NeuroImage 131 (2016) 133–141

Contents lists available at ScienceDirect

NeuroImage

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

Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—A multimodal approach

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ARTICLE INFO

Article history:
Received 1 June 2015
Revised 3 December 2015
Accepted 7 December 2015
Available online 15 December 2015

Keywords:
Physical activity
Resting state networks
fMRI
DMN
Perfusion

ABSTRACT

One step toward healthy brain aging may be to entertain a physically active lifestyle. Studies investigating physical activity effects on brain integrity have, however, mainly been based on single brain markers, and few used a multimodal imaging approach. In the present study, we used cohort data from the Betula study to examine the relationships between scores reflecting current and accumulated physical activity and brain health. More specifically, we first examined if physical activity scores modulated negative effects of age on seven resting state networks previously identified by Salami, Pudas, and Nyberg (2014). The results revealed that one of the most age-sensitive RSN was positively altered by physical activity, namely, the posterior default-mode network involving the posterior cingulate cortex (PCC). Second, within this physical activity-sensitive RSN, we further analyzed the association between physical activity and gray matter (GM) volumes, white matter integrity, and cerebral perfusion using linear regression models. Regions within the identified DMN displayed larger GM volumes and stronger perfusion in relation to both current and 10-years accumulated scores of physical activity. No associations of physical activity and white matter integrity were observed. Collectively, our findings demonstrate strengthened PCC–cortical connectivity within the DMN, larger PCC GM volume, and higher PCC perfusion as a function of physical activity. In turn, these findings may provide insights into the mechanisms of how long-term regular exercise can contribute to healthy brain aging.

Introduction

Normal (non-demented) aging is often associated with brain atrophy (Raz et al., 2005), changes in brain functional responses (Nyberg et al., 2010), and decline in cognitive performance (Rönnlund et al., 2005). However, some individuals resist major age-related brain pathology (Nyberg et al., 2012; Pudas et al., 2013), and a major scientific challenge is to identify what factors contribute to preserved brain health in aging. In the last decade, it has frequently been suggested that physical exercise may have positive global influences on brain health in aging, including spared brain volume (Erickson et al., 2009, 2011; Niemann et al., 2014), improved task-related functional brain responses (Colcombe et al., 2004; Voelcker-Rehage et al., 2010), increased white matter integrity (Johnson et al., 2011; Voss et al., 2013), and maintaining cognitive performance over time (Josefsson et al., 2012). Hence, in order to achieve healthy brain aging, one strategy seems to be to aim for an active lifestyle (Hillman et al., 2008).

Intact brain function in relation to physical fitness may be an indication of preserved neural efficiency within specific regions but could also be expressed as alterations at the level of functional interaction (i.e., functional connectivity) among remote brain regions, which can be measured at rest. Voss et al. (2010a) showed that young and older individuals differed in the level of functional connectivity within the posterior parts of the default-mode network (DMN) and that there was a positive association between aerobic fitness and functional connectivity between posterior cingulate cortex (PCC) and the middle frontal gyrus (MFG). The same group (Voss et al., 2010b) also showed that 1 year of aerobic exercise increased the functional connectivity in frontal and temporal cortices and non-aerobic training had a similar effect within the fronto-parietal network of the aging brain. The possibility that physical fitness can impact resting state networks may be of particular interest given that the functional architecture of these networks is negatively

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http://dx.doi.org/10.1016/j.neuroimage.2015.12.010
1053-8119/

altered in advanced age. It is of particular interest to focus on the most age-sensitive networks (i.e., age explains at least 10% of individual differences in functional connectivity) considering that physical activity may protect from the adverse effects on functional connectivity associated with aging (Voss et al., 2015). In a previous paper (Salami et al., 2014), we identified 24 RSNs of which seven were most severely affected by age. These age-sensitive RSNs included the anterior/posterior DMN, a bilateral fronto-parietal network, a hippocampus (HC) network, a medial parietal network, and a visual network. More specifically, it was shown that advanced age and associated memory deficits were particularly related to reduced functional connectivity within the anterior and posterior DMN, and, in addition, with elevated anterior hippocampus connectivity along with reduced posterior hippocampus connectivity.

The DMN has attracted much interest in studies of aging and age-related diseases, in part due to negative alterations in functional connectivity profiles of two critical nodes of DMN, notably the PCC and the HC (Ferreira and Busatto, 2013). Indeed, it has been discussed that measures of RSNs in general, and the DMN in particular, could serve as valid and reliable biomarkers for neurological disorders (Zhang and Raichle, 2010). If physical activity can positively alter these networks, it could provide new insights into the mechanisms underlying preserved memory and healthy brain aging in older adults who engage in long-term regular exercise (Fratiglioni et al., 2004; Rovio et al., 2005).

Studies investigating physical activity effects on brain integrity have mainly been based on single brain markers (e.g., GM volume, functional brain response, functional/structural connectivity), and few used a multimodal imaging approach. However, in one study, it was shown that aerobic exercise not only increased hippocampal volume but also increased hippocampal resting state functional connectivity in patients with multiple sclerosis (Leavitt et al., 2014). Further, in another study (Burdette et al., 2010), it was found that exercise was associated with greater connectivity between the hippocampus and the anterior cingulate cortex, which was accompanied with higher hippocampal perfusion.

