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Ilona Ruotsalainen

The Association of Physical Activity and Aerobic Fitness with Brain Structure and Functional Connectivity in Adolescents

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF EDUCATION AND
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ABSTRACT

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Over the past decades adolescents have experienced decreased aerobic fitness levels and insufficient physical activity levels. A sedentary lifestyle with little physical activity can be harmful to adolescents' well-being and health. Despite this, the association between adolescents' physical activity and aerobic fitness with brain health remains poorly understood. The primary purpose of this dissertation is to examine the association between physical activity and aerobic fitness with brain structure and function in 13–16-year-old adolescents. Additionally, earlier studies regarding the connections between physical activity and aerobic fitness with executive functions have been contradictory in youth. The second purpose of this dissertation is to investigate whether the brain's white matter properties moderate the relationship between physical activity and aerobic fitness with core executive functions. The first study in this dissertation examined the association between moderate-to-vigorous physical activity and aerobic fitness (assessed using a 20-m shuttle run test) with the brain's gray matter. The results show that higher level of aerobic fitness, but not physical activity, is related to smaller volume in the left superior frontal gyrus and larger volume in the left pallidum. The second study demonstrates that aerobic fitness, but not the physical activity, is associated with white matter properties in several tracts, but most robustly in the corpus callosum and the superior corona radiata. Furthermore, we found that the white matter moderates the connection of physical activity and aerobic fitness with working memory. The third study concentrated on the resting state functional connectivity of the brain. The findings show that adolescents' physical activity, but not aerobic fitness, is related to local functional connectivity. However, they also reveal that neither of them is related to interhemispheric functional connectivity, as indicated by homotopic connectivity. Overall, the results of this dissertation show that both physical activity and aerobic fitness are related to an adolescents' brains. Associations between brain properties and these two measures differ extensively. While aerobic fitness is especially associated with structural measures, physical activity is related to the functional measure at rest. Moreover, the findings related to the moderation analysis suggest that the varying previous results regarding the relationship of physical activity and aerobic fitness with the working memory might be explained by the varying levels of the brain's white matter.

Keywords: physical activity, aerobic fitness, adolescence, gray matter, white matter, functional connectivity, executive functions

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Viimeisten vuosikymmenten aikana nuorten kestävyyskunto on heikentynyt ja fyysisen aktiivisuuden määrä on suurella osalla nuorista liian vähäistä. Runsas paikallaolo ja vähäinen liikunta voivat olla haitallisia nuorten hyvinvoinnille ja terveydelle. Kuitenkaan tutkimustietoa liikunnan ja nuorten aivoterveyden välisestä suhteesta ei juurikaan ole. Tämän väitöskirjan päätarkoitus on tutkia fyysisen aktiivisuuden ja kestävyyskunnon yhteyttä aivojen rakenteisiin ja toimintaan 13–16-vuotiailla nuorilla. Lisäksi aiemmat tutkimustulokset liikunnan vaikutuksista nuorten kognitiivisiin toimintoihin, erityisesti toiminnanohjaukseen, ovat osittain ristiriitaiset eikä ole varmasti tiedossa mikä aiheuttaa nämä ristiriitaiset tulokset. Väitöskirjan toisena tarkoituksena onkin selvittää, vaikuttaako aivojen valkean aineen taso fyysisen aktiivisuuden/kestävyyskunnon ja toiminnanohjauksen välillä olevan yhteyden suuntaan tai voimakkuuteen. Väitöskirjan kahdessa ensimmäisessä tutkimuksessa tutkin keskiraskaan ja raskaan fyysisen aktiivisuuden ja kestävyyskunnon (arvioitu 20 m sukkulajuoksutestillä) yhteyttä sekä aivojen harmaaseen aineeseen että valkean aineen ratoihin. Tutkimuksen tulokset osoittavat, että parempi kestävyyskunto on yhteydessä vasemman yläetupoimun pienempään tilavuuteen sekä vasemman linssitumakkeen pallon suurempaan tilavuuteen. Aivojen valkean aineen osalta kestävyyskunnon havaittiin olevan yhteydessä useiden eri valkean aineen ratojen ominaisuuksiin. Selkein yhteys näkyi kunnon sekä aivokurkiaisen ja ylemmän corona radiatan välillä. Lisäksi valkean aineen havaittiin vaikuttavan fyysisen aktiivisuuden/kestävyyskunnon ja työmuistin väliseen yhteyteen. Fyysisen aktiivisuuden ja aivojen harmaan tai valkean aineen välillä ei havaittu merkittävää yhteyttä. Kolmas tutkimus tarkasteli aivojen lepotilan toimintaa. Tulokset osoittavat, että nuorten fyysinen aktiivisuus, muttei kestävyyskunto, on yhteydessä aivojen paikalliseen yhdistyneisyyteen. Kokonaisuutena tämän väitöskirjan tulokset osoittavat sekä fyysisen aktiivisuuden että kestävyyskunnon olevan yhteydessä nuorten aivojen ominaisuuksiin. Kytkökset näiden kahden liikuntamuuttujan ja aivojen ominaisuuksien välillä kuitenkin eroavat huomattavasti. Kunto on yhteydessä erityisesti aivojen rakenteisiin, kun taas fyysinen aktiivisuus on yhteydessä aivojen toimintaan levossa. Lisäksi tutkimuksen tulokset ehdottavat, että vaihtelevat tulokset liittyen liikunnan ja työmuistin väliseen yhteyteen voivat selittyä aivojen valkean aineen tasolla.

Avainsanat: fyysinen aktiivisuus, aerobinen kunto, nuoruus, harmaa aine, valkea aine, magneettikuvaus, toiminnanohjaus

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Taken into account the instructions and comments given by the co-authors, the author of this thesis formulated the research questions, collected the neuroimaging data, analyzed the data, wrote and reviewed the manuscripts.

FIGURES

TABLES

CONTENTS

1 INTRODUCTION

The brain's ability to modify itself as a result of interaction with the environment was described more than century ago (for a review see Rosenzweig, 1996). This ability has inspired researchers to study potential factors affecting brain structure and function. At the end of the last century, groundbreaking animal studies showed that one factor which can modify the brain is physical exercise (Gómez-Pinilla et al., 1998; Neeper et al., 1995; Van Praag, Christie, et al., 1999; Van Praag, Kempermann, et al., 1999). These early animal studies led to the question of whether physical exercise could also influence the human brain. Indeed, the first human studies demonstrated an association between aerobic fitness and the brain volume in older adults (Colcombe et al., 2003) as well as between physical activity and exercise with the brain function (Hatta et al., 2005; Kamijo et al., 2004). Following these early investigations, several cross-sectional and longitudinal studies have confirmed these relationships (e.g., Chaddock-Heyman et al., 2014; Erickson et al., 2011; Herting et al., 2014; Johnson et al., 2012). Even though a considerable amount of literature has been published on this topic, the studies have mainly concentrated on older adults, and little is known about how physical activity and aerobic fitness are related to the adolescent brain.

The previous literature typically focuses on either physical activity or aerobic fitness. These two terms are even sometimes used interchangeably. While physical activity and aerobic fitness are related to each other, they present different concepts. Physical activity refers to our actions, that is, how much we move. Aerobic fitness, on the other hand, relates to the capacity to perform physical activity or exercise. To increase aerobic fitness levels, a person needs to perform physical activity or exercise with high enough frequency, duration, and intensity. Thus, not all physical activity enhances an individual's aerobic fitness. Comparing the contribution of both of these measures in the same study not only informs us whether actions or capacity are more important for the brain but also helps to build precise training interventions to enhance brain health.

Besides studying the relationship between physical activity and aerobic fitness with the brain, it is important to understand the potential benefits of physical activity or higher aerobic fitness on cognitive performance. Studies, especially in older adults, have suggested that there is a relationship between aerobic fitness and physical activity with cognitive performance (Bherer, 2015; Bherer et al., 2013; Kirk-Sanchez & McGough, 2013). The results concerning children and adolescents, however, are inconsistent (Álvarez-Bueno et al., 2017; Diamond & Ling, 2016; Singh et al., 2019). Several reasons for these inconsistent results have been proposed, but it is not yet known definitely what are the factors that cause these inconsistencies.

The overall aims of this thesis are to investigate the associations of aerobic fitness and physical activity with brain structure and function in the previously understudied adolescent age group. Further, another aim is to study whether white matter properties influence the strength and direction of the association between aerobic fitness and physical activity with core executive functions.

1.1 Brain development in adolescents

Adolescence is a stage of development that occurs between childhood and adulthood, and is characterized by physical and psychosocial maturation. Large hormonal changes during puberty lead to increased growth and changes in physical appearance (Rogol et al., 2002). At the same time, adolescence is also suggested to be a sensitive period for emotional, social, and cognitive development (Bossong & Niesink, 2010; Dow-Edwards et al., 2019). Many behavioral problems as well as psychopathology emerge during this period (Compas et al., 2017). Therefore, adolescence is characterized by significant changes in an individual's life. These fundamental changes occurring during adolescence make it a unique period of brain development and an important period in life to study.

1.1.1 Changes in gray matter volumes

The brain's gray matter consists mainly of neuronal cell bodies and dendrites, and while its importance to our cognition is obvious, interestingly, system-level measures of gray matter such as volume and thickness have proven to be important in understanding behavior, mental health, and cognition (Gogtay & Thompson, 2010; Paus et al., 2008). Due to this importance, the measurement of system-level gray matter changes during adolescence, when many mental health problems emerge and cognitive skills still develop, is of special interest (Gogtay & Thompson, 2010; Paus et al., 2008). Recent developments in neuroimaging have enabled many system-level measures such as volume, thickness, gyrification, surface area, and density. Studies using these measures have provided important details of how the human brain develops. Due to the volumetric measurements used in this thesis, this chapter is mostly focused on volumetric studies.

