 29–36. http://dx.doi.org/10.1162/jocn_a_00300.
Rosen, W.G., Mohs, R.C., Davis, K.L., 1984. A new rating scale for Alzheimer's disease. Am. J. Psychiatry 141, 1356–1364. http://dx.doi.org/10.1176/ajp.141.11.1356.
Salmon, E., Lekeu, F., Garraux, G., Guillaume, B., Magis, D., Luxen, A., Moonen, G., Collette, F., 2008. Metabolic correlates of clinical heterogeneity in questionable Alzheimer's disease. Neurobiol. Aging 29, 1823–1829. http://dx.doi.org/10.1016/j.neurobiolaging.2007.04.016.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356. http://dx.doi.org/10.1523/JNEUROSCI.5587-06.2007.
Sestieri, C., Corbetta, M., Spadone, S., Romani, G.L., Shulman, G.L., 2014. Domain-general signals in the cingulo-opercular network for visuospatial attention and episodic memory. J. Cogn. Neurosci. 26, 551–568. http://dx.doi.org/10.1162/jocn_a_00504.
Sheikh, J.I., Yesavage, J.A., 1986. Geriatric depression scale (GDS) recent evidence and development of a shorter version. Clin. Gerontol. 5, 165–173. http://dx.doi.org/10.1300/J018v05n01_09.
Signorini, M., Paulesu, E., Friston, K., Perani, D., Colleluori, A., Lucignani, G., Grassi, F., Bettinardi, V., Frackowiak, R.S., Fazio, F., 1999. Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and nonquantitative [18F]FDG PET: a clinical validation of statistical parametric mapping. NeuroImage 9, 63–80. http://dx.doi.org/10.1006/nimg.1998.0381.
Sun, F.W., Stepanovic, M.R., Andreano, J., Barrett, L.F., Touroutoglou, A., Dickerson, B.C., 2016. Youthful brains in older adults: preserved neuroanatomy in the default mode and salience networks contributes to youthful memory in Superaging. J. Neurosci. 36, 9659–9668. http://dx.doi.org/10.1523/JNEUROSCI.1492-16.2016.
Suzuki, T., Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., Uemura, K., Lee, S., Park, H., 2012. Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial. BMC Neurol. 121, 128. http://dx.doi.org/10.1186/1471-2377-12-128.
van Uffelen, J.G.Z., Chinapaw, M.J.M., van Mechelen, W., Hopman-Rock, M., 2008. Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. Br. J. Sports Med. 42, 344–351. http://dx.doi.org/10.1136/bjsm.2007.044735.
Voss, M.W., Erickson, K.I., Prakash, R.S., Chaddock, L., Malkowski, E., Alves, H., Kim, J.S., Morris, K.S., White, S.M., Wójcicki, T.R., Hu, L., Szabo, A., Klamm, E., McAuley, E., Kramer, A.F., 2010a. Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia 485, 1394–1406. http://dx.doi.org/10.1016/j.neuropsychologia.2010.01.005.
Voss, M.W., Prakash, R.S., Erickson, K.I., Basak, C., Chaddock, L., Kim, J.S., Alves, H., Heo, S., Szabo, A.N., White, S.M., Wójcicki, T.R., Mailey, E.L., Gothe, N., Olson, E.A., McAuley, E., Kramer, A.F., 2010b. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front. Aging Neurosci. 2, 32. http://dx.doi.org/10.3389/fnagi.2010.00032.
Voss, M.W., Weng, T.B., Burzynska, A.Z., Wong, C.N., Cooke, G.E., Clark, R., Fanning, J., Awick, E., Gothe, N.P., Olson, E.A., McAuley, E., Kramer, A.F., 2016. Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. NeuroImage 131, 113–125. http://dx.doi.org/10.1016/j.neuroimage.2015.10.044.
Wang, C., Yu, J.T., Wang, H.F., Tan, C.C., Meng, X.F., Tan, L., 2014. Non-pharmacological interventions for patients with mild cognitive impairment: a meta-analysis of randomized controlled trials of cognition-based and exercise interventions. J. Alzheimers Dis. 42, 663–678. http://dx.doi.org/10.3233/JAD-140660.
Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., Noedberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., Decarli, C., Erkinjuntti, T., Giaconibi, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., Van Duijin, C., Visser, P., Petersen, R.C., 2004. Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J. Intern. Med. 256, 240–246. http://dx.doi.org/10.1111/j.1365-2796.2004.01380.x.
Wu, Y., Sun, D., Wang, Y., Wang, Y., Ou, S., 2016. Segmentation of the cingulum bundle in the human brain: a new perspective based on DSI tractography and fiber dissection study. Front. Neuroanat. 10 (84). http://dx.doi.org/10.3389/fnana.2016.00084.
Zou, Q., Wu, C.W., Stein, E.A., Zang, Y., Yang, Y., 2009. Static and dynamic characteristics of cerebral blood flow during the resting state. NeuroImage 48, 515–524. http://dx.doi.org/10.1016/j.neuroimage.2009.07.006.