Thus, it appears as if a multimodal imaging approach has the potential to provide a more comprehensive description regarding the effects of exercise on brain health. Yet, the scientific evidence based on combined imaging methods in relation to physical activity is currently limited. Therefore, the aim of the present study was to examine how physical activity is related to multiple measures of brain health in aging. More specifically, we first investigated if current level of physical activity is positively associated with functional connectivity within the most age-sensitive resting state brain networks identified in our previous study (Salami et al., 2014). In order to further quantify if physical activity is related to brain integrity beyond functional connectivity in any observed physical activity-sensitive RSNs, we then examined gray matter volume, white matter integrity, and cerebral perfusion. Moreover, based on studies showing benefits of long-term exercise for maintaining brain health in aging (Ruscheweyh et al., 2011), we examined if an accumulated score of physical activity during 10 years further modified the relationship between physical activity and brain health beyond that of the current physical activity score. We believe that with this approach, a more in-depth interpretation regarding the association between physical activity and brain health in aging can be reached. Specifically, we argue that the accumulated physical activity score should be the best indicator of an individual's physical activity status.

Based on previous studies showing that exercise mainly affects the hippocampus sub-system (Erickson et al., 2011; Maass et al., 2014) and the default-mode networks (Voss et al., 2010a), we hypothesized that we would find the strongest positive association of physical activity with the posterior DMN and the hippocampus sub-system. Based on the association among exercise, GM volume, WM integrity, and perfusion (Erickson et al., 2009; Johnson et al., 2011; Maass et al., 2014), we further hypothesized that within the physical activity-sensitive RSN's these brain markers would also show positive relations with physical activity.

Methods

General overview of the Betula cohort

The participants in the present study come from the ongoing Betula prospective cohort study on memory, health, and aging that started in 1988 (Nilsson et al., 1997). Betula is a study of healthy individuals that have been randomly recruited from the population in a town of about 100,000 inhabitants. Initially, Betula comprised 10 age-cohorts, 35–80 years of age, with 100 individuals in each cohort. Currently, Betula includes six samples (S1–S6) and about 4500 individuals in total. The participants have been re-examined every 5 years. At each test wave (T1 1988–1990; T2 1993–1995; T3 1998–2001; T4 2003–2005; T5 2008–2010; T6 2013–2014), health examinations were performed along with extensive cognitive testing. At T5, structural and functional MRI was performed on a randomly recruited sub-sample of Betula participants from samples 1 and 3, and on an additional new sample of participants in the age range between 25 and 80 years (see Pudas et al., 2013; Salami et al., 2012a, 2012b) for a description of the Imagen cohort).

Subjects

In the present study, we mainly utilized data from the T5 data collection in Betula and only included participants with an MMSE score > 24. For perfusion data, we also excluded participants with cerebrovascular diseases. The sample with complete current physical activity and cognitive data was in total 950 participants. The sample size for the analysis of accumulated physical activity and cognition was 506 individuals. For current physical activity in relation to resting state network, GM volume, and WM integrity analysis, we had a total sample size of 308 individuals. For accumulated physical activity in relation to resting state network, GM volume, and WM integrity analysis, we had a total sample size of 196 individuals. We did not acquire perfusion data at T5. However, we were able to utilize perfusion data from the T6 data collection. Thus, for the analysis of current physical activity and perfusion, the sample size was 196 individuals, and for the analysis of accumulated physical activity and perfusion, the sample size was 118 individuals. The different samples are presented in Table 1.

Physical activity

Physical fitness is a set of health- or skill-related attributes that ranges from low to high. Health-related physical fitness involves cardiorespiratory variables, muscular variables, body composition, and flexibility variables, and these variables are related to individuals' physical activity level (Caspersen and Christenson, 1985). Previous studies

Table 1
Participant characteristics.

	Betula cognition	Imagen-T5	Imagen-T6
Age years (mean, range)	64.6 (25–100)	61.5 (25–80)	62.8 (30–85)
Current physical activity, *n*	950	308	196
Accumulated physical activity, *n*	508	196	196
Gender (% females)	53%	52%	52%
Education years (mean, SD)	10.0 (4.1)	13.9 (3.7)	12.1 (3.8)
Current physical activity, *z*-score (mean, SD)	0.07 (3.4)	0.13 (3.6)	0.16 (3.9)
Accumulated physical activity, *z*-score (mean, SD)	0.48 (7.5)	0.95 (8.3)	1.08 (8.9)
MMSE	27.9 (2.0)	28.4 (1.3)	28.3 (1.3)

Note: Betula cognition represents the participants used in the analysis of cognitive data. Imagen-T5 represents those participants used in the analysis of the physical activity-sensitive resting state network with the follow-up analysis of gray matter volume and white matter integrity. Imagen-T6 represents those individuals used in the perfusion analysis. The three sub-samples were equal in terms of gender, education, and MMSE score.

have shown that higher BMI and waist circumference has been observed for less physically active older women (Pols et al., 1997; Li et al., 2009) and men (Bann et al., 2015; Li et al., 2009). Moreover, physical activity is associated with lower resting heart rate and blood pressure in both men (Bijnen et al., 1996; Mensink et al., 1999; Janney et al., 2010) and women (Pols et al., 1997; Mensink et al., 1999) of all ages. Further, long-term aerobic exercise is associated with higher grip strength throughout the life span (Crane et al., 2013), lower grip strength has been reported in inactive older men and women (Legrand et al., 2013), and grip strength is highly associated with pulmonary function, a measure of physical performance, in older men and women (Turkeshi et al., 2015). In the Betula cohort, variables such as resting pulse, resting systolic and diastolic blood pressure, maximum grip strength (left and right hand) BMI in kg/m^2, and waist circumference in cm have been collected. Thus, an index reflecting physical activity could be calculated.