Studies utilizing structural magnetic resonance imaging (MRI), which can be used to investigate system-level changes in the brain, have shown that the human brain continues structural development from childhood to adulthood. Some of the early as well as recent longitudinal studies demonstrated that the total brain volume increases until mid-to-late adolescence (Giedd et al., 1999; Mills et al., 2016). Global cortical gray matter volume, on the contrary, decreases throughout adolescence (Gennatas et al., 2017; Mills et al., 2016; Pfefferbaum et al., 2016; Tamnes et al., 2017). When looking at the cellular level mechanisms that explain this decrease in the cortical gray matter, synaptic elimination has been proposed. Indeed, histological studies show that dendritic spine intensity peaks at childhood and decreases thereafter (Petanjek et al., 2011). At the same time, myelination of axons in the white matter of the brain also increases (Mah et al., 2017; Yakovlev & Lecours, 1967).

While relatively consistent patterns of global gray matter development have been shown, there are differences in the developmental trajectories of regional gray matter. Most of the brain's gray matter is located near the brain's surface in the cerebral cortex. It is widely suggested that regional gray matter volumes in these cortical regions either decrease with unique region-dependent trajectories or do not change during adolescence (e.g., Pfefferbaum et al., 2016; Sowell et al., 2003; Tamnes et al., 2017). The volume of regions, including temporal and frontal regions, that are crucial for memory and executive functions (Diamond, 2013; Eichenbaum et al., 2007), appears to decrease during adolescence (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 2003). On the other hand, regions related to motor and sensory functions do not seem to undergo large changes in adolescence (Gogtay et al., 2004; Shaw et al., 2008). Although many studies have supported these findings, some contradictory findings have also been presented (Vijayakumar et al., 2016). Perhaps more consistent is the finding concerning cortical thinning during adolescence (Pfefferbaum et al., 2016; Tamnes et al., 2017; Vijayakumar et al., 2016). Indeed, a study by Tamnes et al. (2017) showed that decreases in regional cortical volumes are mainly driven by decreases in cortical thickness.

In addition to cortical gray matter, deeper subcortical gray matter also undergoes structural changes during adolescence. Of these subcortical gray matter structures, amygdala and hippocampus volumes have been reported to increase during adolescence (Goddings et al., 2014; Herting et al., 2018; Mills et al., 2014; Narvacan et al., 2017; Østby et al., 2009). Results concerning basal ganglia volumes are less consistent. While some studies have found that basal ganglia subregion volumes decrease during adolescence (Goddings et al., 2014; Herting et al., 2018; Narvacan et al., 2017; Østby et al., 2009), increases in putamen and pallidum volume have been also reported (Wierenga, Bos, et al., 2018). Interestingly, multisample studies, which compare data measured at different locations but analyzed identically, suggest that factors related to image acquisition or sample might cause these inconsistent results between the studies (Goddings et al., 2014; Herting et al., 2018).

In summary, cortical and subcortical gray matter undergoes substantial region-specific changes during adolescence. While the volume of certain regions peaks already at childhood, some other regions, such as frontal and temporal regions, continue maturing during adolescence.

1.1.2 Development of white matter tracts

In contrast to gray matter, which mainly consists of neuronal cell bodies and dendrites, white matter consists of nerve fibers that connect distinct brain regions to functional networks (Fields, 2010). Many methods can be used to study white matter development. While early histological investigations have provided important insights concerning brain development at the cellular level (Yakovlev & Lecours, 1967), the development of MRI has enabled studying the brain noninvasively. MRI provides an *in vivo* method to characterize and quantify white matter microstructural properties. Methods such as volumetric analysis (Reiss et al., 1996), magnetic transfer ratio (Moura et al., 2016), and T2 relaxometry (Leppert et al., 2009) have been used to investigate white matter changes in development. Furthermore, the utilization of diffusion imaging has produced important additional information about microstructural properties. Diffusion tensor imaging (DTI) is a commonly used diffusion imaging analysis method to study the white matter. Some newer methods (e.g., high angular resolution diffusion imaging [HARDI], diffusion kurtosis imaging [DKI], diffusion spectrum imaging [DSI]) have also been developed to overcome some of the limitations DTI has, such as crossing fibers. However, the availability of these newer methods is still limited. This thesis concentrates on examining the white matter microstructure using DTI, and therefore, this introduction mainly focuses on the developmental results concerning DTI.

Considerable evidence has accumulated showing that distinct white matter tracts mature at different ages. A large number of cross-sectional studies using DTI have investigated the association between age and white matter properties in children and adolescents (for reviews see Blakemore et al., 2010; Lebel et al., 2019; Lebel & Deoni, 2018; Paus, 2010a; Schmithorst & Yuan, 2010). These earlier investigations have revealed that, in most white matter tracts, age is positively associated with white matter fractional anisotropy (FA), which is used to measure the degree of anisotropic diffusion. However, negative associations between age and mean diffusivity ([MD], overall diffusion) have also been found in most white matter tracts.

When comparing the development of different white matter regions, a prolonged development has been demonstrated for frontal and temporal regions (Asato et al., 2010; Lebel & Deoni, 2018; Paus et al., 1999; Tamnes et al., 2010). Moreover, early histological data, as well as some recent neuroimaging data, suggest that posterior white matter regions develop earlier than anterior regions. (Colby et al., 2011; Kinney et al., 1988; Krogsrud et al., 2016; Yakovlev & Lecours, 1967). However, there is considerable variation in the regions that demonstrate age-related associations among the cross-sectional studies making it challenging to make universal interpretations.

Longitudinal studies, on the other hand, can demonstrate within-subject changes that are not possible for cross-sectional studies. Longitudinal studies have shown age-related changes in white matter properties even at relatively short time intervals in children and adolescents (Bava et al., 2010; Genc, Smith, et al., 2018; Krogsrud et al., 2016). More precisely, the evidence suggests that the latest tracts to mature are typically association tracts, such as the cingulum that connect different regions within the same hemisphere, and tracts that connect to frontal regions. These tracts typically mature in early adulthood. On the other hand, the majority of the commissural tracts, which connect similar cortical areas in the opposite hemisphere (e.g., the corpus callosum), and projection tracts, which connect higher and lower brain regions, (e.g., corticospinal tract), have been proposed to mature earlier during childhood and adolescence (Giorgio et al., 2010; Lebel & Beaulieu, 2011; Simmonds et al., 2014; Vanes et al., 2020).

In the context of this thesis, it is also important to look at how motor behavior-related white matter tracts develop during adolescence. Longitudinal studies investigating the white matter demonstrate an early development of motor-related white matter tracts. Several of these motor-related white matter tracts such as the corticospinal tract, the internal capsule, the corpus callosum genu and body, and the superior corona radiata do not change to a large extent during adolescence (Giorgio et al., 2010; Lebel & Beaulieu, 2011; Simmonds et al., 2014; Vanes et al., 2020). Contrary to these findings, the superior longitudinal fasciculus, which connects regions important to motor functions, still matures in adolescence (Lebel & Beaulieu, 2011; Simmonds et al., 2014; Vanes et al., 2020). It should be noted, however, that the superior longitudinal fasciculus also connects to frontal regions, which are proposed to have protracted development. This probably explains the later development of this tract when compared with other motor-related white matter tracts.

The changes in white matter typically appear to accelerate during early childhood and decelerate or level off during adolescence and early adulthood (e.g., Lebel & Beaulieu, 2011). Thus, white matter development is non-linear. As mentioned in the earlier paragraph, there is variation in the development of white matter among brain regions or tracts. The shape of the changes also shows differences depending on the tract (Lebel & Beaulieu, 2011; Simmonds et al., 2014). Thus, acceleration and deceleration of white matter changes during development occur at different times depending on the tract. All this implies that adolescence is a unique phase in brain development, during which the development of specific tracts is already quite stable, while, on the other hand, some tracts still experience large changes.

To better understand these system-level changes in white matter during adolescence, histological and MRI studies have been conducted to elucidate the cellular level mechanisms behind developmental changes. These studies propose that increases in myelin contribute largely to the white matter changes during development (Benes et al., 1994; J. H. Y. Kim & Juraska, 1997; Mah et al., 2017; Yakovlev & Lecours, 1967). In addition to myelination, other cellular mechanisms, such as increased axon caliber and axonal packing, have been suggested as contributing to white matter changes (Mah et al., 2017; Paus et al., 1999). Thus, increased myelination, which is often suggested as a main underlying mechanism, may not be the only reason for the observed changes during development.

1.1.3 Local and interhemispheric functional connectivity

The brain comprises of a large number of different brain areas that process information within a single area but also among anatomically separated brain regions. Resting state functional connectivity, which represents statistical dependencies of neurophysiological events between regions at rest, can be used to study functional communication between these separated regions and also within the brain region (Friston, 2011). Since the discovery of resting state functional connectivity, studies have investigated the relevance of this connectivity to behavior. These investigations have revealed the importance of the brain's functional connectivity for cognition, and that it is still largely developing during adolescence (for reviews see Blakemore, 2012; Constantinidis & Luna, 2019; Grayson & Fair, 2017; Luna et al., 2010; Menon, 2013). Although there are numerous different functional connectivity metrics, this thesis focuses on two specific types of functional connectivity: interhemispheric and local functional connectivity, or more specifically, homotopic connectivity and regional homogeneity, respectively.

