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Physical activity, aerobic fitness, and brain white matter: Their role for executive functions in adolescence

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ABSTRACT

Physical activity and exercise beneficially link to brain properties and cognitive functions in older adults, but the findings concerning adolescents remain tentative. During adolescence, the brain undergoes significant changes, which are especially pronounced in white matter. Studies provide contradictory evidence regarding the influence of physical activity or aerobic-exercise on executive functions in youth. Little is also known about the link between both fitness and physical activity with the brain's white matter during puberty. We investigated the connection between aerobic fitness and physical activity with the white matter in 59 adolescents. We further determined whether white matter interacts with the connection of fitness or physical activity with core executive functions. Our results show that only the level of aerobic fitness, but not of physical activity relates to white matter. Furthermore, the white matter of the corpus callosum and the right superior corona radiata moderates the links of aerobic fitness and physical activity with working memory. Our results suggest that aerobic fitness and physical activity have an unequal contribution to the white matter properties in adolescents. We propose that the differences in white matter properties could underlie the variations in the relationship between either physical activity or aerobic fitness with working memory.

1. Introduction

Physical activity and high aerobic fitness beneficially link to many structural brain properties, such as gray matter volume and white matter microstructure (Chaddock-Heyman et al., 2018; Erickson et al., 2011; Schaeffer et al., 2014; Whiteman et al., 2016). Due to its significance for many cognitive functions (Baum et al., 2017; Engvig et al., 2012; Nagy et al., 2004; Treit et al., 2014), the brain's white matter has been of interest also in association with physical performance. It is particularly important to examine the relation of physical activity on white matter in adolescents, as the physical activity levels decrease with age (Van Hecke et al., 2016) and adolescents worldwide fail to meet physical activity

recommendations (Hallal et al., 2012). Moreover, white matter is still developing in adolescents and its properties have been shown to be crucial for cognition, such as executive functions (Baum et al., 2017; Treit et al., 2014) and for behaviour, such as risk-taking at this age (Jacobus et al., 2013). While earlier studies on other age groups suggest a link between physical activity level and white matter microstructure (Chaddock-Heyman et al., 2018; Oberlin et al., 2016; Strömmer et al., 2018; Tian et al., 2015), this association remains unclear for adolescents.

During puberty (10–17 years old), the body and brain undergo notable changes (Lebel et al., 2008; Spear, 2013) and physical training may influence the brain differently depending on the childhood or

adolescent phase. Indeed, the onset of puberty (mean age 11 for females and 12 for males) has been proposed to affect neural development and plasticity (Piekarski et al., 2017). Furthermore, the white matter growth of specific tracks is different in middle adolescence when compared to both childhood and late adolescence (Simmonds et al., 2014). Thus, the influence of physical activity on the white matter might vary depending on the developmental phase (childhood, middle adolescence or late adolescence).

The earlier studies concerning youth have focused on either childhood or late adolescence and the results from these studies are contradictory. While there was no relation between white matter fractional anisotropy (FA) and either aerobic fitness or self-reported physical activity in 15–18-year-old male adolescents (Herting et al., 2014), these relationships have been found in preadolescent children. In an exploratory study, Chaddock-Heyman et al. (2014) found that 9 to 10-year-old children with a higher fitness demonstrated a greater FA in the body of the corpus callosum, superior corona radiata, and superior longitudinal fasciculus. Two intervention studies suggested that physical activity intervention increased FA of the genu of corpus callosum in normal weight preadolescent children (Chaddock-Heyman et al., 2018) and of the uncinate fasciculus in overweight ones (Schaeffer et al., 2014) but not the FA of the superior longitudinal fasciculus (Krafft et al., 2014a). Despite inconsistencies in findings, these studies suggest that besides the adult population, aerobic fitness and physical activity may be associated with white matter properties in young participants as well. However, due to small number of studies involving child and adolescent participants, conclusive interpretation of these early findings is premature.

While physical activity and high aerobic fitness are beneficial for brain health, some studies further suggest exercise-related improvements in cognitive skills. Especially relevant in this context are executive functions: a set of processes highly important for cognitive control, and also for domain-specific cognitive functions (for a review see Diamond, 2013). Several studies have suggested a relationship between either aerobic fitness or physical activity with executive function in youth (Chaddock et al., 2010a; Davis et al., 2011; Hillman et al., 2014; Kamijo and Masaki, 2016; Mora-Gonzalez et al., 2019; Mora-Gonzalez et al., 2019; Subramanian et al., 2015). However, some studies do not provide evidence for such association (e.g. de Greeff et al., 2016; Krafft et al., 2014b; Schaeffer et al., 2014; Stroth et al., 2009; Tarp et al., 2016). It is unclear what causes this variation between results. Interestingly, biological moderators, such as genes, have been suggested to influence the strength of the relationship between physical performance and cognition (Barha et al., 2017; Singh et al., 2018). Overall, the influence of physical activity and fitness on executive functions is likely to reflect complex pathways with several biological and psychological modulating factors. Identifying factors that moderate or alter this relationship will allow more individualised predictions and recommendations.

White matter integrity provides a factor possibly moderating the relationship between either physical activity or aerobic fitness with executive functions. Various studies report connections between white matter properties and the cognitive function throughout the lifespan (Chaddock-Heyman et al., 2013; Gold et al., 2010; Golestani et al., 2014; Mabbott et al., 2006; Nagy et al., 2004; Seghete et al., 2013). Importantly, studies investigating cognitive training suggest that white matter properties also predict the enhancement of cognitive skills after training and that the change in white matter properties following training relates to behavioural improvements (de Lange et al., 2017d, 2016; Engvig et al., 2012; Mackey et al., 2012). Thus, the level of white matter appears to influence the strength of improvement after cognitive training.

