Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com

Physically active life style is associated with increased grey matter brain volume in a medial parieto-frontal network

K.M. Eyme[a], M. Domin[a], F. Gerlach[a], N. Hosten[b], C.O. Schmidt[c], C. Gaser[d], A. Flöel[e], M. Lotze[a,*]

[a] Functional Imaging Unit, Center for Diagnostic Radiology, University Medicine Greifswald, Germany
[b] Center for Diagnostic Radiology, University Medicine Greifswald, Germany
[c] SHIP, University Medicine Greifswald, Germany
[d] Departments of Psychiatry and Neurology, Jena University Hospital, Germany
[e] Neurology, University Medicine Greifswald, Germany

ARTICLE INFO

ABSTRACT

To examine the association between the amount of sports activity performed during leisure time and gray matter volume (GMV) of the brain we investigated differences in GMV in a large cohort study of community-dwelling older adults. 967 individuals indicated their average weekly sports activity via a questionnaire, and underwent high resolution T1-weighted structural imaging of the brain. We used voxel based morphometry (CAT 12) in a region of interest approach for (1) comparing participants with higher versus lower sports activity (median split) and (2) calculating a linear regression on GMV and sports activity. We carefully corrected for other factors known to have an impact on GMV (sex, age, total brain volume, education, cigarettes and alcohol consumption, body mass index) and excluded pathology (history of psychiatric or neurological disease; visual inspection of brain scans).

Those participants who spend more time performing sports activity per week (median split with > 1 h/week) showed higher GMV in one superior medial parietal cluster comprising the dorsomedial frontal lobe, the superior parietal lobe, and the precuneus/cuneus area. When splitting participants by their median (55.5 years) into two groups we found a stronger protective effect of sports against age related GMV decline for the older part of the cohort.

Overall, a more active lifestyle was associated with increased GMV in areas associated with self-awareness and working memory. These cohort data support data on the protective role of sports activity for the GMV.

1. Introduction

The brain is shaped by physical activity over the lifetime [1]. Studies on subjects with extensive physical training show training-specific changes for those structures repetitively active during training which are cortical and subcortical motor areas (primary motor cortex and basal ganglia [2]:), sensory areas (somatosensory cortex: [2]; auditory: [2,3]; visual cortex [4]:), sensorimotor integration areas (parietal lobe [4]:) and areas engaged in feedforward processing (anterior cerebellar hemisphere [4]:). Keeping in mind that different sports have different needs for functional contribution of the CNS, it is not astonishing that different sports are associated with differential changes in GMV [5]. Correspondingly, short-term limb immobilization can lead to a decrease of cortical thickness in somatosensory and motor areas [6].

A model for understanding structural changes depending on differential requirements on movement execution and sensory input has already been postulated by Hebb in the middle of the last century [7]. Therefore, continuous practice modulates those features of brain anatomy specifically associated with requirements of the respective training task [8]. With respect of the molecular mechanisms behind these gray matter changes, research on animals has shown that fit-

* Corresponding author at: Functional Imaging Unit, Center for Diagnostic Radiology and Neuroradiology, University of Greifswald, Walther-Rathenau-Str.46, D-17475 Greifswald, Germany.
Email address: martin.lotze@uni-greifswald.de (M. Lotze)

https://doi.org/10.1016/j.bbr.2018.10.042
Received 21 September 2018; Received in revised form 29 October 2018; Accepted 31 October 2018
Available online xxx
0166-4328/

ness training is associated with changes in angio- and synaptogenesis [9].

Physical exercise mitigates age-related decline of gray matter volume [10–13] and decreases cognitive decline with age and pathology [14,15]. Areas vulnerable for age-related decline, including medial prefrontal, superior parietal and temporal areas, may be preferentially modified by physical activity in the elderly [16,17]. Aerobic exercise may be particularly beneficial for executive functions in aged healthy volunteers [18]. In 35 older adults [16], reported a relationship between cardiopulmonal fitness and cortical thickness in parietal (e.g. PCC, precuneus, cuneus), prefrontal (OFC, superior frontal cortex) but also temporal brain areas.

In a VBM-study in 331 elderly (75 years of age), GMV of the precuneus and cuneus was associated with self-reported physical activity [19]. Importantly, sports activity reported for leisure time and objective measures for physical fitness are highly associated [20]. However, this is controversially discussed (for review see [21]).

In a cohort study, [22] measured actual and accumulated physical activity, GMV, perfusion and resting state connectivity in 308 healthy participants aged from 35 to 80 years. They found consistent increase in perfusion, GMV, and resting state connectivity positively associated with physical activity in the posterior cingulate cortex. In an intervention study that assessed the impact of nordic walking versus gymnastic versus a control condition in 62 healthy older adults, physical fitness, GMV and memory function [23], an increase in activity (including the intervention but also sports and leisure time activity) was accompanied by an increase in grey matter volume in cingulate (BA 32), superior parietal lobe (BA 7), dorsomedial prefrontal lobe (BA8, 9, 10), and striate visual cortex (BA 17–19).

Until now, no study has investigated associations of low versus high physical activity with GMV in a large community-based sample across the lifespan. Importantly, given the extensive evaluation of participants with regard to other risk factors that may impact brain health, these factors could be carefully controlled for.

We here performed a ROI-statistical approach in a cohort of 967 individuals, drawn at random from the community and thus representative for the area, investigating effects of physical activity on GMV of the brain. Physical activity is defined as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level" with exercise being a subcategory classified as being "planned, structured, and repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" [24]. The terms of exercise, physical activity, and sports are used inconsistently in the literature. In the questionnaire, the term "sports" was used. However, as we do not have any specific information about the type of activity reported, we will use the general term sports activity when talking about our results to be more consistent with current definitions.

We applied voxel-based morphometry (VBM, CAT 12) for comparing participants with higher versus lower physical activity (median split), and for calculating a linear regression on GMV and sports activity. We carefully corrected for other factors known to contribute to GMV (sex, age, total brain volume, education, cigarette and alcohol consumption, body mass index) and excluded pathology (history of psychiatric or neurological disease; visual inspection of brain scans). We searched in those brain areas which had already been described to be associated with physical activity in cohort studies [19,22] but also in response to moderate training in a longitudinal study in elderly [23] and selected these regions as ROIs from common brain atlases: the dorso-medial prefrontal lobe (BA 6, 8–10), the superior parietal lobe (BA 7), precuneus/cuneus, cingulate gyrus (BA 24, 30, 31,32), the hippocampus, the insula cortex, the caudate, and the occipital lobe (BA 17–19).