Earlier studies have demonstrated that, during development from infancy to adolescence, the brain's short-range connectivity decreases and long-range connectivity increases (Dosenbach et al., 2010; Fair et al., 2007; Kelly et al., 2009; Supekar et al., 2009). Recent observations, however, have demonstrated that motion during scanning can affect the strength of these connections (Satterthwaite et al., 2012, 2013). Newer studies taking into account the subject motion have found that short-range connectivity decreases and long-range connectivity increases with age during development, but to a smaller degree than the earlier observations had determined (Satterthwaite et al., 2012, 2013).

Short-range connectivity or local functional interactions can be examined using regional homogeneity (Jiang & Zuo, 2016; Zang et al., 2004). Studies using this method suggest decreases in local connectivity during adolescence. Firstly, studying 11–35-year-old participants, Lopez-Larson et al. (2011) found decreases in regional homogeneity with age. The largest decreases were observed in the cingulate cortex and right temporal lobe. Secondly, Dajani and Uddin (2016) also observed higher regional homogeneity in healthy children than in adolescents or adults.

While a relatively large amount of research has investigated the development of short- and long-range connections, the interhemispheric connections that connect both brain hemispheres have received less attention. Interhemispheric connections are crucial in integrating information between hemispheres. A recent animal study proposes that hemispheric functional specifications occur during development and the interhemispheric functional connectivity decreases (Ma et al., 2018). In humans, a similar finding was reported by Anderson et al. (2011), who found that interhemispheric connectivity decreases with age in healthy 8–34-year-old subjects, particularly in medial cortical areas.

Interhemispheric connectivity has been also studied in homotopic regions, which refers to the geometrically corresponding interhemispheric brain regions. An early study by Fair et al. (2008) found only minimal changes in interhemispheric homotopic connectivity among default mode network regions from childhood to adulthood. Another analysis of homotopic connectivity suggests that changes with age are region-specific. While sensorimotor areas tend to show increases in homotopic connectivity, areas involved in the processing of higher-order functions show decreases from childhood to adolescence and adulthood (Zuo et al., 2010). These early studies suggest that changes in interhemispheric connectivity occur during adolescence. However, more studies, and especially longitudinal studies are required to confirm these observations.

1.1.4 Factors influencing brain development

As presented in the previous sections, many aspects of the brain undergo important changes during adolescence. To better understand the adolescent brain, it is necessary to examine the influence of other factors affecting brain development. The purpose of this chapter is to briefly introduce some of the most important factors influencing the adolescent brain.

Sex-related differences in brain development have been widely studied. A large body of literature demonstrates that males have larger absolute global and regional gray matter volumes than females (e.g., De Bellis et al., 2001; Gennatas et al., 2017; Herting et al., 2018; Paus, 2010b; Sowell et al., 2007). However, results concerning relative regional volumes (corrected for total brain size) and developmental trajectories differ to some extent among studies (Gur & Gur, 2016; Koolschijn & Crone, 2013; Marwha et al., 2017; Ruigrok et al., 2014). Although some of these results suggest that there are sex-related differences in the gray matter development, the effect size of these differences appears to be small (Wierenga, Sexton, et al., 2018).

Sex-related differences have also been examined concerning white matter microstructure. Regional differences have been reported between sexes in some studies (e.g., M.-C. Chiang et al., 2011; Lebel & Beaulieu, 2011), and earlier development of white matter has been suggested for females compared with males (Asato et al., 2010; Seunarine et al., 2016; Simmonds et al., 2014). Despite these results, many studies have not found significant differences in the developmental trajectories of white matter between sexes (Bava et al., 2010; Krogsrud et al., 2016; Lebel et al., 2008). Furthermore, as with the gray matter, the size of the sex differences appears to be small, even smaller than individual variation (Tamnes, Roalf, et al., 2018). Concerning resting state functional connectivity, preliminary findings indicate that there might be regional sex-related differences in functional connectivity during adolescence (e.g., Alarcón et al., 2015; Lopez-Larson et al., 2011; Zuo et al., 2010). However, more studies are needed to confirm this.

The onset of puberty induces large changes in adolescents' bodies (Sisk & Foster, 2004). Due to the hormonal and behavioral changes occurring in this period, an increasing number of studies have investigated the relationship of puberty and brain development (for reviews see Herting & Sowell, 2017; Vijayakumar et al., 2018). Many studies on pubertal effects have reported negative associations between pubertal development and cortical gray matter volumes (Koolschijn & Crone, 2013; Neufang et al., 2009). Concerning subcortical volumes, both positive and negative associations have been found that depend on the region studied (e.g., Blanton et al., 2012; Bramen et al., 2011; Goddings et al., 2014; Neufang et al., 2009; Wierenga, Bos, et al., 2018). The results of the studies regarding the relationship between puberty and gray matter volume are somewhat contradictory. This might be explained by the different ways to measure the pubertal stage. Also, whether or not age is included in the model influences the results and the association of puberty with gray matter appears unclear when age is considered in the model (Vijayakumar et al., 2018).

Concerning white matter microstructure, pubertal development has been shown to be positively related to FA (Chahal et al., 2018; Herting et al., 2012, 2017) and fiber density (Genc, Malpas, et al., 2018), and by contrast, negatively to MD and radial diffusivity (RD) (Chahal et al., 2018; Herting et al., 2017; Menzies et al., 2015). The regions where these associations have been found, however, differ among studies. In addition, some contradictory findings have also been presented. For example, a negative association was found between pubertal development and FA of the genu of the corpus callosum and anterior corona radiata (Herting et al., 2017), but no relationship was found between FA and pubertal development in adolescent boys (Menzies et al., 2015). While these earlier investigations imply that puberty can affect the brain's structural development, it remains to be elucidated if puberty influences regional and homotopic resting state functional connectivity.

Another important factor influencing brain development is genetics. Twin studies have found several gray and white matter brain structures that show high heritability during development. For example, white matter microstructural and network properties show widespread associations with heritability (M.-C. Chiang et al., 2011; Koenis et al., 2015). In addition, both global and regional gray matter volumes show high heritability during development (Brouwer et al., 2017; Peper et al., 2009; Swagerman et al., 2014). The important role of heritability has also been demonstrated in functional connectivity. Teeuw et al. (2019) found that heritability explained up to 53% of the variation in resting state functional connectivity within and between networks. Interestingly, concerning resting-state functional networks, it has been suggested that global, but not local network properties, are under genetic control (van den Heuvel et al., 2013).

While the heritability of the brain structures during adolescence is high (depending on the region and brain measure), it does not exclude the possibility that environment and experience can also influence brain development. Indeed, studies in adolescents have indicated that experiences such as musical training (Hudziak et al., 2014), sleep variability (Telzer et al., 2015), and substance use (Bava et al., 2013) can influence the adolescent brain. Moreover, twin studies that allow the examination of genetic and environmental factors, have revealed that environmental factors also explain individual differences in brain development (Brouwer et al., 2017; M.-C. Chiang et al., 2011; Teeuw, Brouwer, Guimarães, et al., 2019).

In summary, there are a number of important factors that influence brain development during adolescence, but these listed above, are not the only factors that can affect brain development; several other contributing factors including stress (Romeo, 2017), lifestyle (Dutil et al., 2018; Urrila et al., 2017), and substance use (Meruelo et al., 2017; Squeglia & Gray, 2016) have also been suggested. However, many of these require more investigation to confirm their role in development.

1.1.5 Brain plasticity

The brain has the capacity to change and adapt in response to experience, environmental changes, or physiological modifications (Pascual-Leone et al., 2005). This capacity is called plasticity. The discovery that the brain is plastic has been made over a century ago (according to Berlucchi, 2002), but methodological advances in recent decades have enabled studies on plasticity in the human brain non-invasively. The brain's ability to modify itself is a core principle in behavioral neuroscience. Importantly, plasticity provides an opportunity to use interventions to influence the properties of the human brain. It is known that the human brain is plastic to some extent throughout life (for reviews see Fuhrmann et al., 2015; Kolb et al., 2017; Lövdén et al., 2013). However, the level of plasticity may change with age, and especially during development, it appears to be heightened (e.g., Larsen & Luna, 2018; Nemati & Kolb, 2010).

Plasticity is typically considered to be beneficial because it enables the learning of new skills and adaptations to new environments. It has also been shown to beneficially support motor (Karni et al., 1995; Voss et al., 2013) and cognitive functions (Brehmer et al., 2011; Engvig et al., 2012). Yet, these beneficial effects might differ depending on the age. For instance, exercise initiated at adolescence versus adulthood has been found to have differential effects on cognition, hippocampal neurogenesis, and several plasticity-related genes in the hippocampus in animal experiments (O'Leary, Hoban, Cryan, et al., 2019; O'Leary, Hoban, Murphy, et al., 2019). While brain plasticity is beneficial in several cases, it can also make the brain vulnerable to negative effects. For example, the appearance of psychiatric illnesses during adolescence has been suggested to be related to plasticity (Woo, 2014). Thus, plasticity may be beneficial or disadvantageous for the brain and behavior.

The brain's ability to change can be studied at many levels. Human studies have mainly focused on changes in behavior or at the system level (such as functional and structural reorganization). These changes are commonly measured with neuroimaging tools such as (functional) MRI, electroencephalogram (EEG), magnetoencephalography (MEG), or transcranial magnetic stimulation (TMS). For more detailed analysis, animal models provide a possibility to study plasticity at the cellular or molecular level. These models provide information about plasticity mechanisms at the neuronal level, such as changes in synaptic structure.