Given the suggested relationship of also physical activity and fitness with white matter properties, it is conceivable that white matter could have an important role in determining the strength of the relationship between physical performance and cognitive skills. The state of white matter could also explain the discrepancy in the results concerning the relationship between both physical activity and aerobic fitness with executive functions. However, it is currently unknown whether white

matter moderates the relationship between either physical activity or aerobic fitness and executive functions. We hypothesised that the relationship between either aerobic fitness or physical activity with core executive functions is different for individuals with low or high brain white matter FA. The main goals of the present study were to examine whether (1) physical activity and aerobic fitness are related to white matter properties in 12.7 − 16.2-year-old adolescents and (2) white matter FA moderates the connection between either physical activity or aerobic fitness with core executive functions.

2. Methods

2.1. Participants

Participants (12.7–16.2 years old) were recruited from a larger follow-up study (see Joensuu et al. [2018]). Sixty-one right-handed subjects participated in the brain magnetic resonance imaging (MRI) experiments, of which two participants did not complete the diffusion-weighted imaging protocol. A total of 59 subjects (39 female) were included in the analysis concerning physical activity, aerobic fitness, working memory, rapid visual information processing, and white matter measures. From the 59 subjects, 58 were analysed for response inhibition (one participant did not complete the test). Participants were screened for exclusion criteria comprising MRI contraindications; neurological disorders; medication influencing the central nervous system; any major medical condition; and left-handedness, which was assessed by the Edinburgh Handedness Inventory during the first research visit. Furthermore, to evaluate pubertal development, participants self-reported their stage of puberty by using the Tanner scale (Marshall and Tanner, 1970, 1969). The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and prior to the participation, each participant and his or her legal guardian provided written informed consent. The Central Finland Healthcare District Ethical Committee accepted the study. The participants were compensated with a 30-euro gift card for participating in the brain scans.

2.2. Physical activity and aerobic fitness

The physical activity was objectively measured using the triaxial ActiGraph GT3X + and wGT3X + accelerometers (Pensacola, FL, USA; for full details, see Joensuu et al. [2018]). ActiGraph accelerometers were chosen, because ActiGraph is the most frequently used brand by physical activity researchers during the last decade (Wijndaele et al., 2015), and this offers an opportunity to compare the physical activity results to other studies as well. In addition, ActiGraph is easy and comfortable to use. The participants were instructed to wear these devices on their right hip during waking hours for seven consecutive days (except during bathing and swimming). A valid measurement day consisted of at least 10 h of data. Subjects who had at least two valid weekdays and one valid weekend day were included in the analysis. For those subjects who did not meet these criteria, a multiple imputation method (explained in more detail below) was employed to compensate for the missing data. Activity counts were collected in 15-s epochs. When there was a period of at least 30 min of consecutive zero counts, it was considered as a non-wear period. Data were collected at a sampling frequency of 60 Hz and standardly filtered. A customised Visual Basic macro for Excel was used for data reduction. Cut points from Evenson et al.'s study were utilised in the analysis (Evenson et al., 2008; Trost et al., 2011). The moderate-to-vigorous intensity physical activity (MVPA) was converted into a weighted-mean value of MVPA per day ([average MVPA min/day of weekdays × 5 + average MVPA min/day of weekend × 2] / 7).

The maximal 20-m shuttle run test was employed to assess the aerobic fitness of the participants. The test was performed as described by Nupponen et al. (1999) and specified in detail for the present data

collection in Joensuu et al. (2018). Each participant ran between two lines, 20 m apart, at an accelerating pace, which was indicated with an audio signal. The duration that the participants ran until they failed to reach the end lines within two consecutive tones indicated their level of aerobic fitness. The speed in the first and second levels were 8.0 and 9.0 km/h, respectively. After the second level, the speed sequentially increased with 0.5 km/h per level. The duration of each level was one minute. The participants were verbally encouraged to keep running throughout the test.

In addition to the aerobic fitness test, the participants also completed a set of tests measuring muscular fitness (push-ups and curl-ups), flexibility and fundamental movement skills (a 5-leap test and a throwing-catching combination test). This paper focuses on aerobic fitness and physical activity, and the results concerning other fitness tests will be reported elsewhere.

3. Cognitive assessment

Wide scale of cognitive functions were measured with a test battery including four tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTABeclipse version 6) and a modified flanker task (Eriksen and Eriksen, 1974). In the current study, we focused on core executive functions associated with physical activity and fitness in previous studies focusing on different age groups. The core executive functions are also shown to be important for several aspects of life, such as academic achievement (Best et al., 2011), health (Allan et al., 2016) and behavioural control (Denson et al., 2011). Furthermore, earlier studies show that maturation of inhibition, attention, and working memory still takes place during adolescence. For the current study analyses, we therefore included three different tests measuring core executive functions. Two of these tests were from the CANTAB, including the Rapid Visual Information Processing (RVP) and Spatial Working Memory (SWM) tests (CANTAB eclipse version 6). The third test was a modified Eriksen Flanker task that measures response inhibition (Eriksen and Eriksen, 1974). Trained research assistants instructed the participants to perform the tablet-based tests according to the standard protocol in a silent environment.

For the RVP task of sustained attention, an array of numbers from 2 to 9 was presented in a pseudo-random order (100 digits/min). The participant's task is to recognise three specific digit sequences (2-4-6, 3-5-7 and 4-6-8) and to press a response button when they detect the specific target sequence.

The SWM task assesses the participant's ability to retain and manipulate visuospatial information. Participants are asked to find a blue token hidden under a box, which is done by touching boxes on the screen. Once a blue token has been located, the same set of boxes is shown to find the next token. The participants are also told that once a token has been found under a particular box that the same box would not hide any other tokens anymore. The difficulty of the task increases from four to ten boxes.

CANTAB tests produce several variables for each test. The principal component analysis was conducted to reduce the number of variables and was performed separately for individual tests according to Rovio et al. (2016). Component represents cognitive performance related to the particular domain. Components were normalized based on the rank order normalization procedure, resulting in variables, each with a mean value of 0 and a standard deviation of 1.