A principal component analysis (PCA) on the 7 physical activity-related items in Betula was conducted with orthogonal rotation (varimax). The Kaiser–Meyer–Olkin measure verified the sampling adequacy for the analysis (KMO = 0.60), and Bartlett's test of sphericity χ^2 $(21) = 2954.4$, $p < 0.001$ indicated that correlations between items were sufficiently large for PCA. Two components were revealed with eigenvalues over Kaisers criterion of 1. The first component contained all seven items with only pulse with a loading less than 0.3 (0.278). This component explained 60.32% of the variance (see supplementary information online for PCA decomposition and correlation between the 7 physical activity-related items and age).

Current physical activity was derived as a composite score of the 7 physical activity-related variables collected at T5. Each variable was z-transformed and an average *z*-score was then calculated. Since a high value of BMI, waist circumference, pulse, and blood pressure is an indication of poor physical activity, these *z*-scores were reversed by multiplying by −1 giving a high composite score associated with being more physically active. Due to previous studies showing significant benefits of long-term regular physical exercise on brain health in aging (Fratiglioni et al., 2004; Rovio et al., 2005; Ruscheweyh et al., 2011), it is possible that accumulated physical activity over a longer time period may have stronger effects on brain integrity beyond that of current physical activity level. Therefore, we also calculated *accumulated physical activity* based on the same variables as the current physical activity score but here the scores from T3 (except grip strength), T4 and T5 were added in order to reflect a cumulative physical activity score over a time period of 10 years. There was a significant positive correlation among the current physical activity score and the accumulated physical activity score ($r^2 = 0.68$, $p < 0.0001$).

MRI data acquisition

Imaging data collection was performed on a 3 T GE scanner equipped with a 32-channel head coil. High-resolution T1-weighted structural images were collected using the following parameters: 180 slices; 1 mm thickness; TR 8.2 ms; TE 3.2 ms; flip angle 12°; FOV 25 × 25 cm. Functional data were acquired with a gradient EPI sequence with the following parameters: 37 transaxial slices, 3.4 mm thickness, 0.5 mm gap, TR 2000 ms, TE 30 ms, flip angle 80 °, FOV 25 × 25 cm, in plane resolution of 2.6 × 2.6 mm. Diffusion tensor imaging data were collected with a spatial resolution of 0.98 × 0.98 × 2 mm with the following parameters: 64 slices with no gap in between, TR = 8.0 s, TE = 84.4 ms, 256 × 256 matrix, flip angle 90°, $b = 1000$ s/mm^2, 3 repetitions of 32 independent directions and 6 B0 images. For the T6 time point, whole brain perfusion was measured with a 3D pseudo-continuous arterial spin labeling sequence. Labeling time was 1.5 s, post-labeling delay time was 2 s, field of view was 24 cm, slice thickness was 4 mm, number of averages was 3, number of control label pairs was 30, and acquisition resolution was 8 × 512 (arms x data points in spiral scheme). Forty slices covered the whole brain and the reconstructed voxel size was 1.88 × 1.88 × 4 mm.

Resting state networks

The full descriptions of resting state data analyses were given in our previous work (Salami et al., 2014). In short, fMRI data were corrected for time differences between slices within each volume and then motion corrected. Using diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL, Ashburner, 2007), the realigned fMRI images were nonlinearly normalized to the sample-specific group template, affine-aligned into stereotactic space of the Montreal Neurological Institute, and smoothed using an 8.0-mm full width at half maximum Gaussian filter. Structural MRI and functional MRI images were in the same space and had the same resampled voxel size (2 × 2 × 2 mm). The preprocessed resting state fMRI data were then analyzed using temporal concatenation independent component analysis (ICA) as implemented in the gift toolbox (Allen et al., 2011). ICA is a multivariate blind-source separation method that split fMRI data into a set of components/networks that are spatially independent, but temporally coherent. The detailed description of ICA analyses is given before (Salami et al., 2014; preprocessing: intensity normalization; data reduction PCA 1:100 components; data reduction PCA 2: 47 components; back reconstruction using GICA3 with no scaling). As an output, 47 components were extracted using ICA Infomax algorithm (Allen et al., 2011). Twenty-four of the 47 components were topologically meaningful and fulfilled criteria of being considered as resting state networks (RSN; for more information see resting state network selection in Salami et al., 2014). For these 24 RSNs, we extracted 3 ICA-driven measures: (1) voxel-wise connectivity, which reflects the level of functional connectivity of a voxel to other voxels within a component; (2) global connectivity, which reflected connectivity within a component as a whole; (3) amplitude, which reflects the level of activation within a component (see Salami et al., 2014 for a full description about how these measures were computed including a complete description of the 24 RSNs divided into groups based on their anatomical and functional properties). To investigate the effect of age on 24 RSNs, we considered different RSN measures (voxel-wise/global connectivity, amplitude) as dependent variables in a multiple regression. In addition, age, sex, a measure of head motion (frame-wise displacement), and a measure of data quality (temporal signal-to-noise ratio) were set as predictors (see Salami et al., 2014). RSNs were considered age sensitive if global connectivity and amplitude: $r \geq$ m0.20, $p < 0.0001$ and voxel-wise connectivity: $p < 0.05$ (family-wise error-corrected), $k > 20$. As such, 7 age-sensitive RSNs were identified. These networks included anterior/posterior DMN, a left/right fronto-parietal network, a hippocampus network, a medial parietal network, and a visual network.