In addition to the different levels of plasticity, there are also different types of plasticity. Plasticity can be categorized as experience-independent, experience-expectant, and experience-dependent (Kolb & Gibb, 2014). These different types typically take place at different ages. While experience-independent plasticity mainly occurs during prenatal development, the latter two occur during postnatal development (Kolb et al., 2013). Experience-expectant plasticity refers to plasticity that happens after exposure to experiences that are expected or common to humans (Greenough et al., 1987). On the other hand, experience-dependent plasticity occurs as a result of experiences in an individual's life, such as musical training (Steele et al., 2013). It has been suggested that plasticity during adolescence is typically experience-dependent. However, experience expectant plasticity may also take place in adolescence, especially in relation to pubertal hormones (Kolb et al., 2017).

The general argument in the literature is that the adolescent brain experiences heightened plasticity. Thus, it has often been proposed that adolescence is a sensitive period for brain plasticity (Fuhrmann et al., 2015; Larsen & Luna, 2018).

Three possible models for plasticity during adolescence have been put forth. Plasticity in adolescence could be either a 1) stand-alone period of heightened plasticity, 2) continuum of heightened plasticity from childhood, or 3) continuum of plasticity from childhood through adolescence and into adulthood. To confirm which is the most likely model for the adolescent brain, longitudinal studies or comparisons among different age groups would be needed.

It is known that different parts of the brain develop at different times and at different rates (Gogtay et al., 2004; Lebel et al., 2008; Tamnes, Bos, et al., 2018; Vijayakumar et al., 2018). While we know that certain parts of the brain are still developing in adolescence, other parts have already reached their mature structure. For example, certain white matter structures such as the corpus callosum and the inferior longitudinal fasciculus, reach their maximal FA values before adolescence. While other tracts (such as the uncinate fasciculus and the cingulum) reach their maximal FA values in early adulthood (Lebel et al., 2008). Thus, developmental trajectories differ between brain regions or tracts. It is also known that plasticity can depend on the brain region or even on a cortical layer and that it is time-dependent (Kolb & Gibb, 2014). Hence, some brain regions might exhibit heightened plasticity during adolescence while others might not. In relation to behavior, adolescence has been suggested to be a sensitive period especially for emotional, social, and cognitive development (Bossong & Niesink, 2010; Dow-Edwards et al., 2019). It may be possible that the brain regions and networks responsive to these functions might be more plastic during adolescence.

The direct evidence in humans that adolescence is a sensitive period of plasticity is still inconclusive. Longitudinal studies or comparisons between age groups are needed to provide experimental evidence of the sensitive period. Even though the direct evidence of the period of heightened plasticity is lacking, it has been shown that the adolescent brain is capable of changing in response to training. For example, musical training was found to accelerate cortical auditory responses (Tierney et al., 2015) and motor training-induced changes in the functional connectivity of the adolescent participants (Amad et al., 2017). In addition, we know that brain responses to different stimuli vary among children, adolescents, and adults (Bjork et al., 2010; Galvan et al., 2006; Geier et al., 2010). As mentioned previously, adolescence is also believed to be a sensitive period for social (Casey, 2015), cognitive (Fuhrmann et al., 2015; Knoll et al., 2016), and emotional processing (Casey, 2015; Spear, 2013). It could be speculated that brain plasticity might underlie the behavioral plasticity in adolescents. However, this also needs to be confirmed in human studies.

While direct experimental evidence concerning adolescence as a sensitive period of brain plasticity in humans is lacking, animal experiments have provided experimental evidence concerning plasticity differences between age groups. A few studies have investigated plasticity in relation to neurogenesis in adolescents. He and Crews (2007) found that neurogenesis is higher in adolescents than in adults. Later, it was found that several factors have different effects on neurogenesis depending on the age. For example, alcohol exposure during adolescence has been found to lead to persistent loss of hippocampal neurogenesis, but not so in case of adults (Broadwater et al., 2014). In addition, exercise initiated during adolescence was shown to increase markers of neurogenesis to a greater extent than adult-initiated exercise (O'Leary, Hoban, Murphy, et al., 2019). Pattwell et al. (2012) found attenuated fear-extinction learning in adolescents compared with adults and that reduced synaptic plasticity in the prefrontal regions of adolescents was related to the attenuated response. Lastly, the sensitive or more precisely, critical period for specific sensory-related brain areas appears to occur already before adolescence (De Villers-Sidani et al., 2007; Rice & Van Der Loos, 1977). Together, these animal studies indicate that heightened plasticity depends on the stimuli, region, or brain circuit. Thus, adolescence, as such, does not appear to be a sensitive period *per se*.

1.2 Physical activity, aerobic fitness, and the adolescent brain

The level of physical activity, which refers to "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985, p.126) changes considerably during adolescence (Kwan et al., 2012; Yli-Piipari et al., 2012). Recent reports suggest that only a minority of adolescents have sufficient levels of physical activity (Hallal et al., 2012). This lack of adequate physical activity has raised significant concerns as physical activity has been shown to relate to both physical and mental health in adolescents (Hallal et al., 2006). Moreover, it is not currently known if physical activity also relates to brain health in adolescents.

In addition to behavioral changes that occur during adolescence, important changes also occur in the body. While physical activity reflects the behavior, aerobic fitness refers to the capacity to perform continuous physical activity or exercise. Thus, it is a condition or adaptive state that an individual has obtained over previous months or years, partly affected by heredity. Several bodily systems, such as the skeletomuscular and cardiorespiratory systems, contribute to aerobic fitness capacity. Thus, the functional status of these systems affects the measurement of aerobic fitness (Ortega et al., 2008). In addition to physical activity, aerobic fitness is also related to adolescents' health (Janssen & LeBlanc, 2010; Ortega et al., 2008).

Physical activity and aerobic fitness are related to each other. It has been shown that vigorous physical exercise is especially needed to improve aerobic fitness (Gutin et al., 2005; Ruiz et al., 2006). Perhaps, for this reason, the terms are sometimes used interchangeably in the literature. However, as previously noted, they measure different aspects of physical performance, and they are also influenced by different factors. It has been asserted that a relatively large proportion of aerobic fitness level is explained by inheritability during adolescence (Schutte et al., 2016). However, other factors such as intrinsic motivation and environment are also important for physical activity (Da Silva et al., 2017; K. B. Owen et al., 2014; Sallis et al., 2016). Adolescence is a unique period in development, and in order to understand the role and significance of exercise-related measures on brain structure and function, it is essential to compare both behavior (physical activity) and capacity (aerobic fitness).

1.2.1 Gray matter

Participation in physical activity and aerobic fitness relates to brain structure and function at various ages (e.g., Burzynska et al., 2014; Chaddock, Erickson, Prakash, Kim, et al., 2010; Herting et al., 2014; Voss et al., 2010). However, little is known about the association of gray matter with physical activity and aerobic fitness in adolescence, especially after the onset of puberty. The brain's gray matter continues to develop during this age (e.g., Tamnes et al., 2017; Vijayakumar et al., 2016), and animal studies have indicated that brain responses to exercise might be enhanced in adolescents (Hopkins et al., 2011). Given these possibilities, adolescence might be a period during which physical activity more easily influences the brain than adulthood.

Even though some results from animal research have suggested this enhanced influence of physical activity in adolescence, this influence or even association has not been studied in humans. Instead of studying physical activity, earlier studies have focused on aerobic fitness in adolescents (Table 1). In these investigations, aerobic fitness was determined to be positively associated with the thickness of the orbitofrontal cortex in 15–21-year-old participants (N. Ross et al., 2015) and with the volume of the left rostral middle frontal cortex in 15–18-year-old males (Herting et al., 2016). Using group-wise comparisons, higher-fit participants were reported to have a larger hippocampal volume (Herting & Nagel, 2012), and larger surface areas in the right medial pericalcarine, right cuneus, and the left precuneus than in lower-fit adolescents (Herting et al., 2016).

While the amount of literature concerning adolescents is limited regarding a broader understanding of the relationship between gray matter and both physical activity and aerobic fitness, research concerning children is briefly presented here. Aerobic fitness has been associated with gray matter in several studies in children (Table 2). Research concerning the same group of 9–10-year-old children provided evidence that higher-fit children have larger hippocampal and basal ganglia subregion (putamen, globus pallidus, and left caudate) volumes (Chaddock et al., 2012; Chaddock, Erickson, Prakash, Kim, et al., 2010; Chaddock, Erickson, Prakash, VanPatter, et al., 2010). Furthermore, higher-fit children showed decreased cortical thickness in several brain regions (Chaddock-Heyman et al., 2015). Basal ganglia were also studied by Ortega et al. (2019) in 9.7 ± 0.2-year-old children. The authors found that the shapes of several basal ganglia subregions and the hippocampus were related to the fitness level of the participants. In overweight and/or obese children, recent studies have proposed a relationship between aerobic fitness and brain volumes in specific cortical regions and with the average cortical thickness (Esteban-Cornejo et al., 2017; Esteban-Cornejo, Mora-Gonzalez, et al., 2019).

Concerning physical activity, a large cross-sectional study showed that participation in sports is related to larger hippocampal volumes in 9–11-year-old children (Gorham et al., 2019). In addition, self-reported physical activity in 6–10-year-old children was related to larger cortical thickness in the precentral gyrus (López-Vicente et al., 2017).

In children and adolescents, more evidence has been presented concerning aerobic fitness than physical activity. These earlier results indicate that associations between aerobic fitness and gray matter properties are specific and that not all brain regions are associated with aerobic fitness. Interestingly higher aerobic fitness was found to be related to decreased cortical thickness in several regions (Chaddock-Heyman et al., 2015), although higher self-reported physical activity was related to greater cortical thickness (López-Vicente et al., 2017). Thus, these earlier results imply that physical activity and aerobic fitness might have a differential relationship with gray matter.