A modified Eriksen Flanker task was used to measure response inhibition. For this task, an array of five flanking fishes is shown to the participants, and they are asked to react as quickly and accurately as possible to the middle fish. We used four different conditions for this task: compatible congruent (AC), compatible incongruent (AI), incompatible congruent (BC) and incompatible incongruent (BI). The first part of the test was compatible (congruent and incongruent), in which participants were asked to press the button at the side the fish was facing. For the congruent condition, all the other fishes in the array were

swimming in the same direction as the middle fish, and for the incongruent condition, the other fishes were swimming in the opposite direction. The second part of the test was incompatible (congruent and incongruent), in which participants were asked to press the button on the opposite side of where the fish is facing. The average reaction time of the correct answers was used as an outcome measure. Flanker response accuracy was not included as an outcome measure due to ceiling effects observed in some of the variables describing accuracy.

3.1. Multiple imputation of the missing data

Multiple imputation was used to handle missing data. The proportion of missing values was 10 % for the pubertal stage, 15 % for the 20-m shuttle run and 22 % for the MVPA. The reasons for missing values for most individuals included the absence from school during the measurement (e.g. due to sickness) and the insufficient number of valid measurement days (i.e. two weekdays and one weekend day) for physical activity. The incomplete data for several variables were imputed using the multiple imputation under a fully conditional specification (chained equations) (Van Buuren et al., 2006). The analysis was performed under the assumption of data missing at random as the crucial predictors – such as preceding measures (measured approximately six months before the current study) of pubertal stage, shuttle run tests (correlation with preceding 20-m shuttle run test = 0.57) and weekday measures of physical activity (correlation with the total MVPA [also weekend days included] = 0.95) – were available. As advised (Van Buuren, 2012 chapter 2.3.3), 50 imputed datasets were constructed and analysed. Each data set was constructed using 50 iterations of the multiple imputation by a chained equation algorithm to ensure the convergence of the iterative imputation process. The calculations were performed in R 3.4.0 (R Core Team, 2018) using the mice 2.3 package (Van Buuren and Groothuis-Oudshoorn, 2011). The model parameters and their standard errors were estimated for each imputed dataset and combined using Rubin's rules (Van Buuren, 2012 p. 37–38) to obtain the final estimates of parameters and their standard errors. In addition, the differences between the multiple imputation results and complete case analysis results were small. A full description of how the multiple imputation was done in the current study has been described previously (Ruotsalainen et al., 2019).

3.2. MRI acquisition

Imaging data were acquired on a 3 T whole-body MRI scanner (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil at the Aalto NeuroImaging unit, Aalto University, Espoo, Finland. The total scanning time was approximately 45 min for the structural, diffusion-weighted, functional, field map and perfusion imaging. All scans, except perfusion MRI, were acquired using 'Auto Align' to minimise the variation in slice positioning (van der Kouwe et al., 2005). Prior to imaging, the participants were familiarised with the measurement protocol. All participants were instructed to keep their head still during the scanning, and pads were used to minimise head motion. In addition, the participants wore earplugs to reduce the high noise caused by the MRI scanner.

For the diffusion-weighted imaging (DWI), we used a spin-echo based single-shot echo-planar (EPI) sequence with fat saturation. Prior to the DWI, high-order shimming was applied to reduce the inhomogeneities of the main magnetic field. The axial slices were tilted in the anterior-posterior commissure line to avoid aliasing artefacts and artefacts caused by eye motion on the imaging slices. Seventy slices without gap were collected in 30 different diffusion gradient orientations. Two sets of images with b = 1000s/mm2 and ten T2-weighted EPI images (b = 0 images) were acquired with two opposite phase encoding directions (anterior to posterior and posterior to anterior). The acquisition parameters were as follows: repetition time (TR) = 11,100 ms, echo time (TE) =78 ms, field of view (FOV) = 212 mm, matrix size =

106, voxel size = 2 × 2 × 2 mm3, GRAPPA acceleration = 2 and phase partial Fourier = 6/8. The scanning time for each DWI series was 7 min 47 s.

3.3. Image analysis

Diffusion-weighted images were processed using the FMRIB Software Library (FSL 5.0.11, www.fmrib.ox.ac.uk/fsl). The magnetic susceptibility distortions were corrected using the topup tool (Andersson et al., 2003). Eddy current-induced distortions and subject movements were corrected using the eddy tool (eddy_cuda), including the slice-to-volume motion model and the outlier replacement (Andersson et al., 2017, 2016; Andersson and Sotiropoulos, 2016). This was followed by the removal of non-brain tissue using the Brain Extraction Tool (BET). Then, DTIFIT was used to fit the diffusion tensor model, and obtain voxel-wise maps of the FA, mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD).

Voxel-wise statistical analysis of the FA, MD, RD, and AD data was carried out using Tract-Based Spatial Statistics (TBSS) – for methodological details, see Smith et al. (2006). First, every FA image was aligned to every other image to identify the 'most representative' image, which was used as a target image. Then, this target image was affine aligned into a Montreal Neurological Institute (MNI)152 standard space, and all subject's FA data were transformed into MNI152 space by combining the nonlinear transform of the target FA image with the affine transform from that same target to the MNI152 space. Next, the mean FA image was created and thinned to create a mean FA skeleton that represents the centres of all tracts. Each subject's aligned FA data were then projected onto this skeleton, and the resulting data fed into the voxel-wise cross-subject statistics. The skeleton was thresholded at an FA value of 0.2.

To test the relationship of both physical activity and aerobic fitness with white matter tract measures (FA, MD, RD and AD), we used FSL's randomise tool with 10,000 permutations (Winkler et al., 2014). The age, pubertal stage, and sex were used as covariates. The T-value difference in the voxel clusters was considered significant when the values passed – after the threshold-free cluster enhancement (TFCE) and family-wise error correction – a threshold of p < 0.05. The anatomical location of significant clusters was labelled using the JHU ICBM-DTI-81 atlas. For the TBSS analysis, we used the average values of the imputed datasets (for the physical activity, aerobic fitness, and pubertal stage). All the images were visually inspected for excessive motion and one subject was excluded based on this manual inspection. Further, a mean head motion was calculated using eddy_restricted_movement_rms -files, and an additional TBSS analysis was conducted using the head motion (eddy_restricted_movement_rms) as a covariate; however, this had negligible effects on the results. The analysis pipeline is available at Open Science Framework (https://osf.io/rg6zf/).