GM volume segmentation

In order to anatomically segment the structural T1-weighted images, FreeSurfer automated cortical and subcortical parcellation tools were used (http://surfer.nmr.mgh.harvard.edu/). Detailed descriptions of these methods have previously been presented (Destrieux et al., 2010; Fischl et al., 2002). In short, images were first normalized and motion corrected, then a hybrid watershed/surface deformation procedure was used to remove non-brain tissue, followed by transformation of the images to the Talairach space. To localize the boundary between gray matter, white matter, and cerebrospinal fluid, the maximum shift in signal intensity was used. The white matter surface was tessellated with a triangular mesh, deformed, and inflated to visualize the gyral and sulcal areas simultaneously. Next, the white matter, subcortical gray matter structures, and cortical surface were segmented. The distance from the white and gray matter boundary to the pial surface was estimated by an automated algorithm and used as a measure of cortical thickness. Surface area was calculated for each vertex and the summed areas of these vertices used as the total cortical surface area. Multiplying cortical thickness with cortical area for each segmented cortical region derived cortical volumes.

WM integrity

Fractional anisotropy (FA) represents the tendency of water molecules to diffuse in a preferred direction and ranges between 0 and 1. FA values are one way to describe the integrity of the white matter, with higher values indicating better white matter integrity. Diffusion-weighted data analysis was performed using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) package (http://www.fmrib.ox.ac.uk/fsl) and the Tract-Based Spatial Statistics (TBSS) as part of the FMRIB software package. The full details of DTI data analyses were given elsewhere (Salami et al., 2012a, 2012b). In short, DTI data were corrected for both motion and eddy current distortion. Then DTIfit was used to fit a diffusion tensor to each voxel of the brain. As such, voxel-wise maps of fractional anisotropy (FA) were yielded. The remaining processing stream followed the TBSS method. In short, all subject-specific FA maps were nonlinearly normalized to a standard space (FMRIB58_FA) and then fed into a skeletonize program to make a skeleton of common white matter tracts across all subjects. Averaged FA along the spatial course of certain major WM tracts were computed with reference to JHU ICBM-DTI-81 white matter labels, which are part of the FSL atlas tools, developed at John Hopkins University and distributed with the FSL package (Wakana et al., 2004). The extraction of FA values for the Betula cohort has previously been extensively described in Salami et al. (2012a, 2012b). In the study of Salami et al. (2012a, 2012b), an age-related increase/decrease of FA and MD values was shown, which is consistent with other studies (Bennett et al., 2010; Burzynska et al., 2010). Therefore, and in order to reduce the number of analyses, we decided to only use FA values in the current manuscript.

Perfusion

Perfusion (in ml/100 g/min) was calculated from the control label pairs based on a mathematical model in agreement with recent recommendations (Alsop et al., 2014) using the manufacturer provided software as has been described previously (Zarrinkoob et al., 2015). Then by applying DARTEL, all perfusion images were nonlinearly normalized to a T6-specific group template, affine-aligned into stereotactic space of the Montreal Neurological Institute, and finally smoothed using an 8.0-mm full width at half maximum Gaussian filter.

Cognitive performance

The cognitive tests included in Betula had to be rooted in extant theories of memory as well as sensitive to various memory deficits in old age (Nilsson et al., 1997). The cognitive tests available from the Betula test battery have been extensively described in previous publications (Nilsson et al., 1997, 2004). Both principal component analysis and confirmatory factor analysis have shown that the tests included in the episodic and semantic memory scores, respectively, indeed hold true for these two kinds of tasks (Nyberg, 1994; Nilsson et al., 1997; Nyberg et al., 2003). Further, the tests included in Betula demonstrate moderate to high reliabilities and stability coefficients (Nyberg, 1994; Nyberg et al., 2003), including substantial 5- and 10-year stability coefficients ($r = 0.77$–0.83) at the composite level (Rönnlund and Nilsson, 2006; Mousavi et al., 2014).

Episodic memory

For the purpose of this study, an episodic composite measure of 4 tests reflecting episodic memory was created from the Betula test battery. The episodic composite comprised free recall of sentences learned with or without enactment, and cued recall of sentences learned with or without enactment. These tests have previously shown to be sensitive for age-related changes (Josefsson et al., 2012) with good test–retest reliability (Pudas, 2013).

Semantic memory

Four tests were used as a composite reflecting semantic memory performance, including 3 tests of fluency: (1) generate as many words with the initial letter A in 1 min, (2) generate as many 5-letter words with the initial letter M in 1 min, and (3) generate as many professions with the initial letter B in 1 min. The fourth included test in the semantic composite was a vocabulary test (SRB, Dureman, 1960) in which the participants were to indicate which of 5 words were synonymous to a target word.