Previous literature has provided important knowledge to advance our understanding of the relationship between the brain's gray matter and both physical activity and aerobic fitness in youth. Despite this, there are still several questions that remain unanswered. First, it is not yet known how physical activity is related to gray matter in adolescents. Second, earlier studies in children used questionnaires to evaluate the amount of physical activity. While questionnaires are very useful at the population level, they are, however, influenced by recall biases and other factors (Shephard, 2003). Therefore, there is a need for objective measurement of physical activity. Lastly, although valuable research has been conducted regarding the relation between aerobic fitness and gray matter during late adolescence, the period of adolescence after the onset of puberty remains to be studied.

TABLE 1 Studies on the association between aerobic fitness and gray matter in adolescents.

Reference	Age	N, % female	Measure of physical activity and/or fitness	Analysis	ROIs	Results
Herting et al. 2012	15–18 y	34, 0%	Self-reported PA (results not reported), VO2max	ROI-based volumetric analysis	Hippocampus, gray matter, total intracranial volume	CRF positively correlated with both the L and R hippocampus volume (only left when pubertal status was added as a covariate in the model). No correlations were found between CRF and total gray matter or ICV.
Herting et al. 2016	15–18 y	34, 0%	VO2max	General linear model for average cortical thickness, surface area, and volume	Whole-brain	Higher-fit showed larger R medial pericalcarine and cuneus and L precuneus surface areas than lower-fit. VO2max positively correlated with L rostral middle frontal cortical volume. No associations were found regarding cortical thickness.
N. Ross et al. 2015	15–21 y	63 obese, 43 non-obese, 58%	Six min walk test	ROI-based volumetric and cortical thickness analysis	The OFC, the anterior cingulate cortex, global	OFC thickness was correlated with better fitness. The volume or thickness of other regions was not correlated with fitness.

Note. CRF: cardiorespiratory fitness/aerobic fitness, ICV: intracranial volume, L: left, OFC: orbitofrontal cortex, PA: physical activity, R: right, ROI: region of interest

TABLE 2 Studies on the association between aerobic fitness and gray matter in children.

Reference	Age	N, % female	Measure of physical activity and/or fitness	Analysis	ROIs	Results
Chaddock et al. 2010 *	9–10 y	28 lower-fit, 21 higher-fit, 59%	VO2max	ROI-based volumetric analysis	Hippocampus, nucleus accumbens	Higher-fit children showed larger L and R hippocampal volumes than lower fit children. The volume of the L and R nucleus accumbens did not differ between groups.
Chaddock et al. 2010 *	9–10 y	30 lower-fit, 25 higher-fit, 55%	VO2max	ROI-based volumetric analysis	L and R caudate nucleus, putamen, nucleus accumbens, and globus pallidus	Higher-fit children showed larger L and R putamen and globus pallidus, and L caudate nucleus volumes than lower-fit children. No fitness-based differences in volume were found for the R caudate nucleus and nucleus accumbens.
Chaddock-Heyman et al. 2015 *	9–10 y	24 lower-fit, 24 higher-fit, 54%	VO2max	ROI-based thickness analysis	Frontal (ant., middle, sup.), parietal (sup., inf.), temporal (sup., middle, inf.), and lateral occipital regions	Higher-fit children showed decreased cortical thickness in the superior frontal cortex, superior temporal cortex, and lateral occipital cortex compared with lower-fit children. No differences in thickness between groups in anterior and middle frontal cortex, middle and inferior temporal cortex, superior parietal cortex, and inferior parietal areas.
Ortega et al. 2019	9.7±0.2 y	44, 45%	20-m shuttle run, also measured: speed agility and muscular strength ***	ROI-based shape analysis	14 nuclei: L and R accumbens, amygdala, caudate, hippocampus, pallidum, putamen and thalamus	CRF was positively associated with expansion of the L accumbens, R amygdala, R hippocampus, L globus pallidus, and bilateral putamen. Higher aerobic fitness was associated with contractions in the L accumbens and R hippocampus. CRF was not associated with the shape of caudate or thalamus, or with expansion in the R accumbens, L amygdala, L hippocampus, and R globus pallidus. The contraction in 12/14 areas did not associate with CRF.

López-Vicente et al. 2017	6–10 y	Sports participation - 911, 20% ; type of sport - 175, 0%	Self-reported PA (sports participation, type of sport)	General linear model for average cortical thickness	Whole-brain	Cortical thickness in the L precentral gyrus was positively associated with sports participation. There was a thinner cortex in boys in team sports than those in individual sports in two clusters: 1) sup., medial orbital and rostral middle frontal cortices, and 2) pars triangularis, orbitalis, opercularis, and CMFc.
Gorham et al. 2019	9–11 y	4191, 48%	Self-reported PA (No. of activities/ sports, participation in a team, individual, and structured sport)	ROI-based volumetric analysis	Hippocampus	Greater participation in every category of sport and/or activity, except for individual sports and nonsport activities, was associated with larger hippocampal volume. The number of nonsport activities and participation in an individual sport was not associated with hippocampal volume.
Esteban-Cornejo et al. 2017 **#	8–11 y	101, 39.6%	20-m shuttle run, also measured: speed agility and muscular strength ***	Whole-brain general linear model (volume)	Whole-brain	CRF was positively associated with volumes in 10 clusters located in the orbitofrontal cortex, PMc, posterior cingulate cortex, hippocampus, STG, PHG, fusiform gyrus, calcarine cortex and cerebellum VI.
Esteban-Cornejo et al. 2019 **#	8–11 y	101, 39.6%	20-m shuttle run, also measured: speed agility and muscular strength ***	ROI-based thickness analysis	R PMc, R SMc, L inferior frontal gyrus, L IFG, R PHG, R STG, R calcarine cortex, average cortical thickness, and total surface area	CRF was positively correlated with overall cortical thickness in 2/4 models. CRF did not correlate with the total surface area. CRF was not related to cortical thickness in any *a priori* defined ROI.

*Participants from the same cohort.

** Participants from the same cohort.

*** In this table, only results concerning the 20-m shuttle run are only reported.

Study concerning only overweight and/or obese participants.

Note. ant.: anterior, CMFc: caudal middle frontal cortex, CRF: cardiorespiratory fitness/aerobic fitness, IFG: inferior frontal gyrus, inf.: inferior, L: left, PHG: parahippocampal gyrus, PMc: premotor cortex, R: right, SMc: supplementary motor cortex, STG: superior temporal gyrus, and sup.: superior.

1.2.2 White matter

The brain's white matter enables the communication between distinct brain regions and is crucial for many cognitive functions including executive functions (Baum et al., 2017; Treit et al., 2014) and behavior, such as risk-taking in adolescence (Jacobus et al., 2013). Previous research have suggested that there is a link between the level of physical activity and white matter microstructure for children and older adults (Chaddock-Heyman et al., 2018; Oberlin et al., 2016; Strömmer et al., 2020; Tian et al., 2015). This association, however, remains unclear for adolescents. The generalizability of these earlier results from other age groups to adolescents is not straightforward. The brain's white matter is still developing during adolescence, and the onset of puberty has been proposed to affect neural development and plasticity (Piekarski et al., 2017). Furthermore, white matter growth differs depending on the developmental phase (childhood, middle adolescence, late adolescence) (Simmonds et al., 2014).

The earlier studies investigating the link between white matter and either physical activity or aerobic fitness in youth have focused on either childhood or late adolescence, and to the best of my knowledge, only one study has investigated adolescents. In the first study concerning adolescents, Herting et al. (2014) found that neither aerobic fitness nor self-reported physical activity was associated with the brain's white matter microstructure in a whole-brain analysis in 15–18-year-old men. The authors also conducted an exploratory analysis concerning 14 major white matter tracts and found a negative relationship between FA in the left corticospinal tract and aerobic fitness (Table 3).

Studies in children have focused both on normal weight (Chaddock-Heyman et al., 2014, 2018; Rodriguez-Ayllon, Derks, et al., 2020) and overweight and/or obese children (Esteban-Cornejo, Rodriguez-Ayllon, et al., 2019; Krafft, Schaeffer, et al., 2014; Rodriguez-Ayllon, Esteban-Cornejo, et al., 2020; Schaeffer et al., 2014). In normal-weight children (Table 3), physical activity intervention that did not affect aerobic fitness of the participants increased FA and decreased RD in the genu of the corpus callosum in the intervention group when compared to the control group (Chaddock-Heyman et al., 2018). However, the intervention did not affect axial diffusivity (AD) or any white matter properties of the other tested tracts (body and splenium of the corpus callosum, corona radiata, superior longitudinal fasciculus, posterior thalamic radiation, and uncinate fasciculus). Further, a large cross-sectional study (N = 2532) investigated the association between self-reported physical activity and white matter properties of 15 different white matter tracts. The results indicate that the total amount of physical activity was not related to the FA of any of the studied tracts but was related to the MD in several tracts (Rodriguez-Ayllon, Derks, et al., 2020). At the global level, however, the total amount of physical activity was positively related to FA.

Apart from physical activity, aerobic fitness has been shown to be positively associated with FA in the body of the corpus callosum, bilateral superior corona

TABLE 3 Studies on the association between physical activity and aerobic fitness with the white matter in normal-weight children and adolescents.