3.4. Regression and moderation analyses

Aerobic fitness, physical activity, and executive functions: Multiple linear regression, taking into account all 50 imputed datasets, was used to analyse the associations between core executive functions, physical activity, and aerobic fitness. The following multiple regression model was used:

$$EF_i = \beta_0 + \beta_1 X_i + \beta_2 Age_i + \beta_3 Sex_i + \beta_4 Puberty_i + \varepsilon_i$$

In the model, EF_i is the score of the executive function test of each test for a subject i, X_i is the physical activity or aerobic fitness, Age_i, Sex_i and $Puberty_i$ are the age, sex and pubertal stage, respectively and ε_i is the error term. The error variables were independent and identically distributed normal random variables with zero mean and the same standard deviation. All predictors were entered simultaneously into the model. The residual plots and Q-Q plots were used to check the assumptions of linearity as well as the normality and homoscedasticity of

the residuals. In addition, homoscedasticity was tested using the Breusch–Pagan test (bptest) from the R package lmtest (Breusch and Pagan, 1979; R Core Team, 2018; Zeileis and Hothorn, 2002). The means of the residuals in all models were close to zero. The highest pairwise correlation was found between the pubertal stage and an age r of 0.59, indicating that the multicollinearity was not a factor of concern. All variance inflation factors were < 2. We used the false discovery rate (FDR) to adjust for the multiple comparisons, and the results with an alpha level smaller than 0.05 after the FDR adjustment were considered noteworthy (Benjamini and Hochberg, 1995).

Aerobic fitness, physical activity, FA and executive functions: A moderation analysis was applied to examine whether white matter FA in predetermined tracts changed the association of either aerobic fitness or physical activity with core executive functions. Here moderation was studied (instead of mediation) to define the conditions (the level of FA) under which the relationship between either physical activity or aerobic fitness and core executive functions occur. Based on previous literature investigating the relationship between either aerobic fitness or physical activity with white matter FA in young participants, we used the following white matter tracts as regions of interest: the body and genu of corpus callosum, the bilateral superior corona radiata, the bilateral superior longitudinal fasciculus and the bilateral uncinate fasciculus (Chaddock-Heyman et al., 2018, 2014; Schaeffer et al., 2014). We focused our moderation analysis only to concern FA and not the other white matter measures since it is the most studied white matter measure in relation to physical activity, aerobic fitness and core executive functions in adolescents. Moreover, the earlier evidence concerning the relationship between white matter and physical activity/aerobic fitness was strongest for FA. These regions were masked from the white matter skeleton using the JHU ICBM-DTI-81 atlas, and the mean FA value was extracted for each region of interest. For the moderation analysis, we used the same model as for assessing the associations between core executive functions and either aerobic fitness or physical activity; however, the main effect of FA and an interaction term (FA*physical activity or FA*aerobic fitness) was added to the model. The variables involved with the interaction term were mean centred. For significant interaction effects, we conducted a simple slopes analysis to assess the relationships at high (+1 SD) or low (−1 SD) levels of the moderator. All statistical analyses were performed using the R 3.5.1 software (R Core Team, 2018) with the moderation analysis; the mitml 0.3–7 package was utilised (Grund et al., 2019). The results with an alpha level < 0.05 were considered noteworthy.

4. Results

4.1. Participant demographics

Table 1 describes the participant demographics (59 participants; 58 for the Flanker task). Body mass index (BMI) distribution of the participants is presented in Supplementary Fig. 1.

4.2. Associations between white matter, aerobic fitness, and physical activity

The TBSS analysis showed that aerobic fitness was positively associated with FA in several white matter tracts (Fig. 1 and Table 2). Aerobic fitness was associated with eight FA clusters of which the centres of mass localised to the left and right superior corona radiata and the body of the corpus callosum. Besides FA, higher aerobic fitness was associated with a lower MD, RD, and AD in several white matter areas, such as corpus callosum and the bilateral superior corona radiata, although the associations were more widespread than those for FA. A complete list of clusters with MNI coordinates and overlapping anatomical tracts is given in Table 2. There were no associations between physical activity and FA, MD, RD, or AD. All statistical maps can be found in our Neurovault collection (https://neurovault.org/collections/5206/)

Table 1
Participant demographics.

	Mean ± SD	Range
Age (years)	14.3 ± 0.9	12.7–16.2
BMI	20.6 ± 2.7	14.6–31.1
Pubertal stage	3.5 ± 0.9	1.5–5
20-m shuttle run (min)	5.7 ± 2.4	1.5–11.6
MVPA (min/day)	49.1 ± 19.2	18–105.9
Flanker BI (ms)	492.8 ± 126.4	315.7–900.0
Flanker BC (ms)	466.7 ± 111.9	299.4–801.4
Flanker AI (ms)	419.7 ± 80.0	284.1–682.5
Flanker AC (ms)	397.5 ± 74.4	278.3–629.5
Rapid visual processing	−0.03 ± 1.01	−3.11–1.96
Spatial working memory	1.47 ± 1.08	−2.08–3.57
N = 59 (58 for the Flanker tasks),		
female = 39 (38 in total for the Flanker tasks)		

BMI: body mass index, MVPA: moderate-to-vigorous physical activity, BI: incompatible incongruent, BC: incompatible congruent, AI: compatible incongruent, AC: compatible congruent.

(Gorgolewski et al., 2015). The correlation between 20-m shuttle run and MVPA was r(57) = 0.48, p = 0.0001, between 20-m shuttle run and BMI z-score r(57) = -0.41, p = 0.001, and between MVPA and BMI z-score r(57) = -0.20, p = 0.13

4.3. Associations between physical activity, aerobic fitness, and core executive functions

Multiple linear regression analysis revealed no significant associations between core executive functions (rapid visual information processing, spatial working memory, and response inhibition) and either aerobic fitness or physical activity (Supplementary Table 1).