2. Methods

2.1. Cohort

We analyzed 1182 individuals selected from the SHIP-2-cohort of the SHIP-Study (Study of Health in Pomerania), a population-based cohort study conducted in Northeast Germany [25,26]. The cohort was representative for the population when being started in 1998 (SHIP-0). The study protocol was approved by the Ethics Committee of the University Medicine of Greifswald and written informed consent was obtained from each subject.

2.2. Questionnaire for sports activity

Participants filled in a questionnaire indicating the weekly sports activity during summer and winter times. The exact question was formulated as follows: "How often do you do sports in summer/winter?". Answer options were ">2 h per week" (= 1), "1-2 h per week" (= 2), "<1 h per week" (= 3), "no sports at all" (= 4). The scores of summer and winter were highly positively associated ($r = 0.72$; $p < 0.0001$).

2.3. Image acquisition

High resolution magnetic resonance imaging data were obtained using a 1.5-T Siemens MR imaging scanner (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) using a T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence and the following parameters: 176 slices, matrix = 256 × 176 pixel, voxel size = 1.0 mm isotropic, slice thickness = 1.0 mm, repetition time = 1900 ms, echo time = 3.37 ms, flip angle = 15°.

2.4. Quality control and exclusion of pathologies

All MRI head scans were visually inspected with regard to image artifacts and clinical abnormalities. Any brain images indicating stroke, multiple sclerosis, epilepsy, Parkinson's disease, dementia, cerebral tumor, intracranial cyst or hydrocephalus were excluded, leaving 1081 images. Furthermore, subjects with recorded intake of anxiolytics or opioids and with PHQ9 [27] depression scores greater than 14 were excluded, leaving 1037 images. Finally, all subjects with incomplete datasets for possible confounds (i.e., sex, age, years of education, nicotine intake, alcohol consumption, body mass index) were excluded. The final sample comprised 967 participants.

2.5. Preprocessing

T1-weighted images were preprocessed using Statistical Parametric Mapping 12 (SPM12; Wellcome Department of Cognitive Neurology, University of London) and the toolbox CAT12 (Computational Anatomy Toolbox; http://www.neuro.uni-jena.de/cat; Structural Brain Mapping Group, Jena University Hospital) running on MATLAB (The MathWorks, Natick, MA). Default parameters of the CAT12 toolbox were used. Images were first corrected for magnetic field inhomogenities and were segmented into grey matter, white matter and cerebrospinal fluid. In the segmentation process we applied a hidden Markov Random Field model and accounted for partial volume effects. Finally, the segmented images were spatially normalized using the DARTEL algorithm, followed by Gaussian smoothing using a kernel of 8 mm (full width at height maximum; FWHM). Furthermore, all scans underwent an automated quality check protocol, revealing a so-called IQR (index of quality rating) score, which later

was used as additional covariate in the statistical model. Finally, *(total intracranial volume, TIV)* was calculated, also to be used later as a covariate.

2.6. Statistical analysis

We averaged the scores for sports activity in summer and winter and used this value for regression analysis. In addition, we included those with a mean ≤2 (more than one hour a week) into the "more sports activity" group and those with a mean >2.5 (less than one hour a week) into the "less sports activity" group, using an independent samples *t*-test to evaluate for the hypothesized differences in GMV. We included the following confounds into the analysis known to be an important modulator of GMV: sex (male/female; [28], age [29], BMI [30] and alcohol and cigarettes ([31]. In addition, we corrected for total intracranial volume (TIV) and the quality of images (index of quality rating, IQR) calculated by CAT12 during the preprocessing as covariates. For the design matrix of the *t*-test design see Fig. 1A. For the regression analysis we used an average of the seasonal sports activity scores as the main regressor and the same variables of no interest as for the group comparison. For the design matrix of the linear regression design see Fig. 1B.

Since most previous studies investigated effects in an older population (Erickson et al., [12]: n = 299, aged on average 78 years; Gow et al., [32]: n = 691, aged on average 73 years; Ho et al., [23]: n = 226 participants, aged on average 78 years) we tested the interaction age*sports using a 2 by 2 Full Factorial design factorial (sports: less /more sports; age: younger/older). For that analysis we differentiated the younger and the older group for the *t*-test by median split. This revealed 475 participants younger than 55.5 years (average: 44.9 years; range: 31–55 years) and 492 participants older than 55.5 years (average: 65.8 years; range: 56–90 years). For descriptive purpose we performed a linear regression for the betas of GMV-analysis in association with age (Fig. 2 top) and in association with frequency of sports (Fig. 2, bottom). The steepness for the linear trend line was plotted for the SPL as an example.

Statistical comparisons were restricted to regions of interest known to express an increase of GMV by moderate sports activity in an elder group of healthy participants described before [22,23]. These comprised: the dorso-medial prefrontal lobe (BA 6, 8–10), the superior parietal lobe (BA 7), the precunes and cuneus, the cingulate gyrus (BA 24, 30, 31,32), the hippocampus, the insula, the caudate nucleus, and the occipital cortex (V1-V3; BA 17–19). ROIs were selected for those already classified cytoarchitecturally from the ANATOMY atlas (version 2.2b). For the differentiation of the insula we used Neuromorphometrics (Neuromorphometrics, Inc.) as provided with the SPM12 package. Effect sizes were calculated for the highest activated voxels t-value per ROI using the following formula: Cohen´s d = (2 × t-value) / $\sqrt{967}$.

3. Results

3.1. Comparison of scores between sports activity intensity groups

Brain volume in total and for the three classes of segmentation did not differ between groups (Table 1). Overall, those who performed more sports activity were 1.6 years older, had higher education, scored better in the mini mental status exam (MMSE), smoked less frequently, and had a trend for a slightly lower BMI (see Table 1).

These group differences signal the importance of inserting these variables as confounds into the statistical analysis.

3.2. Association of scores and demographic factors

Performing more sports activity was positively associated with age (r = 0.065; p = 0.045) and negatively with smoking (r = -0.14; p < 0.001). Those who did more sports activity were those with more years of education (r = 0.15; p < 0.001).