Reference	Age	N, % female	Measure of PA and/or fitness	ROIs	Results
Herting et al. 2014	15–18 y	34, 0%	Self-reported PA, VO2max, daytime activity (watch)	FMA, FMI, AF, ATR, CST, IFOF, ILF, and UNC for each hemisphere; and whole-brain analysis	A negative relationship between CRF and FA in a small portion of the L CST. Lower PA group had fewer streamlines in CST and FMI. Neither self-reported PA nor VO2 peak was associated with FA in whole-brain analysis. Self-reported PA did not correlate with FA in any of the tracts of interest. CRF was not related to any streamline measures.
Chaddock-Heyman et al. 2014	9–10 y	24, 38%	VO2max	Genu, body, and splenium of the corpus callosum, and bilateral SLF, PTR, cerebral peduncle, and corona radiata	Higher-fit children showed greater FA in the body of the corpus callosum, bilateral SCR, and bilateral SLF. Higher-fit children also had lower in RD in the SCR and SLF. No group differences were found in white matter properties in the genu and splenium of the corpus callosum, PTR, and cerebral peduncle between groups. No group differences were found in the AD in any white matter tracts.
Chaddock-Heyman et al. 2018	7–9 y	76 intervention, 67 control, 51%	VO2max (intervention)	Corpus callosum, corona radiata, SLF, PTR, and UNC	Exercise intervention increased FA and decreased RD in the genu of the corpus callosum when compared with the control group. There were no group differences in FA or RD at post-test. No effects for AD in the genu of the corpus callosum. There were no Group×Time interactions for FA in other tracts.
Rodriguez-Ayllon, Derks et al. 2020	10.12±0.58 y	2532, 50 %	Self-reported PA	Global, 15 large fiber bundles, including MCP, ML, CST, AR, ATR, STR, PTR, SLF, ILF, IFOF, UNC, CGC, CGH, FMI, and FMA	Total PA was negatively associated with MD in CST, AR, ATR, SLF, ILF, IFOF, UNC, CGC, CGH, FMI, and STR. Total PA was positively related to global FA and negatively with global AD, RD, and MD. Outdoor play was negatively associated with global RD, AD, and MD. Sport participation was positively associated with global FA and negatively with global MD and RD. There was no association between total PA and FA within individual tracts. Active commuting did not associate with any white matter measure.

Note. AD: axial diffusivity, AF: arcuate fasciculus, AR: acoustic radiation, ATR: anterior thalamic radiation, CGC: cingulate gyrus part of cingulum, CGH: hippocampal part of the cingulum, CRF: cardiorespiratory fitness, CST: corticospinal tract, FA: fractional anisotropy, FMA: forceps major, FMI: forceps minor, IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, L: left, MCP: middle cerebellar peduncle, MD: mean diffusivity, ML: medial lemniscus, PA: physical activity, PTR: posterior thalamic radiation, RD: radial diffusivity, ROI: region of interest, SLF: superior longitudinal fasciculus, STR: superior thalamic radiation, UNC: uncinate fasciculus, and WMV: white matter volume.

radiata, and bilateral superior longitudinal fasciculus, but not with the genu and splenium of the corpus callosum, posterior thalamic radiation, and cerebral peduncle in children (Chaddock-Heyman et al., 2014).

Studies on overweight or obese children have focused on specific white matter tracts (Table 4). An intervention study with 18 children (10 in the exercise group) found that an eight-month after school exercise program affected white matter properties in the uncinate fasciculus (Schaeffer et al., 2014), but not in the superior longitudinal fasciculus (Krafft, Schaeffer, et al., 2014), when compared with the control group. Krafft, Schaeffer, et al. (2014) found, however, that attendance in the exercise program was related to white matter properties in the superior longitudinal fasciculus. In a larger cross-sectional study by Rodriguez-Ayllon, Derks, et al. (2020), neither self-reported nor objectively measured physical activity was related to white matter properties of any of the seven studied tracts. However, self-reported physical activity was related to global FA. Furthermore, objectively measured physical activity was related to global FA and RD, but only when specific cut points (Hildebrand-ENMO hip cut-points) were used in the analysis of physical activity. Recently, white matter volume has also been studied in relation to aerobic fitness in overweight and obese children. Esteban-Cornejo, Rodriguez-Ayllon, et al. (2019) determined that, depending on the cohort, white matter volumes of specific tracts are related to aerobic fitness.

Overall, there seems to be some evidence to indicate that physical activity and aerobic fitness are related to white matter properties in youth. However, much uncertainty still exists about which of the brain regions are affected by physical activity or aerobic fitness. It is also worth noting that different brain areas have been investigated in different studies. Thus, there is a need for replication of earlier studies. Although the previous literature provides a good foundation, there remain gaps in the knowledge. It is not yet known whether aerobic fitness and physical activity are related to white matter in adolescents after the onset of puberty. Herting et al. (2014) have provided valuable knowledge concerning male adolescents over 15-years-old, but the period of middle adolescence remains to be studied. Lastly, to have an unbiased estimation of physical activity levels, studies using objectively measured physical activity in adolescents are needed.

TABLE 4 Studies on the association between physical activity and aerobic fitness with the white matter in obese and/or overweight children.

Reference	Age	N, % female	Measure of PA and/or fitness	ROIs	Results
Kraft et al. 2014	9.9±0.6 y	18 (10 exercise, 8 control), 50%	- (intervention)	L and R SLF	Higher attendance at the exercise program was associated with increased FA and decreased RD in the bilateral SLF (increased FA and decreased RD). PA intervention did not affect FA, MD, RD, or AD measures
Schaeffer et al. 2014	9.9±0.6 y	18 (10 exercise, 8 control), 50%	VO2max (intervention)	L and R UNC	The exercise group showed a greater positive change in bilateral UNC FA and greater negative change in L UNC RD than the control group. No significant correlations were found between changes in the FA and RD and VO2 peak. The exercise did not affect the R UNC RD.
Rodriguez-Ayllon, Esteban-Cornejo et al. 2020	10.02± 1.15 y	99, 41 %	Accelerometer measured PA (total, light, and moderate-to-vigorous) and sedentary time, self-reported PA and sedentary behavior	7 large fiber bundles (cingulate gyrus part of the cingulum, CST, FMA, FMI, ILF, SLF, and UNC), global white matter	Self-reported total and objectively measured PA (light PA, MVPA, total PA) was positively associated with global FA. Objectively measured total PA was negatively associated with global RD only when Hildebrand-ENMO cut-points were used. No association between either self-reported sedentary behavior or any PA variables with global MD/AD and tract-specific FA/MD was found.
Esteban-Cornejo et al. 2019	7–11 y	Study1=100, 40%, Study2=142, 54%	VO2max, 20-m SRT, muscular fitness(max. handgrip strength and standing long jump tests), motor fitness (4 × 10-m STR)	Whole-brain analysis	Study1: CRF was positively associated with WMV in IFOG and ITG; motor fitness was related to greater WMV in the IC, caudate, bilateral STG, and SMG; muscular fitness was associated with greater WMV in the bilateral caudate and cerebellum IX. Study2: in overweight/ obese children, CRF was positively associated with WMV in ITG, cingulate gyrus, middle occipital gyrus, and FG. No correlation between CRF and WMV among normal-weight children was found.

Note. AD: axial diffusivity, CRF: cardiorespiratory fitness, CST: corticospinal tract, FA: fractional anisotropy, FG: fusiform gyrus, FMA: forceps major, FMI: forceps minor, IC: insular cortex, IFOG: inferior fronto-opercular gyrus, ILF: inferior longitudinal fasciculus, ITG: inferior temporal gyrus, L: left, MD: mean diffusivity, PA: physical activity, R: right, RD: radial diffusivity, ROI: region of interest, SLF: superior longitudinal fasciculus, SMG: supramarginal gyrus, SRT: shuttle run test, STG: superior temporal gyrus, UNC: uncinate fasciculus, and WMV: white matter volume.

1.2.3 Functional connectivity

~~The~~ relationship between aerobic fitness and physical activity with resting state functional networks during development is still poorly understood. To date, only two studies have investigated this. Krafft, Pierce, et al. (2014) examined the effect of an eight-month after school aerobic exercise training program on functional connectivity in overweight 8–11-year-old children. They found that synchrony decreased in the default mode, cognitive control, and motor networks in the exercise group compared with the control group. Increased synchrony in the exercise group was only found between the motor network and a frontal region. Y. J. Kim et al. (2015) used an exploratory cross-sectional approach and studied the differences in functional connectivity between the cerebellum and the rest of the brain in children practicing taekwondo and controls. They found that children practicing taekwondo had increased connectivity between the cerebellum and the right inferior frontal gyrus. In addition, increased amplitude of low-frequency fluctuations, which estimates the magnitude of slow fluctuations, was found in the taekwondo group in the right frontal precentral gyrus compared with controls. It is difficult to make strong claims about the relationship between physical activity and functional connectivity in youth based on these results. The number of subjects in these studies was relatively small (13 participants in the exercise group in Krafft, Pierce et al. [total n=22] and in 15 in the taekwondo group in Y.J. Kim et al. [total n=28]), and the latter study did not correct for multiple comparisons.

These studies indicate that physical activity and/or aerobic fitness could link to the brain's functional connections in youth. To confirm this in adolescents, larger sample sizes and adolescent participants are needed. This is especially relevant in respect to adolescence since altered functional connectivity has been linked to psychopathology in adolescents (Ernst et al., 2015).

Although few data exist about the relationship of physical activity and aerobic fitness with the brain's functional connections in youth, several interventions and cross-sectional investigations in adults have demonstrated this relationship (Boraxbekk et al., 2016; Ikuta & Loprinzi, 2019; Talukdar et al., 2018; Tozzi et al., 2016; Voss et al., 2016). Furthermore, executing movements is linked with functional connectivity in the brain (e.g. Deng et al., 2016; Lv et al., 2013). Thus, experimental evidence suggests that physical behavior can modify the brain's functional connectivity, but this remains to be shown in adolescents.