4.4. White matter FA as a moderator of links between either aerobic fitness or physical activity with core executive functions

To study whether white matter FA moderates the relationship between either physical activity or aerobic fitness with the core executive functions, we conducted an exploratory moderation analysis. We found that white matter FA in the body of the corpus callosum and in the right superior corona radiata moderated the relationship between the 20-m shuttle run performance and spatial working memory. The interaction effect for FA of the body of corpus callosum*20-m shuttle run was β = −5.56, t = −2.64, p = 0.012, 95 % confidence interval (CI) = −9.82, −1.30. For the FA of the right superior corona radiata*20-m shuttle run, this was β = −5.25, t = −2.14, p = 0.038, 95 % CI = −10.19, −0.31. In addition, white matter FA in the body of the corpus callosum and in the genu of corpus callosum moderated the association between the MVPA and spatial working memory. The interaction effect for FA of the body of corpus callosum*MVPA was β = −0.81, t = −2.52, p = 0.016, 95 % CI = −1.47, −0.16. For the FA of the genu of corpus callosum, this was *MVPA β = −0.65, t = −2.30, p = 0.026, 95 % CI = −1.23, −0.08.

A follow-up simple slopes analysis was performed to examine the nature of the interaction (Fig. 2). These results revealed that the simple slopes were negative with high FA values and positive with low FA values. More specifically, with high FA values in the body of the corpus callosum, the aerobic fitness was negatively associated with working memory (β = −0.21, t = −2.19, p = 0.034, 95 % CI = −0.41, −0.02). Nevertheless, with low FA values, there were no significant associations between aerobic fitness and working memory. Aerobic fitness did not significantly associate with working memory, neither with high or low FA values in the right superior corona radiata. Regarding the relationship between physical activity and working memory, we found that with low FA values in the body and genu of corpus callosum, physical activity was positively related to working memory (low FA in the body of corpus callosum: β = 0.03, t = 2.38, p = 0.023, 95 % CI = 0.01, 0.06 and low FA in the genu of corpus callosum: β = 0.02, t = 2.20, p = 0.034, 95 % CI =

0.00, 0.05). Whereas with high FA values, physical activity did not associate with working memory. Furthermore, we did not find evidence of white matter moderation on the link between other core executive functions and either physical activity or aerobic fitness.

5. Discussion

The purpose of the current study was to determine 1) whether physical activity and aerobic fitness are related to white matter properties in adolescents and 2) whether white matter FA moderates the relationship of physical activity and aerobic fitness with core executive functions. We found that aerobic fitness (tested by a 20-m shuttle run test) is associated with white matter properties (FA,MD,RD, and AD) of several white matter tracts in adolescents. On the contrary, we did not find evidence for a relationship between physical activity (MVPA) and white matter. Our exploratory analysis suggests that the relationship between either aerobic fitness or physical activity with working memory was moderated by FA in specific white matter tracts.

The whole-brain analysis revealed that the association between aerobic fitness and white matter FA was apparent in many white matter tracts, most robustly in the corpus callosum and the bilateral superior corona radiata. The negative associations between aerobic fitness and white matter MD, RD, and AD were even more widespread (Fig. 1., Table 2). Our findings are consistent with the study conducted by Chaddock-Heyman et al. (2014) who investigated preadolescent children and demonstrated that a higher aerobic fitness was related to a greater FA in the body of the corpus callosum, the superior corona radiata and the superior longitudinal fasciculus in children. The current results, however, differ from Herting et al. (2014) as they did not find evidence for a relationship between aerobic fitness and FA in whole-brain analyses of 15 − 18-year-old male participants. This discrepancy between the results might be explained by subject-related and methodological differences between the studies, such as age and sex of the participants. In addition, the method to evaluate aerobic fitness levels of participants differed between the studies.

In addition to the studies of the connection between aerobic fitness and white matter FA, a few additional studies have investigated the link between physical activity and white matter in children or adolescents. Our findings that show no association between physical activity and FA are in line with a study concerning older male adolescents (Herting et al., 2014) and a study investigating the effect of exercise intervention (exercise group vs. controls) on white matter in overweight preadolescent children (Krafft et al., 2014a). In contrast to our study and the one of (Herting et al., 2014; Chaddock-Heyman et al., 2018) reported an increase in FA in the genu of the corpus callosum after an exercise intervention that did not affect aerobic fitness. However, they did not show associations between exercise and any of the other white matter tracts studied. In line with some earlier studies (Chaddock-Heyman et al., 2018, 2014; Herting et al., 2014), we did not find support for a link between physical activity and FA of the uncinate fasciculus, which was reported by Schaeffer et al. (2014).