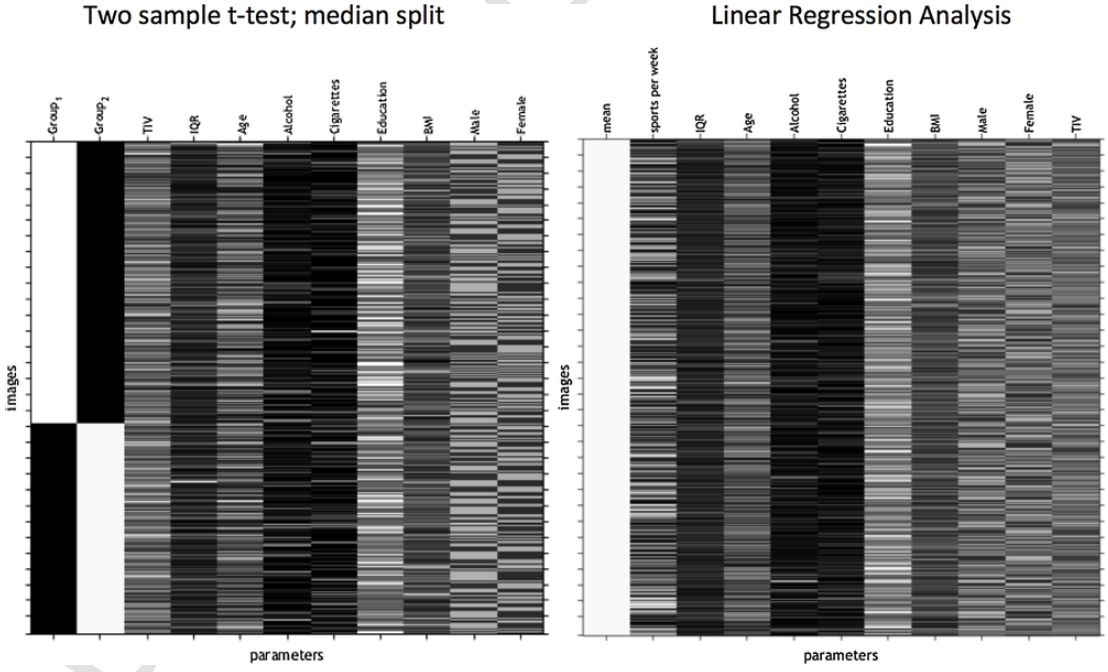

Fig. 1. Statistical analysis. The original design matrix used in SPM12/CAT12.Fig. 1, left: Median split *t*-test; abbreviations: "Group 1" = sports activity > 1 h/ week; "Group 2" = sports activity < 1 h/ week; TIV = total intracranial volume; IQR = index of quality rating; Alcohol = alcohol consumption; Cigarettes = cigarette consumption, BMI = body mass index. Fig. 1, right: Linear regression analysis for sports activity per week; the other confounds are the same as for the *t*-test.

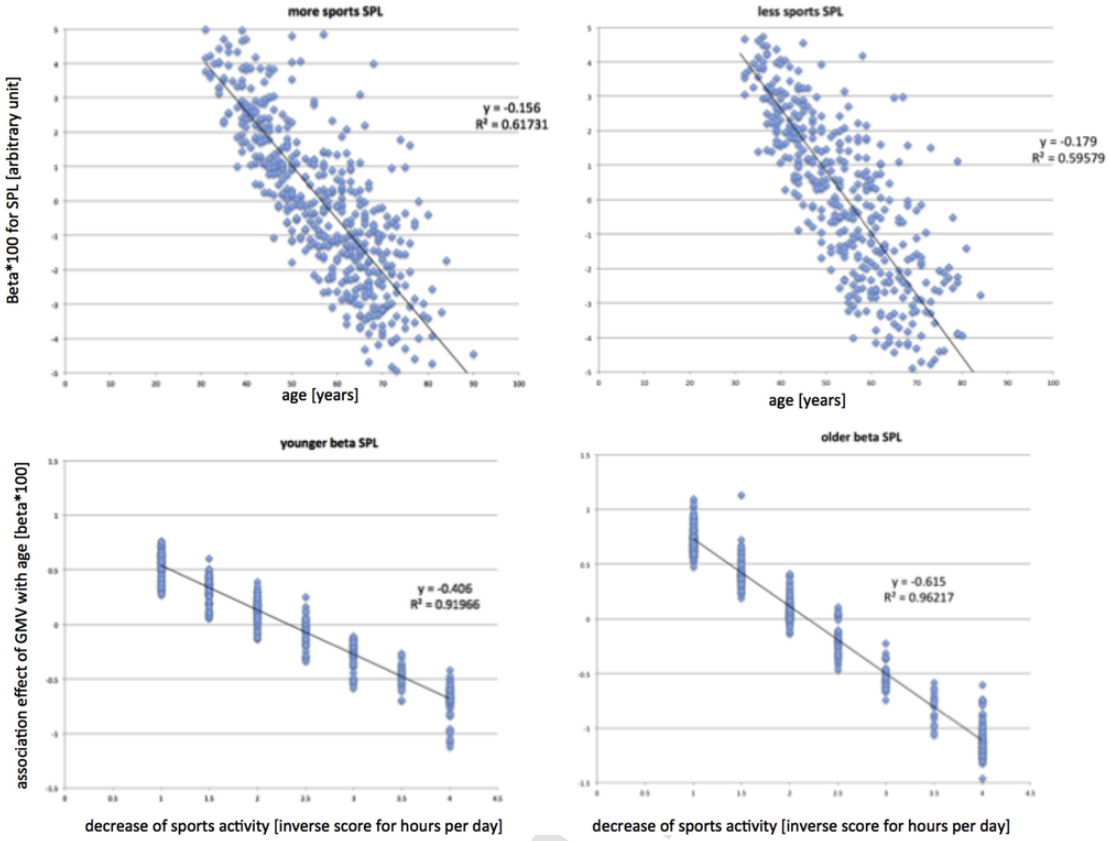

Fig. 2. Illustration of the effect of sports on GMV-decrease with age on the superior parietal lobe. Top: Those with more sports had less age decline in SPL (MNI-coordinate: 0: -69, 32; left: -0.156) than those with less sports (right: -0.179). Bottom: Younger (left) participants had a lower effect of sports activity on GMV decline (left: -0.406) than the older group (right: -0.615).

Table 1
Demographic characteristics in Means ± Standard Deviations.

