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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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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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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.