Our differential findings for aerobic fitness and physical activity might be driven by genetic factors which, presumably, are at least partly different for fitness and physical activity. Indeed, aerobic fitness and physical activity are different concepts: while physical activity indicates the movement that is produced by skeletal muscles, aerobic fitness can be interpreted as a capacity that an individual has to perform physical activity or exercise. In the current study, aerobic fitness was related to white matter FA most robustly in the corpus callosum and the superior corona radiata. These tracts connect with motor regions and have an important role in motor functions (Fabri et al., 2014; Kim and Pope, 2005; Wahl et al., 2007). They also develop relatively early and FA of these structures stays at the same level during adolescence (Lebel et al., 2008; Simmonds et al., 2014). Perhaps the fact that only aerobic fitness (and not physical activity) was associated with FA in the corpus callosum and superior corona radiata reflects the relatively strong
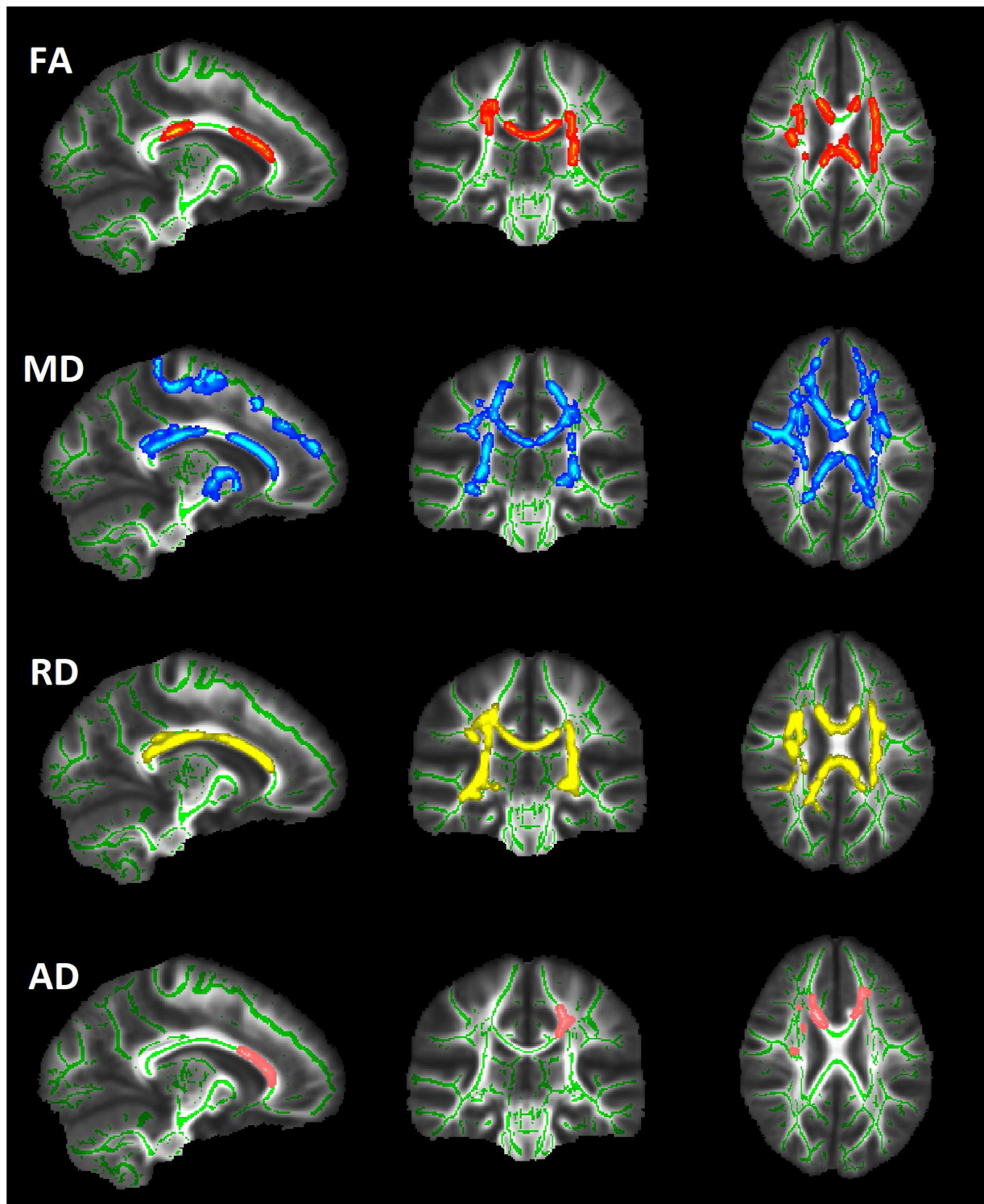
Fig. 1. Associations (p < 0.05, corrected for family-wise error) between aerobic fitness and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). The results are overlaid on an MNI152 1-mm template (MNI coordinates of all slices are −12, −24 and 25). The association between aerobic fitness and FA (red) was positive, and the association between aerobic fitness, MD (blue), RD (yellow), and AD (pink) was negative. The significant regions are thickened for illustrative purposes (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

emphasis of genetic factors both in fitness level and in the structuring of these tracts (Chiang et al., 2011) during development. While it has been also shown that the trainability of aerobic fitness and exercise responses are partly predicted by genetic factors (Bouchard et al., 2011; Ross et al., 2019), supporting a possible common genetic pathway underlying fitness and white matter FA. To summarize, the state of the body

(aerobic fitness), but not physical behaviour (physical activity) is important in relation to white matter in adolescents.

Even though we found an association between aerobic fitness and white matter properties, we did not find a clear association between either aerobic fitness or physical activity with core executive functions. The earlier results of these relationships are inconsistent. For instance,

Table 2
Characteristics of clusters that correlated with aerobic fitness.

Measure	Cluster	Cluster size (voxels)	Anatomica location of clusters (center of mass)	t	p-value	MNI coordinates		
						X	Y	Z
FA	1	801	Superior corona radiata L[a]	2.39	0.025	−25.4	−12.1	26.5
FA	2	563	Superior corona radiata R[b]	2.34	0.037	27.6	−17.2	32.2
FA	3	431	Body of corpus callosum[c]	2.36	0.039	−1.5	14.9	20.4
FA	4	319	Body of corpus callosum[d]	2.34	0.044	−4.15	−24	26.7
FA	5	83	Superior corona radiata R[e]	2.51	0.047	24.3	11.2	30.6
FA	6	25	Unclassified[f]	2.09	0.05	30.5	6.84	25.6
FA	7	2	Superior corona radiata R	3.29	0.05	22.5	−14.5	35.5
FA	8	1	Superior corona radiata R	3.43	0.05	21	−13	35
MD	1	15494	Body of corpus callosum[g]	1.99	0.03	1.92	−4.17	28.4
RD	1	7674	Unclassified[h]	2.02	0.032	9.33	−15.6	25.6
AD	1	2117	Anterior limb of internal capsule R[i]	1.85	0.026	21.9	20.3	10.1
	2	980	Body of corpus callosum[j]	1.85	0.031	−17.8	5.9	32.5
	3	67	Unclassified	3.02	0.046	33.9	21.6	19.3
	4	34	Unclassified	3.14	0.047	16.6	21.1	38.9

The MNI coordinates indicate the anatomical location of the centre of mass for each cluster. The p-values were derived from the clusters and were revealed by the threshold-free cluster enhancement (TFCE) and controlled for the family-wise error rate (FWER). JHU ICBM-DTI-81 atlas does not encompass all the white matter voxels, for this reason, some voxels are labelled as "unclassified".