	More sports activity	Less sports activity	Difference between groups
Participants (female)	551 (300)	416 (206)	chi-square: 0.73; n.s.
gray matter volume	614.17 (66.67)	613.28 (68.24)	t = 0.21; n.s.
Age [years]	56.26 (12.33)	54.62 (12.37)	t = 2.04; p = 0.042
Alcohol [g]*	9.97 (12.42)	10.64 (14.45)	t = 0.78; n.s.
Smoking [cig./day]**	6.56 (9.44)	8.75 (11.25)	t = 3.28; p < 0.001
Education [years]	12.89 (2.54)	12.25 (2.40)	t = 4.01; p < 0.001
PHQ9***	3.1 (3.09)	3.38 (3.02)	t = 1.33; n.s.
BMI	27.40 (4.24)	27.96 (4.59)	t = 1.95; n.s. (p = 0.051)
mini mental status exam ***	28.69 (1.49)	28.33 (1.66)	t = 2.22; p = 0.027

* Absolute amount of alcohol [g] for each day averaged from data about the last 30 days.
** Maximum number of cigarettes ever smoked daily in the period of one year (correlation with pack years highly significant).
*** Question was not answered by every individual that was included into the analysis.

3.3. GMV-analysis

3.3.1. Full factorial model

Although age and sports as single factors showed significant effects, the interaction did not reach significance (highest F-value was 12.98 for BA 6; F-value of significance for the BA 6-ROI would be F ≥ 18.67). The factors age and sports revealed significant effects.

3.3.2. Two sample T-test

The more and the less sportive active group were compared for gray matter differences within ROIs. Table 2 and Fig. 2 shows significant effects for this comparison. We identified more GMV in the more sportive group in a large medial cluster covering the SPL, the precuneus, the cuneus, and the posterior cingulate cortex. In addition right posterior insula and right BA8 showed higher GMV in the more

Table 2
Two sample *t*-test (all areas height threshold FWE corrected for ROI with p < 0.05).

Region	Hemisphere	t-value	Effect size[a]	Cluster size	MNI coordinates		
					x	y	z
SPL (BA 7; precuneus)	R	4.36	0.28	330*	0	−69	32
Cuneus		4.01	0.26	101	0	−70	30
Insula (posterior)	R	3.76	0.24	25	46	−9	4
BA 8	R	3.68	0.24	63	8	27	52
	R	3.57	0.23	101	24	22	54
Post. cingulate gyrus (BA 32)	L	3.42	0.22	17	−3	−58	30
Caudate nucleus	R	3.37	0.22	72	8	10	4

[a] Effect size: Cohen´s d.
* Result also significant for FWE p < 0.05 cluster correction for the whole brain.

sportive group. The effect sizes for these differences (Cohen´s d) were small.

In a linear regression analysis over the amount of sports over the whole sample the same ROIs showed a significant GMV-effect. In addition, this analysis identified higher GMV going along with higher sports activity in the visual cortex and the hippocampus (see Table 3).

The age × sports interaction in the Full Factorial design did not reach significance. However, we plotted the betas for the association of GMV with age (Fig. 2, top) and for GMV/age effects in association with sportive activity (Fig. 2, bottom) for illustration purpose for the SPL voxel with highest effect size (MNI-coordinate: 0: -69, 32). The slope of the effect of sport activity on GMV decrease by age was stronger for the older part of the cohort than for the younger.

Fig. 3 provides an overview for the results from both the *t*-test and the regression analysis in a color coded overlay on a segmented MNI-space brain. There was a high overlap (red and blue color coded) for the clusters in the cuneus, BA 8 and posterior insula for both type of analyses. The occipital cluster (red) was only present for the regression analysis.

4. Discussion

4.1. Main results

The current study aimed to identify differences in brain structure associated with higher commitment to sports activity, here indicated by higher frequency of sports activity per week, in a large representative cohort from the community. When comparing those with more and those with less sports activity per week we observed higher GMV in four clusters: the superior parietal lobe (SPL; BA 7, precuneus/cuneus) together with the posterior cingulate cortex, the posterior insula, the dorsomedial PFC (BA 8), and the caudate nucleus. A voxelwise linear regression analysis confirmed the group comparison but in addition detected higher GMV associated with higher sports activity also for the hippocampus and visual cortex. Both type of analyses revealed a high overlap of results. Associations of GMV and amount of sports activity performed were stronger for the older participants (age average 66 years; range: 56–90 years) than for the younger (average age 45 years; range: 31–55 years), although an interaction failed significance.

4.2. Less sports activity associated with lower GMV in the DMN, executive network and salience network

A cluster of medial parietal areas including the precuneus/cuneus and the posterior cingulate cortex was the most striking result in our study since this cluster showed high statistical significance without prior hypotheses. This area is a robust finding showing higher gray matter for cohort studies [22] and intervention studies (e.g. [23]. It also underlines findings of other studies based on self-reports [19] or cardiopulmonary fitness measures [16].

An association of cerebral blood flow (CBV) and GMV in the precuneus, cuneus and parietal lobe with sports activity has been described already in a prospective cohort study [22]. This study investigated resting state network, perfusion imaging and GMV analysis in 308 participants ranging from 35 to 80 years. In addition, they recorded both accumulated physical activity over a decade, and current physical activity. Especially GMV in the posterior cingulate cortex (PCC) was associated with accumulated physical activity. In addition, for the resting state data the posterior part of the default mode network (anterior part of the posterior cingulate cortex; PCC) was sensitive to accumulated ((MNI-coordinates: -6; -32; 26) and current physical activity (MNI-coordinates: -8, -36, 26). These coordinates are within our PCC cluster of GMV association on sports activity. The authors discussed their results with respect to exercise induced gene expressions stimulating neurogenesis and resistance to brain ischemia [33]. The precuneus/cuneus as well as the PCC form part of the default mode network (DMN), which is involved in processes including self-awareness and memory function. The DMN is active during task-free paradigms and associated with internally directed mental states but also with tasks requiring directed attention [34]. During aging, functional connectivity in the DMN decreases, paralleled by GMV decrease [35].

On the network level a high positive association on functional connectivity between the posterior cingulate cortex and the middle frontal gyrus with aerobic fitness has been described in young and older healthy volunteers [36]. These authors later postulated [35] that physical activity can protect from the adverse effects of functional connectivity caused by aging. Changes in the default mode network at rest might well be associated with GMV in these areas. Poorer functional connectivity has also been described for older adults in the executive control network (prefrontal lobe) and the salience network (insula; Voss et al., 2010b). In our study only the elderly showed a relevant positive GMV modulation by sports activity in the same areas. Physical activity therefore seems to prevent age-related decline in GMV in areas of the DMN, the dorsomedial prefrontal cortex and the insula.

There is a variety of cross-sectional studies providing evidence for a positive association of cardiopulmonary fitness levels (Vo^2max) and GMV in prefrontal areas in older adults [12,18,38–43]. Positive effects on GMV in frontoparietal areas in this group might well be associated with the effect of physical training on cognitive function among older adults, prominently on executive functions [18].