1.3 Core executive functions in adolescents

Executive functions refer to "a family of top-down mental processes needed when you have to concentrate and pay attention, when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible" (Diamond, 2013). They may be further divided into core executive functions and higher-order executive functions (Diamond, 2013; García-Madruga et al., 2016).

Diamond (2013) indicates that there is a general agreement that core executive functions include inhibition, interference control, working memory, and cognitive flexibility. However, more recently, some different views of the specific cognitive functions included in core executive functions have been presented (García-Madruga et al., 2016). The importance of core executive functions in adolescents is also widely recognized, and they have a critical role in everyday life, such as in school success (Abreu-Mendoza et al., 2018; Gathercole et al., 2004; Poon, 2018), mental health (Fairchild et al., 2009; Peeters et al., 2014; Rodrigue et al., 2019), and social functioning (Hilton et al., 2017; Holmes et al., 2016). In this thesis, core executive functions were examined due to their importance in various aspects of life including academic achievement (Best et al., 2011), health (Allan et al., 2016) and behavioral control (Denson et al., 2011), and although the earlier evidence is inconsistent, these functions have been associated with physical activity and aerobic fitness in different age groups. Furthermore, as described in the following section, these functions are still developing during adolescence. This dissertation focuses on core executive functions: inhibition, working memory, and attention.

1.3.1 Inhibition, working memory, and sustained attention

Inhibition refers to “ignoring a stimulus that is competing for attention to enable focus on goal - relevant information” (Nigg, 2017). Thus, inhibitory control makes it possible to resist, for example, internal impulses and external stimuli to achieve goals. It is important for cognitive functions, including reading and math performance (Brookman-Byrne et al., 2018; Kieffer et al., 2013) as well as health and wealth, throughout life (Moffitt et al., 2011). Although inhibition appears to develop strongly in childhood (Cragg & Nation, 2008), it has also been reported to continue to mature during adolescence (Bodmer et al., 2018; Luna, 2009; Luna et al., 2004). Due to its importance in everyday life, intervention studies have been conducted to improve inhibition. Some of these training studies have shown potential in improving inhibition. However, future studies are needed to specify how long-lasting these improvements are and the properties of an optimal training program (for reviews see Diamond, 2013; Diamond & Lee, 2011; Diamond & Ling, 2016; Verburgh et al., 2014).

The second core executive function investigated in the current study is working memory. Working memory refers to storing and processing information in the mind (Baddeley & Hitch, 1974). It is also needed for higher-order cognitive skills such as reasoning and problem-solving (Chuderski & Jastrzebski, 2018; Dehn, 2017; Fung & Swanson, 2017; Simms et al., 2018). Like inhibition, working memory performance has also been shown to further develop in adolescence, and this prolonged development has been linked to brain development (Cowan, 2016; Gómez et al., 2018; Sowell et al., 2001; Ullman et al., 2014). Several intervention studies have also been conducted to investigate whether working memory capacity could be enhanced by training. While increases in working memory performance have been observed after training, the effects appear to be short-lasting and the transfer effect to other skills inconsistent (for reviews see Constantinidis

& Klingberg, 2016; Karbach & Unger, 2014; Melby-Lervåg & Hulme, 2013; Sala & Gobet, 2020).

Sustained attention can be defined as maintaining sensitivity to detect unpredictable incoming stimuli for prolonged periods of time (Sarter et al., 2001). It is a part of attentional control and has an important role in learning as well as in academic achievement (L. C. Erickson et al., 2015; Lehman et al., 2010). Furthermore, it is thought to be closely associated with working memory performance (Awh et al., 2006; Libedinsky & Fernandez, 2019; Silver & Feldman, 2005). The developmental studies have revealed that sustained attention matures later than some executive functions and is still developing during adolescence (Boelema et al., 2014; Fortenbaugh et al., 2015; Thillay et al., 2015). This prolonged development has also been linked to the development of frontal brain areas (Boelema et al., 2014). While more studies are still needed, it seems that sustained attention can be improved with training (MacLean et al., 2010; O'Connell et al., 2008; Ziegler et al., 2019).

1.3.2 Core executive functions and white matter in adolescents

As described earlier, white matter works as the brain's structural network that enables the communication among distinct brain regions. Neuroimaging studies have shown that, during cognitive functioning, such as working memory, inhibition, and attention, many separate brain regions are activated (e.g. Zhang et al., 2017). This implies that communication between these regions is crucial for these functions. Indeed, several studies have examined whether the properties of these tracts enabling the communication between distinct regions are related to the cognitive performance itself.

Multiple brain regions and networks are involved in inhibitory control (Zhang et al., 2017). Specific white matter tracts that contribute to inhibition during adolescence have been investigated in many studies. The regions that were determined to be related to inhibition varied between these studies (Fjell et al., 2012; Liston et al., 2006; Madsen et al., 2010; Seghete et al., 2013; Tamnes et al., 2012; Treit et al., 2014). This can be partly explained by the different ROIs in the studies. Overall, however, evidence suggests that from childhood to early adulthood increases in FA are associated with better inhibition performance (Fjell et al., 2012; Liston et al., 2006; Madsen et al., 2010; Seghete et al., 2013; Tamnes et al., 2012). However, Treit et al. (2014) reported that, in 5–16-year-old children and adolescents, worse inhibition performance was associated with higher FA in frontal and posterior white matter. When different developmental stages were compared, the results also differed to some extent. Fjell et al. (2012) did not find significant associations between white matter and inhibition performance during middle adolescence, while Seghete et al. (2013) demonstrated one. Furthermore, the relationship between inhibition and white matter might be different in early and late adolescence (Simmonds et al., 2014).

The relationship between working memory and white matter has been studied quite extensively in adolescents (e.g., Bathelt et al., 2018; Krogsrud et al., 2018; Nagy et al., 2004; Østby et al., 2011; Peters et al., 2012; Treble et al., 2013; Ullman & Klingberg, 2017; Vestergaard et al., 2011). The results indicated that the properties of many white matter tracts including the inferior longitudinal fasciculus (Krogsrud et al., 2018), uncinate fasciculus (Krogsrud et al., 2018), superior longitudinal fasciculus (Østby et al., 2011; Peters et al., 2012), corpus callosum (Bathelt et al., 2018; Nagy et al., 2004; Treble et al., 2013), and forceps major (Krogsrud et al., 2018), are associated with working memory performance. It should be noted, however, that since these studies mainly focus on *a priori* defined ROIs that differ among these studies, only some of the results were replicated. When looking at developmental differences in the relationship between working memory and white matter, this relationship was found to be more pronounced in childhood than in adolescence (Bathelt et al., 2018; Ullman & Klingberg, 2017). Longitudinal studies have also been conducted to determine if the changes in working memory performance relate to changes in white matter. Krogsrud et al. (2018) found that enhancement in visuospatial working memory was associated with decreased MD, RD, and AD in inferior longitudinal fasciculus, uncinate fasciculus, forceps major, and the inferior fronto-occipital fasciculus. Furthermore, future working memory capacity could be predicted by white matter FA in the fronto-parietal and fronto-striatal tracts (Darki & Klingberg, 2015). Based on these pieces of evidence, it appears that the white matter properties of specific tracts are related to working memory in adolescence.

Concerning sustained attention, less is known of its relation to white matter microstructure in adolescents. Stave et al. (2017) reported that sustained attention was associated with white matter properties of anterior, posterior, and superior corona radiata in 4–17-year-old children and adolescents. Furthermore, sustained attention was related to white matter microstructure in tracts between the caudate and dorso-lateral prefrontal cortex (H. L. Chiang et al., 2015). However, no associations were found between white matter and sustained attention in healthy 12–18-year-old adolescents (Vollmer et al., 2017), or in 6–19-year-old children after controlling for age (Mabbott et al., 2006). Overall, the evidence concerning the relationship between sustained attention and white matter in adolescents is still scarce, and more studies are needed to better understand this possible relationship.

1.4 Relationships between physical activity and aerobic fitness with core executive functions in adolescents

In recent years, the relationship between physical activity and aerobic fitness with cognition have attracted wide interest. Much research has been conducted to elucidate this relationship (for reviews see Álvarez-Bueno et al., 2017; Bherer et al., 2013; Esteban-Cornejo et al., 2015; Singh et al., 2018). Despite this interest, the number of studies investigating adolescents, especially the relation of physical activity/aerobic fitness with core executive functions in adolescents is limited. In a systematic review, Esteban-Cornejo et al. (2015) reported that five studies have found a positive association between physical activity and cognition, and only one study reported a negative association in adolescents. However, the studies in the review did not include cognitive measures considered in the current research. In a recent meta-analysis, Álvarez-Bueno et al. (2017) found that physical activity interventions had a small positive effect on inhibition and working memory. This meta-analysis included 4–18-year-old children and adolescents, but most of the studies included only children. Thus, the results might have differed if only studies with adolescents had been included.

Studies investigating the effect of physical activity intervention on core executive functions have reported different results. While two large school-based physical activity interventions (n=108 and n=632) did not find effects on working memory (Sjöwall et al., 2019) or inhibition (Sjöwall et al., 2019; Tarp et al., 2016), a smaller (n=20) school-based intervention did report beneficial effects on working memory (Ludyga et al., 2018). Furthermore, small improvements in overall executive functions were reported after an aerobic exercise program (Costigan et al., 2016).