The footnotes list all the tracts that each cluster overlaps with according to the JHU ICBM-DTI-81 atlas and indicates the proportion of voxels that overlap with that particular tract in each cluster.

JHU ICBM-DTI-81 tracts (% of voxels) FA: Fractional anisotropy, MD: Mean diffusivity, RD: Radial diffusivity, AD: axial diffusivity, L: left, R: right, ACR: Anterior corona radiata, ALIC: Anterior limb of internal capsule, CC: Corpus callosum, PCR: Posterior corona radiata, PLIC: Posterior limb of internal capsule, PTR: Posterior thalamic radiation, RLIC: Retrolenticular part of internal capsule, SCR: Superior corona radiata, SFOF: Superior fronto-occipital fasciculus, SLF: Superior longitudinal fasciculus.

[a] SCR L (76.5), PLIC (12.9), PCR L (5.9), RLIC (4.7).
[b] SCR R (43.2), Unclassified (21.6), PCR R (20.3), SLF R (14.9).
[c] Body of CC (66.0), Genu of CC (34.0).
[d] Body of CC (92.5), Splenium of CC (5.0), Unclassified (2.5).
[e] SCR R (77.8), ACR R (22.2).
[f] SLF R (66.7), SCR R (33.3).
[g] Unclassified (52.5), Body of CC (6.4), Genu of CC (4.6), Splenium of CC (4.5), SCR L (3.8), SCR R (3.7), ACR R (3.4), SLF R (3.2), PLIC L (2.8), ALIC L (1.9), RLIC L (1.8), PLIC R (1.6), RLIC R (1.4), PCR R (1.4), ACR L (1.4), PCR L (1.3), SLF L (1.1), ALIC R (0.9), PTR L (0.8), External capsule L (0.4), SFOF L (0.3), Sagittal stratum R (0.2), External capsule R (0.2).
[h] Unclassified (29.7), Body of CC (13.7), SCR R (9.1), SCR L (9.0), SLF R (6.9), Genu of CC (6.3), RLIC R (4.1), PLIC L (3.8), Splenium of CC (3.1), PCR R (2.9), PLIC R (2.7), RLIC L (2.3), ACR L (2.1), PCR L (0.8), External capsule L (0.6), SLF L (0.6), Sagittal stratum R (0.5), Fornix / Stria terminalis R (0.4), Fornix / Stria terminalis L (0.4), External capsule R (0.3), Cerebral peduncle R (0.2), ACR R (0.2), ALIC L (0.1).
[i] ACR (32.3), Unclassified (25.5), Genu of CC (13.7), ALIC R (11.4), Body of CC (7.2), SCR R (4.2), PLIC R (3.8), External capsule R (1.5), Uncinate fasciculus (0.3).
[j] Unclassified (43.1), Genu of CC (18.5), SCR L (15.4), ACR L (13.1), Body of CC (6.2), PCR L (3.8).

aerobic fitness has been associated with executive functions (e.g. Chaddock et al., 2010b; Huang et al., 2015; Westfall et al., 2018), but not all studies have shown this association (e.g. de Greeff et al., 2016; Stroth et al., 2009). So, even though a meta-analysis in children and adolescents (Álvarez-Bueno et al., 2017) suggests a minimal positive effect of physical activity intervention on working memory (Cohen's d = 0.14) and a small positive effect on selective attention and inhibition (Cohen's d = 0.26), the matter still remains debatable (Diamond and Ling, 2019, 2016; Hillman et al., 2018).

Interestingly, moderation analysis revealed that white matter FA had a moderation effect on working memory but not on the other tested cognitive functions. By showing that brain white matter integrity influences the strength of the relationship between physical activity and aerobic fitness with working memory, our results suggest that the disparity in earlier findings may reflect underlying neurobiological factors in the brain. Indeed, white matter properties have been suggested to contribute to the level of improvement by cognitive interventions (de Lange et al., 2017d; Engvig et al., 2012; Mackey et al., 2012) and may also represent one of the neurobiological targets for the physiological effects of exercise. Our results indicate that it is relevant to consider the individual variation in white-matter integrity in order to understand the role of physical activity in improving cognitive performance.

We demonstrated that in this sample of adolescents, physical activity was positively associated with working memory only at low levels of FA in the body and genu of the corpus callosum. At high levels of FA, no significant association was found between physical activity and

cognition. However, at high FA levels of the body of the corpus callosum, higher aerobic fitness was related to a poorer working memory performance. This means that after reaching a certain level of FA, fitness does not positively correlate with working memory and on the other hand when FA is low enough physical activity is positively correlated with working memory. Thus, the FA of the corpus callosum seems to have an important role in altering the direction of the relationship between working memory and both aerobic fitness and physical activity.

What could explain the positive relationship between physical activity and working memory with low FA values and on the contrary the negative relationship between aerobic fitness and working memory with high FA values? The link between physical activity, FA and working memory as such is not surprising. Corpus callosum has an important role in interhemispheric communication and synchrony (Ellis et al., 2016; Engel et al., 1991). Indeed, white matter microstructural properties, measured by means of DWI, have been shown to affect brain synchrony (Bells et al., 2017) which in turn has shown to be critical for working memory (Miller et al., 2018). As even small changes in white matter microstructure can affect brain synchrony (Pajevic et al., 2014), it is possible that synchrony related mechanisms might be behind the moderation results. These results suggest that when examining the influence of physical activity or aerobic fitness on spatial working memory, the level of white matter specifically in corpus callosum could affect the improvements in working memory.