Age related decline of GMV is decreased by physical activity [10–13]. Cognitive, social and physical demand also has a positive effect on cognitive decline connected with age or pathology [14,15]. Thus, areas vulnerable for age-related decline might therefore be protected by physical activity in elderly [16,17]. Our study thus corroborates previous findings from cohort [22] and intervention studies [23], demonstrating that areas that showed higher GMV in more

Table 3
Linear regression (all areas height threshold corrected for ROI with $p < 0.05$).

Region	Hemisphere	t-value	Effect size[a]	Cluster size	MNI coordinates		
					x	y	z
BA 8	R	3.57	0.23	157	24	22	54
SPL (BA 7; precuneus)	R	3.86	0.25	130	0	−69	32
Cuneus	R	3.71	0.24	62	0	−70	30
	L	3.70	0.24	68	−6	−92	14
Visual Cortex (V1)	L	3.76	0.24	241	−3	−92	12
Hippocampus	L	3.35	0.22	9	−18	−4	−12
Caudate nucleus	R	3.51	0.23	72	6	10	3

[a] Effect size: Cohen´s d.

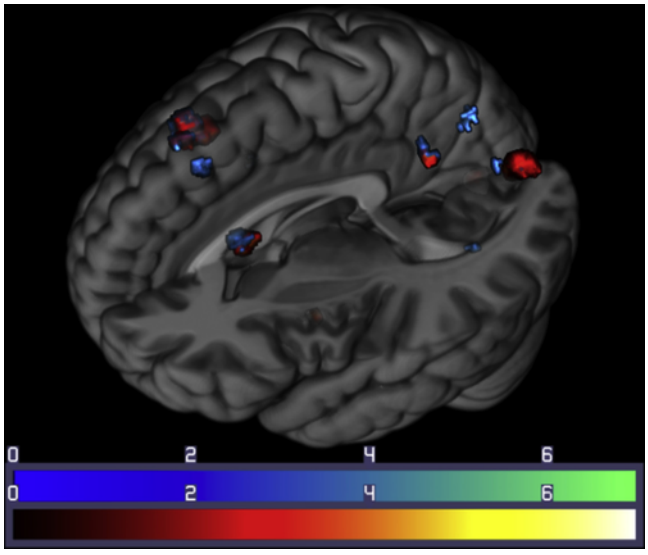

Fig. 3. Result from the two-sample *t*-test (blue) and linear regression analysis (red; color code provided at bottom of Figure). The fronto-parietal cluster shows strong overlap whereas the occipital cluster did only show up in the regression analysis. The statistical maps have been thresholded with $p < 0.001$ for illustration purpose and masked for all ROIs. The segmented high resolution MNI-brain (Collins brain) was used for overlaying functional maps on structural data. The cut in the segmented brain was adjusted in the level of the maximum of occipital activation (x = -3 and z = 12)).

physically active participants comprise regions that are prone to age-related atrophy.

4.3. Effects of GMV and physical activity observed in young participants

Similar to finding in older adults, positive associations of physical fitness and cognitive achievement have been demonstrated in young adults as well (see overview: [44], most prominently on executive function. However, some recent studies on younger adults demonstrated lower cortical thickness for those with higher cardiopulmonal fitness, for example [16] in a group of 32 younger adults (21 years). Of note, cortical thinning in the early 20 s is associated with higher IQ, with this association reversing in the early 40 s [45]. Therefore, a general consolidation of gray matter during early adulthood might well influence impact of physical activity on grey matter volume in later adulthood. We here found a lower slope of sport activity on GMV in the younger part of our cohort suggesting that with increasing age the effect of physical activity on GMV might be stronger.

4.4. Hippocampus GMV-differential findings as a function of age

Hippocampus GMV associated with physical activity has previously been found in both cross-sectional and longitudinal studies [12,15,46]. A hippocampal functional network sensitive to physical training has recently been postulated [22,35]. Age-related reductions in hippocampal volume are less pronounced among more highly educated individuals [47] pointing to the necessity of controlling for education as a confounder. We detected an association of hippocampal GMV with the amount of sports activity for the linear regression analysis. For the hippocampus GMV total minutes of weekly sports activity correlated significantly with volume of the right hippocampus in a previous study on 61 healthy adults aging 18–45 years [48]. Other longitudinal and interventional studies on physical activity in aged participants did not observe GMV changes in this area [23,49]. Herting and Nagel (2012), who found a correlation between higher exercise intensity and higher hippocampal volume, postulated that changes in hippocampal GMV might only be found for high-intensity exercise. Furthermore, it has been hypothesized that the hippocampus is particularly responsive to aerobic training [15]. For our study, only regression analysis detected higher GMV in the hippocampus in more physically active participants.

4.5. Limitations

First, information about the participant's sports activity per week was collected via questionnaire, and question on "sports" only. Thus, reports may have been unreliable with regard to sports as such, and also might systematically underestimate the total amount of physical activity in the older participants, while overestimating the amount in the younger participants. However, self-reported physical activity has been proven to be reliable measures of physical activity levels [51,52] and has been used in several previous studies investigating the connection of activity levels and GMV [19,39,48]. Nevertheless, in future studies more objective parameter measuring cardiorespiratory fitness or objective movement performance per day using accelerators should be included to validate our findings [17].

Second, although we controlled for a variety of factors known to have an impact on GMV, the more and less physically active groups might have differed in parameters not included into the present analyses, or the analysis might not have fully controlled for these effects. However, we controlled for the most important factors known to have an impact on GMV, and the associations of sports activity with GMV robustly emerged in our study for different analysis approaches. Other studies removed their effect when including these factors. For instance, Gow et al. [31] investigated 226 older participants (77 years) and found an effect of sports activity on GMV which vanished after including BMI in the model. Thus, we are confident that we successfully controlled for important confounders, and the areas showing differential GMV for different activity groups at least partially represent effects of sports activity. We found group differences (high versus low sports) for education, BMI and age. Therefore it is important to use these parameters as confounds when comparing VBM between groups. When performing a *t*-test between the high and low sports group without the confound "education" and "BMI" we found almost exactly the same results for the ROIs. Therefore, the control for these two factors was not important for the GMV differences reported. However, when leaving out the factor age as a confound our results were markedly reduced in effect size, and -besides of SPL- did not reach significance threshold. This indicated the importance for inserting the factor age in GMV analyses-especially when groups differ for that item.

Third, a comprehensive testing of cognitive parameters was not performed in this study. We found a small difference in Mini-Mental-Status-Examination between activity groups, with better scores for the higher activity group. However, differences were small, and more detailed testing not available in this cohort. Thus, this issue needs to be addressed in more detail in future studies.