Block design

We used performance on blocked design from the Wechsler Adult Intelligence Scale, WAIS (Wechsler, 1981) as a visuospatial task. Here the participants were asked to place red and white blocks so that the blocks matched a pattern shown on a picture (maximum 9 designs).

Working memory/updating

Updating is according to one of three related, although separable, executive functions of Miyake et al. (2000), which are functions that involves cognitive control processes responsible for the regulation of behavioral activities. In an updating task, the participant must monitor incoming information, and continuously modify the content of working memory. Updating is reflected as an essential part of working memory (Smith and Jonides, 1999). In the Betula test battery, a 2-back test of 20 words was used as a measure of working memory.

Statistical analysis

Brain imaging data

To investigate the association between physical activity and the negative age-related alterations in functional connectivity of the seven most age-sensitive resting state networks, we used multiple regression with voxel-wise connectivity as the dependent variable, and age and physical activity score as predictors. Voxels with $p < 0.05$ FDR-corrected, $k > 10$ were considered to have a significant association with physical activity. For any physical activity-sensitive RSN (current and/or accumulated), we then examined if GM volume, WM integrity, and cerebral perfusion also showed relationships with physical activity. Thus, following the voxel-wise connectivity analysis, the GM volumes of the specific sub-regions from the physical activity-sensitive RSNs were added in a linear regression model with current or accumulated physical activity as the predictors. Then we identified the white matter tracts associated with the observed physical activity-sensitive RSN regions, and added the average Fractional anisotropy (FA) values in a linear regression model with current or accumulated physical activity as the predictors. The last step was to examine the cerebral perfusion within the physical activity-sensitive RSNs sub-regions. For this purpose, the average perfusion of each sub-region of interest was calculated and related to physical activity using linear regression. For each analysis, we controlled for age and sex. For GM volume analysis, we also controlled for intra-cranial volume (ICV). For follow-up analyses, we Bonferroni-corrected the statistical thresholds (see below for exact thresholds) for current and accumulated physical activity analyses, respectively. In a final step, a stepwise regression analysis was performed in order to disentangle the unique relationship of our brain measures with the physical activity scores.

Cognitive data

Separate linear regressions were performed with current and accumulated physical activity scores as the predictors and cognitive scores (episodic memory composite, semantic memory composite, block design, working memory) as the dependent measures. In the analysis of cognition, we controlled for age, sex, and education. For cognitive data, a Bonferroni-corrected statistical threshold ($p < 0.0125$) was considered significant.

Results

Resting state network functional connectivity

Of the seven most age-sensitive RSNs identified by Salami et al. (Salami et al., 2014) one exhibited association with current physical activity ($n = 308$). The voxel-wise connectivity analysis revealed positive associations between current physical activity and one of the key regions of the posterior DMN (Fig. 1) specifically the anterior parts of the PCC (XYZ = −8 -36 26, t = 4.19, k = 284).

Consistent with the current physical activity analysis, we also found a positive association between accumulated physical activity ($n = 196$) and the PCC (XYZ: −6 −32 26; $t = 4.30$, $k = 68$).

GM volumes

The identified regions involved in the physical activity-sensitive posterior DMN included the left and right posterior cingulate cortex and the left and right precuneus. Thus, GM volumes from these regions were entered in the regression analysis (Table 2). The results showed that current physical activity ($n = 308$) was also significantly positively associated with the volume of the right ($p = 0.001$) and the left ($p = 0.006$) PCC. That is, a higher physical activity score was related to larger GM volume in bilateral PCC. There was no significant association with current physical activity and GM volumes of left or right precuneus ($p > 0.05$).

When examining the GM volumes of PCC and precuneus in relation to accumulated physical activity ($n = 196$) no volumes survived the Bonferroni-corrected threshold ($p < 0.008$). However, there was a trend for both the left PCC, $p = 0.032$ and the right PCC, $p = 0.046$.

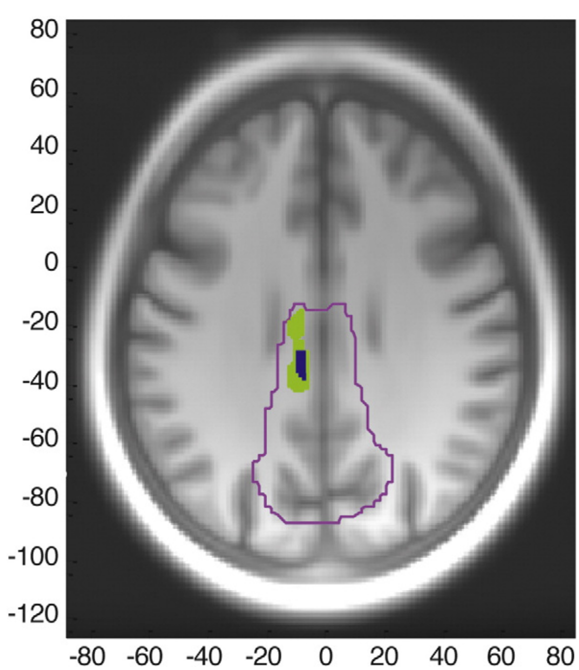

Fig. 1. The physical activity-sensitive posterior DMN network overlaid on a brain template from the Betula participants. The purple contour outlines the age-sensitive posterior DMN network specified by Salami et al. (2014). The green region is the 284 voxels showing a positive association with current physical activity score, and the blue colored region is the 68 voxels showing a positive association with accumulated physical activity score.