The result of a negative association between fitness and working memory at high levels of FA is more puzzling. Higher fitness predicted higher FA values, independent of age, but at high FA values, higher
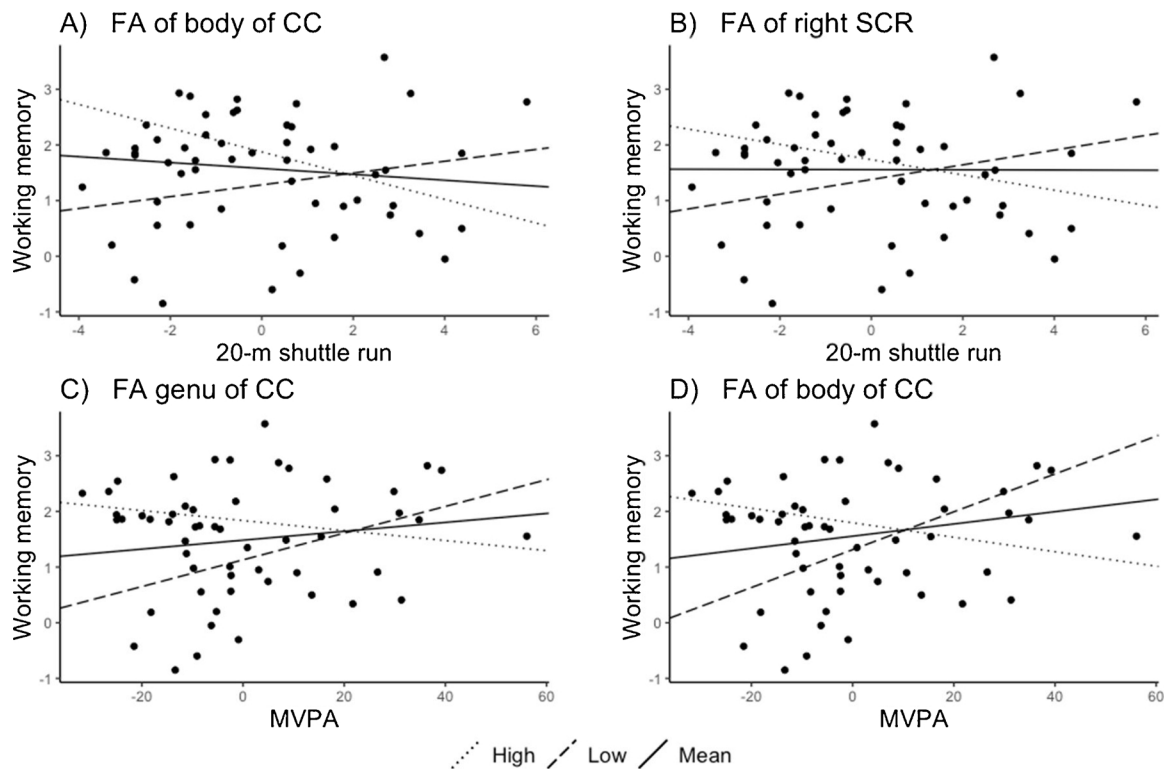
Fig. 2. The moderating effect of FA of (High: + 1 SD, Low: −1 SD) (A) the body of corpus callosum (CC), and (B) the right superior corona radiata (SCR) regarding the relationship between working memory and the 20-m shuttle run performance. The moderating effect of FA of (C) the genu and (D) the body of corpus callosum regarding the relationship between working memory and the moderate-to-vigorous physical activity (MVPA).

fitness did not associate with better working memory (in fact, on the contrary). Furthermore, at low FA values, physical activity relates with better working memory performance. The degree of FA is thought to be influenced by myelin (Chang et al., 2017). While animal studies suggest that myelination constrains the brain plasticity, experience-related increases in myelination may both stabilize the connections and suppress plasticity (McGee et al., 2005). Thus, high FA values may indicate a state of suppressed plasticity. In this scenario, at high FA levels, no relationship would be expected between fitness and working memory; the slight negative association in our data needs to be explored in further studies.

Few limitations are present in the current study. Firstly, the sample size (n = 59/58) may not be large enough to detect weak associations, and the limited age group 12.7–16.2-year-old may not allow large generalisations. Secondly, even though accelerometers are widely used and provide an objective measure of physical activity, the same amount of physical activity may produce different physiological responses for each individual. Further, the application of different cut-points may yield different estimates of MVPA, limiting the comparability between studies. Thirdly, due to computational restrictions, the averages of the imputed values were used in TBSS analysis. Even though a relatively large amount of data for some variables were imputed, we could utilize data from the earlier measurements and good proxies for the variables with missing observations, which improves the precision of the imputations (for details see Ruotsalainen et al., 2019). Fourthly, we assessed the level of aerobic fitness with 20-m shuttle run test, which is not a direct measure of cardiorespiratory fitness, however, it is considered to have good validity for estimating maximal oxygen uptake. Another possible limitation is that the BMI is not included as a predictor in the analyses. While BMI is related to performance in the 20-m shuttle run task, it appears to have a minimal effect on the correlation between shuttle run task performance and maximal oxygen consumption (Mahar et al., 2018). Further, the relationship between white matter microstructure and BMI seems to be contradictory in adolescents (Alosco

et al., 2014; Carbine et al., 2019). Lastly, excluding the only obese participant in the current study, did not affect the results. Finally, our cross-sectional data do not allow causal interpretations and the exploratory moderation analysis results need to be interpreted cautiously.

6. Conclusions

We found that aerobic fitness and physical activity have an unequal contribution to brain white matter properties in adolescents. Aerobic fitness – assessed with a 20-m shuttle run test – positively associated with FA and negatively with MD and RD in several white matter tracts. However, we did not find these associations when studying physical activity. This result might be driven by genetic factors, which underlie fitness more strongly than those of the physical activity measures. It is also possible that only physical activity sufficient to increase aerobic fitness is needed to influence white matter. Overall, our findings concerning the exploratory moderation analysis further suggest that the level of white matter FA of specific white matter tracts may influence the relationships between either aerobic fitness or physical activity with the spatial working memory. Future studies should compare adolescents to other age groups to identify unique aspects of the relationship between physical activity, aerobic fitness and white matter as well as the moderator effect.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100765.

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