Fourth, our sample was not representative any more since it was the third measurement of representative sample 15 years later on. Since the youngest participants in the representative cohort were aged 18 years the median split of the 15 years later measured cohort showed an average age of the younger group of 45 years.

Fifths, we used VBM to detect structural differences in GMV. Although it is assumed that underlying processes are due to adjustments on the cellular level, we have only limited knowledge how GMV differences between groups correspond to cellular mechanisms. However, several researchers found associations due to interventions in small cohorts [10,49]. We therefore complement their findings by describing a comparable association in a representative cohort.

Sixth, this is only a cross-sectional study leaving open whether more frequently performing sports results in higher GMV or vice versa.

5. Conclusions

Overall, this study confirms findings from other cross sectional and longitudinal studies that sports activity is "the real polypill" [53] for preventing age related GMV decrease. In addition, although not presenting a representative cohort, our GMV results on sports were extended to a population with a broader age range. However, our study did also show that higher sports activity have a slightly larger effect on age decline of GMV in the older participants than in the younger. Specifically, our large representative cohort of community-dwelling adults across the lifespan demonstrates that GMV is sensitive to sports activity for a frontoparietal network with a small to medium effect size. Our results encourage the propagation of physical activity in the older population to maintain brain health.

Declarations of interest

None.

Uncited references

[37,50].

Acknowledgements

We would like to thank Katharina Wittfeld for quality check of the T1-weighted images. Katharina Eyme is scholarship holder of the Konrad Adenauer Foundation and the German Academic Scholarship Foundation.

References

[1] K. Zilles, Neural plasticity is an adaptive property of the central nervous system, Ann. Anat. 174 (1992) 383–391.

[2] B. Kleber, R. Veit, C.V. Moll, C. Gaser, N. Birbaumer, M. Lotze, Voxel-based morphometry in opera singers: increased gray-matter volume in right somatosensory and auditory cortices, Neuroimage 133 (2016) 477–483, https://doi.org/10.1016/j.neuroimage.2016.03.045.

[3] G. Schlaug, L. Jancke, Y. Huang, H. Steinmetz, In vivo evidence of structural brain asymmetry in musicians, Science (80-.) 267 (1995), 699 LP-701.

[4] B.Y. Tseng, J. Uh, H.C. Rossetti, C.M. Cullum, R.F. Diaz-Arrastia, B.D. Levine, H. Lu, R. Zhang, Masters athletes exhibit larger regional brain volume and better cognitive performance than sedentary older adults, J. Magn. Reson. Imaging38 (2013) 1169–1176, https://doi.org/10.1002/jmri.24085.

[5] J. Hänggi, N. Langer, K. Lutz, K. Birrer, S. Mérillat, L. Jäncke, Structural brain correlates associated with professional handball playing, PLoS One 10 (2015) 1–27, https://doi.org/10.1371/journal.pone.0124222.

[6] N. Langer, J. Hänggi, N.A. Müller, H.P. Simmen, L. Jäncke, Effects of limb immobilization on brain plasticity, Neurology 78 (2012) 182–188, https://doi.org/10.1212/WNL.0b013e31823fcd9c.

[7] D.O. Hebb, The organization of behavior: a neuropsychological approach, Am. J. Psychol. (1949) https://doi.org/10.2307/1418888.

[8] B. Draganski, C. Gaser, V. Busch, G. Schuierer, U. Bogdahn, A. May, Changes in grey matter induced by training, Nature 427 (2004) 311–312, https://doi.org/10.1038/427311a.

[9] J.A. Adkins, D.L. Boychuk, J. Remple, M.S. Kleim, Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord, J. Appl. Physiol. 101 (2006) 1776–1782.

[10] S. Colcombe, K. Erickson, P. Scalf, J. Kim, R. Prakash, E. McAuley, S. Elavsky, D. Marquez, L. Hu, A. Kramer, Aerobic exercise training increases brain volume in aging humans, J. Gerontol. Ser. A-Biol. Sci. Med. Sci. 61 (2006) 1166–1170, doi:61/11/1166.

[11] B.A. Gordon, E.I. Rykhlevskaia, C.R. Brumback, Y. Lee, S. Elavsky, J.F. Konopack, E. McAuley, A.F. Kramer, S. Colcombe, G. Gratton, M. Fabiani, Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education, Psychophysiology 45 (2008) 825–838, https://doi.org/10.1111/j.1469-8986.2008.00676.x.

[12] K.I. Erickson, R.S. Prakash, M.W. Voss, L. Chaddock, K.S. Morris, S.M. White, T.R. Wójcicki, E. Mcauley, A.F. Kramer, Aerobic fitness is associated with hippocampal volume in elderly humans, Hippocampus 19 (2009) 1030–1039, https://doi.org/10.1002/hipo.20547.Aerobic.

[13] C. Niemann, B. Godde, U.M. Staudinger, C. Voelcker-Rehage, Exercise-induced changes in basal ganglia volume and cognition in older adults, Neuroscience 281 (2014) 147–163, https://doi.org/10.1016/j.neuroscience.2014.09.033.

[14] J. Kulmala, A. Solomon, I. Kåreholt, T. Ngandu, T. Rantanen, T. Laatikainen, H. Soininen, J. Tuomilehto, M. Kivipelto, Association between mid- to late life physical fitness and dementia: evidence from the CAIDE study, J. Intern. Med. 276 (2014) 296–307, https://doi.org/10.1111/joim.12202.

[15] K.I. Erickson, M.W. Voss, R.S. Prakash, C. Basak, A. Szabo, L. Chaddock, J.S. Kim, S. Heo, H. Alves, S.M. White, T.R. Wojcicki, E. Mailey, V.J. Vieira, S.A. Martin, B.D. Pence, J.A. Woods, E. McAuley, A.F. Kramer, Exercise training increases size of hippocampus and improves memory, Proc. Natl. Acad. Sci. 108 (2011) 3017–3022, https://doi.org/10.1073/pnas.1015950108.

[16] V.J. Williams, J.P. Hayes, D.E. Forman, D.H. Salat, R.A. Sperling, M. Verfaellie, S.M. Hayes, Cardiorespiratory fitness is differentially associated with cortical thickness in young and older adults, Neuroimage 146 (2017) 1084–1092, https://doi.org/10.1016/j.neuroimage.2016.10.033.

[17] K. Erickson, R. Leckie, A. Weinstein, Physical activity, fitness, and gray matter volume, Neurobiol. Aging (2014) https://doi.org/10.1016/j.neurobiolaging.2014.03.034.