WM integrity

As reported in our previous work (Salami et al., 2012a, 2012b), the tract-based analyses were conducted with reference to JHU ICBM-DTI-81 white matter labels. In reference to this atlas, the cingulum (cingulate gyrus, a tract that connect PCC to MPFC, Greicius et al., 2009) and the spelenium part of the corpus callosum are associated to the PCC. When examining the association between the average FA of these tracts and the current physical activity ($n = 308$), the results (Table 2) revealed no significant association for either tract ($ps > 0.05$).

When examining the posterior tracts (splenium and cingulum) in relation to accumulated physical activity ($n = 196$), there was no significant association observed, $ps > 0.05$ (Table 2).

Perfusion

A masks was generated based on the FDR-corrected map of the current physical activity ($n = 196$) analysis of the age-sensitive RSN, representing the posterior DMN network cluster, and subsequently used in the perfusion analysis. The perfusion survived the Bonferroni-corrected threshold of $p < 0.025$ and displayed positive significant relationships with current physical activity (PCC mask, $p = 0.002$). That is, higher current physical activity score was related to higher perfusion in RSN physical activity-sensitive regions (see Fig. 2).

For accumulated physical activity ($n = 118$), the perfusion within the PCC displayed a significant positive relationship to accumulated physical activity score ($p = 0.019$).

Stepwise regression

The only indication of a relationship between the physical activity scores and the brain measures concerned the posterior DMN. Thus, in order to examine the independent relationships between the posterior DMN brain measures and fitness, we conducted a stepwise regression analysis with the following predictors: posterior DMN connectivity, posterior DMN perfusion, PCC gray matter volume, splenium FA values, and cingulum FA values. Age and gender were included as nuisance covariates in the analyses. The results revealed independent relationships of posterior DMN functional connectivity ($p < 0.0001$; $\beta = 0.27$) and posterior DMN perfusion ($p = 0.021$; $\beta = 0.15$) with current physical activity score, $n = 182$. The other measures revealed no independent

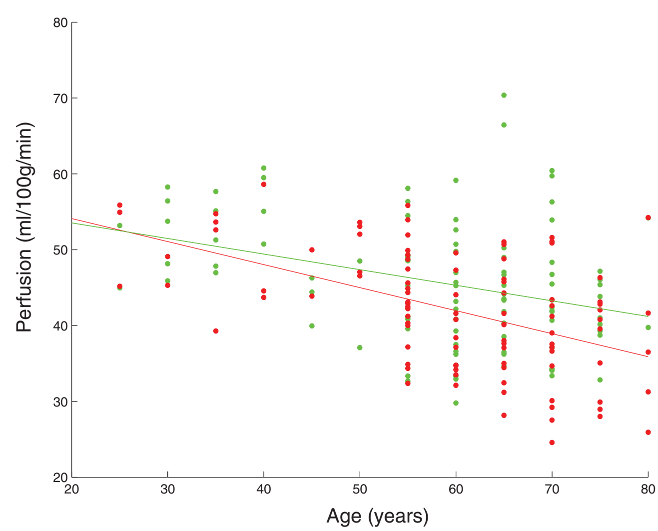

Fig. 2. Perfusion trajectories corresponding to subjects with high versus low current physical activity score. The lines represent results from linear regression. The groups were calculated using a median split on current physical activity score (residualized for age and sex). The colors green and red corresponds to high and low current physical activity score, respectively.

Table 2
Regression coefficients of GM volume, WM integrity, perfusion, and cognitive performance in relation to current and 10 years accumulated physical activity scores.

	Current physical activity			Accumulated physical activity		
	Standardized β	r^2	p^a	Standardized β	r^2	p^a
GM volume						
Left precuneus	0.08	0.008	0.1	0.1	0.007	0.1
Right precuneus	0.09	0.01	0.07	0.04	0.002	0.5
Left PCC	0.16	0.09	**0.006**	0.10	0.03	0.032
Right PCC	0.14	0.11	**0.001**	0.14	0.02	0.046
WM integrity						
Splenium of corpus callosum	0.048	0.005	0.4	0.023	0.002	0.7
Cingulum (cingulate gyrus)	0.070	0.006	0.2	0.09	0.005	0.2
Cingulum (HC)	0.035	0.002	0.6	0.024	0.002	0.7
Perfusion						
PCC	0.24	0.05	**0.002**	0.26	0.05	**0.039**
Cognitive performance						
Episodic memory	0.018	0.003	0.2	0.027	0.03	0.048
Semantic memory	0.005	0.001	0.7	0.032	0.008	0.5
Block design	0.025	0.07	**0.006**	0.089	0.004	**0.005**
Working memory	0.005	0.003	0.2	0.004	0.008	0.8

Note: Linear regressions were performed on GM volume, WM integrity, and perfusion based on specific regions within the physical activity-sensitive resting state network.
[a] Bold numbers identify significant relationships with a Bonferroni-corrected threshold (see Results).

relationships (right PCC GM, $p = 0.14$; left PCC GM, $p = 0.09$; FA splenium, $p = 0.3$; FA cingulum (HC), $p = 0.9$; cingulum (cingulate gyrus), $p = 0.3$). When repeating the analysis for the accumulated physical activity score, the general pattern in standardized beta-coefficients was maintained, but only the posterior DMN functional connectivity reached significance ($p > 0.0001$) possibly due to a reduced power in the latter analysis.