[18] S. Colcombe, A.F. Kramer, Fitness effects on the cognitive function of older adults, Psychol. Sci. 14 (2003) 125, https://doi.org/10.1111/1467-9280.t01-1-01430.

[19] C. Benedict, S.J. Brooks, J. Kullberg, R. Nordenskjöld, J. Burgos, M. Le Grevès, L. Kilander, E.M. Larsson, L. Johansson, H. Ahlström, L. Lind, H.B. Schiöth, Association between physical activity and brain health in older adults, Neurobiol. Aging 34 (2013) 83–90, https://doi.org/10.1016/j.neurobiolaging.2012.04.013.

[20] M.-L. Løchen, K. Rasmussen, The Tromso study, physical fitness, self reported physical activity, and their relationship to other coronary risk factors, J. Epidemiol. Community Heal. (1992) 103–107.

[21] J.F. Sallis, B.E. Saelens, Assessment of physical activity by self-report: status, limitations, and future directions, Res. Q. Exerc. Sport 71 (2000) 1–14, https://doi.org/10.1080/02701367.2000.11082780.

[22] C.J. Boraxbekk, A. Salami, A. Wåhlin, L. Nyberg, 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, Neuroimage 131 (2016) 133–141, https://doi.org/10.1016/j.neuroimage.2015.12.010.

[23] R. Ruscheweyh, C. Willemer, K. Krüger, T. Duning, T. Warnecke, J. Sommer, K. Völker, H.V. Ho, F. Mooren, S. Knecht, A. Flöel, Physical activity and memory functions: an interventional study, Neurobiol. Aging 32 (2011) 1304–1319, https://doi.org/10.1016/j.neurobiolaging.2009.08.001.

[24] Physical Activity Guidelines Advisory Committee, Physical Activity Guidelines Advisory Committee Report, Washingt. DC US. 67, 2008683, https://doi.org/10.1111/j.1753-4887.2008.00136.x.

[25] K. Hegenscheid, J.P. Kühn, H. Völzke, R. Biffar, N. Hosten, R. Puls, Whole-body magnetic resonance imaging of healthy volunteers: pilot study results from the population-based SHIP study, Rofo 181 (2009) 748–759, https://doi.org/10.1055/s-0028-1109510.

[26] H. Völzke, D. Alte, C.O. Schmidt, D. Radke, R. Lorbeer, N. Friedrich, N. Aumann, K. Lau, M. Piontek, G. Born, C. Havemann, T. Ittermann, S. Schipf, R. Haring, S.E. Baumeister, H. Wallaschofski, M. Nauck, S. Frick, A. Arnold, M. Jünger, J. Mayerle, M. Kraft, M.M. Lerch, M. Dörr, T. Reffelmann, K. Empen, S.B. Felix, A. Obst, B. Koch, S. Gläser, R. Ewert, I. Fietze, T. Penzel, M. Dören, W. Rathmann, J. Haerting, M. Hannemann, J. Röpcke, U. Schminke, C. Jürgens, F. Tost, R. Rettig, J.A. Kors, S. Ungerer, K. Hegenscheid, J.P. Kühn, J. Kühn, N. Hosten, R. Puls, J. Henke, O. Gloger, A. Teumer, G. Homuth, U. Völker, C. Schwahn, B. Holtfreter, I. Polzer, T. Kohlmann, H.J. Grabe, D. Rosskopf, H.K. Kroemer, T. Kocher, R. Biffar, U. John, W. Hoffmann, Cohort profile: the study of health in Pomerania, Int. J. Epidemiol. 40 (2011) 294–307, https://doi.org/10.1093/ije/dyp394.

[27] B. Löwe, K. Kroenke, W. Herzog, K. Gräfe, Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9), J. Affect. Disord. 81 (2004) 61–66, https://doi.org/10.1016/S0165-0327(03)00198-8.

[28] A.N.V. Ruigrok, G. Salimi-Khorshidi, M.-C. Lai, S. Baron-Cohen, M.V. Lombardo, R.J. Tait, J. Suckling, A meta-analysis of sex differences in human brain structure, Neurosci. Biobehav. Rev. 39 (2014) 34–50, https://doi.org/10.1016/j.neubiorev.2013.12.004.

[29] G. Ziegler, R. Dahnke, L. Jäncke, R.A. Yotter, A. May, C. Gaser, Brain structural trajectories over the adult lifespan, Hum. Brain Mapp. 33 (2012) 2377–2389, https://doi.org/10.1002/hbm.21374.

[30] D. Janowitz, K. Wittfeld, J. Terock, H.J. Freyberger, K. Hegenscheid, H. Völzke, M. Habes, N. Hosten, N. Friedrich, M. Nauck, G. Domanska, H.J. Grabe, Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples, Neuroimage (2015) https://doi.org/10.1016/j.neuroimage.2015.07.086.

[31] H.-C. Fritz, K. Wittfeld, C.O. Schmidt, M. Domin, H.J. Grabe, K. Hegenscheid, N. Hosten, M. Lotze, Current Smoking and Reduced Gray Matter Volume—a Voxel-Based Morphometry Study, Neuropsychopharmacology 39 (2014) 2594–2600, https://doi.org/10.1038/npp.2014.112.

[32] A.J. Gow, M.E. Bastin, S. Muñoz Maniega, M.C. Valdés Hernández, Z. Morris, C. Murray, N.A. Royle, J.M. Starr, I.J. Deary, J.M. Wardlaw, Neuroprotective lifestyles and the aging brain, Neurology 79 (2012) 1802–1808, https://doi.org/10.1212/WNL.0b013e3182703fd2.

[33] R.K. Dishman, H.R. Berthoud, F.W. Booth, C.W. Cotman, V.R. Edgerton, M.R. Fleshner, S.C. Gandevia, F. Gomez-Pinilla, B.N. Greenwood, C.H. Hillman, A.F. Kramer, B.E. Levin, T.H. Moran, A.A. Russo-Neustadt, J.D. Salamone, J.D. Van Hoomissen, C.E. Wade, D.A. York, M.J. Zigmond, Neurobiology of exercise, Obesity 14 (2006) 345–356, https://doi.org/10.1038/oby.2006.46.

[34] J.R. Andrews-Hanna, A.Z. Snyder, J.L. Vincent, C. Lustig, D. Head, M.E. Raichle, R.L. Buckner, Disruption of large-scale brain systems in advanced aging, Neuron 56 (2007) 924–935, https://doi.org/10.1016/j.neuron.2007.10.038.