Cognitive performance

When examining cognitive performance in relation to current physical activity score ($n = 950$), there was a positive association to block design ($p = 0.006$). The present sample did not show any significant association of current physical activity with episodic memory, semantic memory, or working memory, $ps > 0.05$ (Table 2).

When examining cognitive performance in relation to accumulated physical activity score ($n = 506$), there was a positive association with block design ($p = 0.005$). There was a trend for a positive significant association with episodic memory performance ($p = 0.048$). There was no significant association between accumulated physical activity and semantic memory or working memory $p > 0.05$.

Discussion

The present study examined how physical activity modifies functional connectivity in age-sensitive resting state networks. The results confirmed our hypothesis of a physical activity-related effect within the posterior DMN. Furthermore, within the posterior DMN, GM volume and perfusion measures were also positively associated with physical activity. Notably, the posterior DMN has been considered a central hub for achieving good brain health throughout the life span (Buckner et al., 2009; Leech et al., 2011). We also observed a strong association between physical activity and block design, which has previously been strongly linked to the functional connectivity of the posterior DMN (Salami et al., 2014). Overall, the strongest observation of a physical activity–brain health association was when using the current physical activity score and, unexpectedly, the results of the accumulated physical activity score were in general somewhat weaker. It should be noted, however, that the current and accumulated physical activity scores were highly correlated. Nevertheless, the present data suggest that current physical activity appears to be a better predictor of brain health. It is possible to view that the absence of an added value of physical activity over a decade, as expressed in the accumulated physical activity score, as evidence that physical activity over time, may not build up a reserve for brain health (cf., Stern, 2009). However, considering the rather long interval between testing occasions in Betula, it is also plausible that the current physical activity score is a reflection of an individual's cumulative physical activity over the years preceding the testing occasion, which then would argue in favor of the possibility of a potential reserve. The issue of whether physical activity can be used to maintain brain health throughout the life span with or without the buildup of a reserve is an important question that should be addressed in future studies with a longitudinal design. Next, we will discuss the main findings of the present study.

Resting state connectivity and physical activity

The PCC has a high metabolic rate (Raichle et al., 2001), is highly connected to other brain regions (Hagmann et al., 2008), and serves a central role within the DMN (Leech et al., 2011). It has been proposed that reduced PCC functional connectivity is not only associated with aging but specifically with age-related cognitive impairment (Andrews-Hanna et al., 2007; Salami et al., 2014) and potentially an accurate and early marker of Alzheimer's disease (Mevel et al., 2011) sensitive to amyloid deposition (Sperling et al., 2009). Functionally, the PCC has been suggested to support internally directed cognition (Raichle et al., 2001; Buckner et al., 2008) and may have a direct role in regulating focus of attention (Hahn et al., 2007). Improved PCC functional connectivity, as a function of increased physical activity score, may therefore be an indication of maintained brain health throughout the life span (cf., Nyberg et al., 2012), and further studies could examine if increased physical activity translates into a reduced risk or delayed onset for dementia. Hence, we provide support that physical activity has positive effects on a prominent part of one of the brain's central networks, the posterior DMN, in a population-based sample with generally good health.

In the present sample, physical activity scores did not reverse the negative effect of age on HC connectivity. However, it should be noted that previous studies have shown that increased exercise has been related to increased HC volume (Erickson et al., 2011; Niemann et al., 2014) strengthened HC connectivity (Burdette et al., 2010) and improved HC perfusion (Maass et al., 2014) underlining the importance of physical activity for HC function.

It is also possible that investigating less age-sensitive networks will yield additional physical activity associations. In the present study, however, we limited the analysis to the most age-sensitive networks as presented by Salami et al. (2014).

GM volumes within PCC in relation to physical activity

Atrophy in the cingulate cortex has been related to several aspects of cognitive decline in aging (Vaidya et al., 2007). Across a range of neurological and psychiatric disorders, the PCC is repeatedly found to be structurally and functionally abnormal (Leech and Sharp, 2013), and successful aging is associated with spared PCC volume (Kalpouzos et al., 2009; Mann et al., 2011). Further, in Alzheimer's dementia, the PCC has been shown to be metabolically impaired with early signs of beta amyloid deposition (Buckner et al., 2005; Chételat et al., 2003; Greicius et al., 2004) affecting the posterior DMN (Chételat et al., 2003; Gili et al., 2011). Hence, the findings presented here with larger PCC volume for those with higher physical activity score offer important insights regarding the underlying mechanisms of the relation between physical activity and maintained brain health in aging (Ruscheweyh et al., 2011). Moreover, these findings may potentially be an important link between the association of the benefits of long-term exercise and delayed onset of dementia (Fratiglioni et al., 2004; Rovio et al., 2005), but this is for future studies to directly adress.

White matter integrity and physical activity

In the present study, we found no support for an association between our physical activity scores and WM integrity of the physical activity-related RSN, using fractional anisotropy values. For the posterior parts of the skeleton, where we had the strongest relation between physical activity and RSN, GM volume, as well as perfusion, there were no significant associations with FA values. Hence, based on the present observations, it appears as if physical activity is more associated with functional connectivity of the posterior DMN rather than with structural connectivity of the DMN (extracted from JHU atlas). It is important to stress that although we found no evidence in support of the association between physical activity score and white matter integrity of the physical activity-sensitive networks, the possible effects of physical activity on other white matter pathways (and also other DTI-driven measures such as AD and RD) should not be ruled out.

Perfusion within posterior DMN in relation to physical activity

Exercise-induced alterations in gene expressions stimulates neurogenesis and resistance to brain ischemia (Dishman et al., 2006), with concomitant beneficial changes in local cerebral vasculature (Pereira et al., 2007). In previous studies, increased aerobic capacity resulted in increased perfusion in the hippocampus of both younger (Pereira et al., 2007) and older individuals (Burdette et al., 2010; Maass et al., 2014) and could potentially represent a therapeutic strategy capable of delaying of reversing the perfusion deficits seen in various stages in Alzheimer's disease (Binnewijzend et al., 2014). This observation is in line with observations that fitness attenuates age reductions in blood velocities of cerebral feeding arteries (Ainslie et al., 2008; Bailey et al., 2013). It is likely that the increased PCC volume in relation to physical activity score is closely linked to improved perfusion, but it remains unclear if increased perfusion leads to cell proliferation, synaptogenesis, or dendritic branching.

Cognitive performance and physical activity

In Salami et al. (2014), the relationship between the functional connectivity of the posterior DMN was associated with both visuospatial and episodic memory functioning. Here we observed that block design was positively related to both current and accumulated physical activity. It is thus likely that increased posterior DMN connectivity in individuals with higher physical activity score has been translated to a higher performance on the block design task. There is also previous evidence that improved fitness is associated with increased spatial learning (Holzschneider et al., 2012). When using the accumulated physical activity score, there was a trend toward a relationship with episodic memory performance. This is of particular interest due to the importance of episodic memory as an early predictor of late onset dementia (Boraxbekk et al., 2015; Bäckman et al., 2001; Albert, 2011) and further highlights the link between long-term regular exercise and reduced risk of dementia (Fratiglioni et al., 2004).

Limitations

Limitations in the present study include the physical activity measure. It is primary aerobic exercise that has been shown to be related to improved brain function and cognitive performance (Hillman et al., 2008), but strength has also been shown to be associated with, e.g., hippocampus volume (Niemann et al., 2014) and positively altered functional brain responses (Voelcker-Rehage and Windisch, 2013; Voelcker-Rehage et al., 2010). Our physical activity score should be considered a combined measure of both aerobic and non-aerobic fitness, but more direct measurements of physical fitness (e.g., aerobic capacity) is desired in future studies. Further, our current findings are based on cross-sectional brain imaging data, but in order to better understand the causal relationship between physical activity and brain health, longitudinal data will be needed in which it will be possible to examine how change in physical activity relates to change in functional connectivity, structural connectivity and ultimately cognition. As the Betula study continues, in the future, it will allow a detailed examination of longitudinal relationships between physical activity and brain health. Then it will also be possible to further tease apart using a multivariable regression model and include measures of change in RSN, GM, WM, and perfusion in the same model to examine both related and non-related effects. In the present study, we focused on to further qualify the significant physical activity-related RSN regions based on previously reported age-sensitive networks (Salami et al., 2014) and explored the unique relationship of our brain measures with physical activity score using a stepwise regression model.

Moreover, RSN data, GM data, WM data, and cognitive data were collected during the T5 data collection, but the perfusion data was collected at T6 (five years later). How such time period affected the present results is unknown but should be considered as a limitation in the present study.

As in any longitudinal cohort, attrition occurs between testing occasions. In Betula, it has previously been shown that there is higher attrition of lower-performing individuals as well as those experiencing accelerated decline in memory (Josefsson et al., 2012; Rönnlund et al., 2005), this is also true for the imaging sample, with a slightly biased attrition rate for older individuals (Pudas, 2013). In the present study, however, this should only make it more difficult to detect effects of physical activity since the sample is relatively healthy.

Multimodal association with physical activity

In the present study, we show that a higher physical activity score positively affects negative age-related decreases in functional connectivity of posterior DMN, increases PCC GM volume, strengthens PCC perfusion, and improves visuospatial task performance. The stepwise regression analysis showed that only functional connectivity of posterior DMN and PCC perfusion displayed independent relationship with physical activity. Thus, the multimodal approach undertaken in the present study indicates that physical activity exerted an influence on brain-cognition functioning, but the effect was much more regionally specific than what has been suggested in some past studies.

Acknowledgments

We thank the staff and the participants of the Betula project and the staff at Umeå center for Functional Brain Imaging. This study was supported by the Swedish Science Council, the UmU-KI strategic Neuroscience Network, a Wallenberg Scholar Grant to L.N, and Torsten and Ragnar Söderberg's foundation (L.N.).

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.12.010.

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