[35] M.W. Voss, T.B. Weng, A.Z. Burzynska, C.N. Wong, G.E. Cooke, R. Clark, J. Fanning, E. Awick, N.P. Gothe, E.A. Olson, E. McAuley, A.F. Kramer, Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging, Neuroimage 131 (2016) https://doi.org/10.1016/j.neuroimage.2015.10.044.

[36] M.W. Voss, K.I. Erickson, R.S. Prakash, L. Chaddock, E. Malkowski, H. Alves, J.S. Kim, K.S. Morris, S.M. White, T.R. Wójcicki, L. Hu, A. Szabo, E. Klamm, E. McAuley, A.F. Kramer, Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition?, Neuropsychologia48 (2010) 1394–1406, https://doi.org/10.1016/j.neuropsychologia.2010.01.005.

[37] M.W. Voss, R.S. Prakash, K.I. Erickson, C. Basak, L. Chaddock, J.S. Kim, H. Alves, S. Heo, A.N. Szabo, S.M. White, T.R. Wójcicki, E.L. Mailey, N. Gothe, E.A. Olson, E. McAuley, A.F. Kramer, Plasticity of brain networks in a randomized intervention trial of exercise training in older adults, Front. Aging Neurosci. 2 (2010) 1–17, https://doi.org/10.3389/fnagi.2010.00032.

[38] M.L. Alosco, J. Gunstad, B.A. Jerskey, X. Xu, U.S. Clark, J. Hassenstab, D.M. Cote, E.G. Walsh, D.R. Labbe, R. Hoge, R.A. Cohen, L.H. Sweet, The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease, Brain Behav. 3 (2013) 626–636, https://doi.org/10.1002/brb3.171.

[39] J.M. Bugg, D. Head, Exercise moderates age-related atrophy of the medial temporal lobe, Neurobiol. Aging 32 (2011) 506–514, https://doi.org/10.1016/j.neurobiolaging.2009.03.008.

[40] K.I. Erickson, S.J. Colcombe, S. Elavsky, E. McAuley, D.L. Korol, P.E. Scalf, A.F. Kramer, Interactive effects of fitness and hormone treatment on brain health in postmenopausal women, Neurobiol. Aging 28 (2007) 179–185, https://doi.org/10.1016/j.neurobiolaging.2005.11.016.

[41] R.A. Honea, G.P. Thomas, A. Harsha, H.S. Anderson, J.E. Donnelly, W.M. Brooks, J.M. Burns, Cardiorespiratory fitness and preserved medial temporal lobe volume in Alzheimer disease, Alzheimer Dis. Assoc. Disord. 23 (2009) 188–197, https://doi.org/10.1097/WAD.0b013e31819cb8a2.

[42] A.M. Weinstein, M.W. Voss, R.S. Prakash, L. Chaddock, A. Szabo, S.M. White, T.R. Wojcicki, E. Mailey, E. McAuley, A.F. Kramer, K.I. Erickson, The association between aerobic fitness and executive function is mediated by prefrontal cortex volume, Brain Behav. Immun. 26 (2012) 811–819, https://doi.org/10.1016/j.bbi.2011.11.008.

[43] T.D. Verstynen, B. Lynch, D.L. Miller, M.W. Voss, R.S. Prakash, L. Chaddock, C. Basak, A. Szabo, E.A. Olson, T.R. Wojcicki, J. Fanning, N.P. Gothe, E. McAuley, A.F. Kramer, K.I. Erickson, Caudate nucleus volume mediates the link between cardiorespiratory fitness and cognitive flexibility in older adults, J. Aging Res. 2012 (2012) https://doi.org/10.1155/2012/939285.

[44] C.H. Hillman, K.I. Erickson, A.F. Kramer, Be smart, exercise your heart: exercise effects on brain and cognition, Nat. Neurosci. 9 (2008) 58–65, https://doi.org/10.1038/nrn2298.

[45] H.G. Schnack, N.E.M. van Haren, R.M. Brouwer, A. Evans, S. Durston, D.I. Boomsma, R.S. Kahn, H.E. Hulshoff Pol, Changes in Thickness and Surface Area of the Human Cortex and Their Relationship with Intelligence, Cereb. Cortex 25 (2015) 1608–1617, https://doi.org/10.1093/cercor/bht357.

[46] J.M. Bugg, K. Shah, D.T. Villareal, D. Head, Cognitive and neural correlates of aerobic fitness in obese older adults, Exp. Aging Res. 38 (2012) 131–145, https://doi.org/10.1080/0361073X.2012.659995.

[47] K.G. Noble, S.M. Grieve, M.S. Korgaonkar, L.E. Engelhardt, E.Y. Griffith, L.M. Williams, A.M. Brickman, Hippocampal volume varies with educational attainment across the life-span, Front. Hum. Neurosci. 6 (2012) 1–10, https://doi.org/10.3389/fnhum.2012.00307.

[48] W.D.S. Killgore, E.A. Olson, M. Weber, Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans, Sci. Rep. 3 (2013) 3457, https://doi.org/10.1038/srep03457.

[49] M. Tamura, K. Nemoto, A. Kawaguchi, M. Kato, T. Arai, T. Kakuma, K. Mizukami, H. Matsuda, H. Soya, T. Asada, Long-term mild-intensity exercise regimen preserves prefrontal cortical volume against aging, Int. J. Geriatr. Psychiatry30 (2015) 686–694, https://doi.org/10.1002/gps.4205.

[50] M.M. Herting, B.J. Nagel, Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents, Behav. Brain Res. 233 (2012) 517–525, https://doi.org/10.1016/j.bbr.2012.05.012.

[51] I. Frey, A. Berg, D. Grathwohl, J. Keul, Freiburger Fragebogen zur körperlichen Aktivität - Entwicklung, Prüfung und Anwendung, Soz. Praventivmed. 44 (1999) 55–64, https://doi.org/10.1007/BF01667127.

[52] T. Slanger, E. Mutschelknauss, S. Kropp, W. Braendle, D. Flesch-Janys, J. Chang-Claude, Test-retest reliability of self-reported reproductive and lifestyle data in the context of a german case-control study on breast cancer and postmenopausal hormone therapy, Ann. Epidemiol. 17 (2007) 993–998, https://doi.org/10.1016/j.annepidem.2007.07.094.

[53] C. Fiuza-Luces, N. Garatachea, N.A. Berger, A. Lucia, Exercise is the Real Polypill, Physiology 28 (2013) 330–358, https://doi.org/10.1152/physiol.00019.2013.