Cross-sectional studies examining the association between physical activity and inhibition in adolescents have reported both positive associations (Lee et al., 2014; Wickel, 2017) and no associations (Pindus et al., 2015). In addition, sustained attention did not relate to physical activity in 12-year-old participants (Syväoja et al., 2014), and a positive association was reported between physical activity and working memory during late adolescence (Lee et al., 2014).

Inconsistency in the results is also present in studies that have examined the association between aerobic fitness and core executive functions in adolescents. Aerobic fitness levels were reported to be associated with inhibition task performance (Huang et al., 2015), whereas some studies have not found this association (Cancela et al., 2019; Stroth et al., 2009). In addition, concerning working memory, both significant associations (N. Ross et al., 2015) and no associations (Cancela et al., 2019) have been reported in adolescents.

Thus, the results concerning the relationship between physical activity/aerobic fitness (cross-sectional and intervention studies) and core executive functions in adolescents are to some extent contradictory. It is not yet known what the reasons are that could explain these different results. Subject-related as well as methodological factors such as differences in cognitive tests, could explain some of the observed variability in the results. Furthermore, it remains to be elucidated if brain-related factors, such as white matter properties, could also explain these inconsistent findings.

1.5 Aims of the research

This research consists of three studies that aimed to investigate the relationship of physical activity and aerobic fitness with brain structure and function in 13–16-year-old adolescents. Specifically, the purpose is to determine whether physical activity and aerobic fitness are related to the brain's regional volumes, structural connectivity, and functional connectivity. Furthermore, the aim is to study whether the white matter structural connectivity moderates the association between physical activity and aerobic fitness with core executive functions. In all three studies, physical activity was measured using accelerometers, and the level of aerobic fitness was assessed with a 20-m shuttle run test.

Study I examines how both physical activity and aerobic fitness are related to regional grey matter volumes using structural MRI. ROIs were selected based on the earlier literature (for more detailed description, please see section 2.5.1), and both cortical and subcortical regions were studied. We hypothesized that higher levels of physical activity and aerobic fitness would associate with higher volumes in basal ganglia and hippocampus.

Using diffusion MRI, **Study II** aims to identify white matter tracts that associate with physical activity and aerobic fitness. The second aim is to test whether white matter moderates the relationship between both physical activity and aerobic fitness with core executive functions. We hypothesized that the connection between physical activity and aerobic fitness with core executive functions depends on the level of white matter.

Study III investigates the associations of both physical activity and aerobic fitness with resting state fMRI. Based on the findings of **Study II**, we examined the association between physical activity and aerobic fitness with homotopic connectivity between hemispheres. Furthermore, more local aspects of functional connectivity were studied using regional homogeneity analysis. We hypothesized that aerobic fitness would be related to the homotopic connectivity of the participants.

2 METHODS

2.1 Participants

Participants (12.7–16.2-year-old adolescents, Table 5) for this research were recruited from a larger follow-up study (see Joensuu et al., 2018). Prior to participation in the MRI experiment, subjects were screened for exclusion criteria: MRI contraindications, major medical conditions, neurological disorders, medications influencing the central nervous system, and left-handedness, which was assessed by the Edinburgh Handedness Inventory during the first research visit. Furthermore, participants' pubertal development was assessed with the self-reported stage of puberty by using the Tanner scale (Marshall & Tanner, 1969, 1970). A total of 61 right-handed subjects were scanned. In **Study I**, one participant was removed from the analysis owing to excessive motion artifacts. Thus, 60 adolescents were included in the final analysis. In **Study II**, two participants did not complete a diffusion-weighted imaging protocol, and 59 subjects were included in the final analysis concerning physical activity, aerobic fitness, working memory, rapid visual information processing, and white matter measures. From the 59 subjects, 58 were analyzed for the behavioral test of response inhibition (one participant did not complete the test). A total of 59 subjects were also included in **Study III** (one subject did not finish resting state fMRI imaging protocol, and one subject was excluded due to excessive motion during scanning). The research was conducted according to the ethical principles stated in the Declaration of Helsinki, and the Central Finland Healthcare District Ethical Committee accepted the study. Before the participation, each participant and his or her legal guardian provided written informed consent. Each participant was also compensated with a 30-euro gift card for participating in the neuroimaging part of the research.

TABLE 5 Participant demographics.

	Study I		Study II		Study III	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
N(n female)	60 (40)		59 (39)		59 (39)	
Age (years)	14.3 ± 0.9	12.7–16.2	14.3 ± 0.9	12.7–16.2	14.3 ± 0.9	12.7–16.2
Pubertal stage	3.5 ± 0.9	1.5–5	3.5 ± 0.9	1.5–5	3.5 ± 0.9	1.5–5
MVPA	49.1 ± 20.0	18.0–105.9	49.1 ± 19.2	18.0–105.9	48.5 ± 19.0	18.0–105.9
20-m SRT	5.8 ± 2.4	1.5–11.6	5.7 ± 2.4	1.5–11.6	5.6 ± 2.3	1.5–11.6

Note. MVPA: moderate-to-vigorous physical activity (min/day), SD: standard deviation, SRT: shuttle run test (min)

2.2 Aerobic fitness and physical activity

The physical activity levels in the current research were measured using triaxial ActiGraph GT3X+ and wGT3X+ accelerometers (Pensacola, FL, USA). ActiGraph is the brand most frequently used by physical activity researchers over the last decade (Wijndaele et al., 2015), and thus offers an opportunity to compare the physical activity results with those of other studies as well. The participants were instructed to wear accelerometers on their right hip during waking hours for seven consecutive days (except while bathing or 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. For any 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 customized Visual Basic macro for Excel was used for data reduction. Cut-points from Evenson et al. (2008) were used to extract the amount of moderate-to-vigorous physical activity (MVPA). The 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 day × 2] / 7).

To estimate the level of aerobic fitness a 20-m shuttle run test was employed. The shuttle run test is an indirect estimate of cardiorespiratory fitness. The participants in this study were part of a large longitudinal study with hundreds of participants (Joensuu et al., 2018) in which the assessment for aerobic fitness was conducted. The performance in the 20-m shuttle run was chosen as an estimate of aerobic fitness because it is easy to implement for a large number of participants. In addition, it is a widely used test and the correlation between the 20-m shuttle run test performance and the maximal oxygen consumption as well as the reliability of this test is suggested to be relatively high (Castro-Pinero et al., 2010; Liu et al., 1992; Mayorga-Vega et al., 2015).

The maximal 20-m shuttle run 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 by 0.5 km/h per level. The duration of each level was one min. The participants were verbally encouraged to keep running throughout the test.

In addition to physical activity and aerobic fitness measures, the subjects completed a set of tests measuring muscular fitness (push-up and curl-up), flexibility (four different measurements), and fundamental movement skills (5-leap test, throwing-catching combination test), which are not included in the current research, but were utilized in the multiple imputations, as explained below.

2.3 Multiple imputation

In all three studies included in this dissertation, multiple imputations were used to compensate for the missing data that occurred in the pubertal stage, 20-m shuttle run, and MVPA. The percentage of missing values was 10% for the pubertal stage, 15% for the 20-m shuttle run test, and 22% for the MVPA. Most of the missing values were due to participant absences from school during the measurement (e.g. due to illness), or an insufficient number of measurement days for MVPA (i.e. two weekdays and one weekend day). 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 the 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, section 2.3.3), 50 imputed datasets were constructed and analyzed. These variables as well as age, gender, height, body mass index (BMI), results of throw and catch test, and grey matter volume in ROIs were used as predictors in the imputation model. 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 Multivariate Imputation by Chained Equations (mice) 2.3 package (Van Buuren & 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. A more detailed description of the multiple imputations has been described in Ruotsalainen et al. (2019).

2.4 Cognitive assessment

In **Study II**, we tested the performance in response inhibition, working memory, and sustained attention. The response inhibition was tested with a modified Eriksen Flanker task (Eriksen & Eriksen, 1974). In 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 was 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.

To assess working memory performance, the Spatial Working Memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTABeclipse version 6) was used. This task is used to assess the participants' ability to retain and manipulate visuospatial information. In this task, subjects were 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 again. The difficulty of the task increases when the choices increase from four to ten boxes.

To measure participants' sustained attention, the Rapid Visual Information Processing (RVP) task from the CANTAB test battery was used. In this task, an array of numbers from 2 to 9 was presented in a pseudo-random order (100 digits/min). The participant's task is to recognize 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.

For the CANTAB tests (working memory and sustained attention), we used principal component analysis separately for individual tests, according to Rovio et al. (2016), to reduce the number of variables. A 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 an SD of 1.

2.5 MRI measures

2.5.1 Structural MRI

Volumetric analysis of structural MRI images was used in **Study I**. The use of multiple imputation restricted the choice of analysis methods and ROI-based analysis was chosen. The following rationale was used to choose the ROIs for **Study I**. Subcortical regions involved in motor behavior were chosen as well as the hippocampus, since earlier studies have demonstrated its relation to aerobic fitness in animal and human experiments (Chaddock, Erickson, Prakash, Kim, et al., 2010; Herting & Nagel, 2012; Nokia et al., 2016). A few studies have suggested that aerobic fitness and physical activity are related to executive functions and the contribution of frontal brain regions is critical to these functions (Donnelly et al., 2016; A. M. Owen et al., 1996; Scudder et al., 2016; Vanhelst et al., 2016). For that reason, frontal brain areas that have been shown to relate to either physical activity or aerobic fitness were chosen. Lastly, two additional brain regions related to motor behavior (precentral and postcentral gyrus) were also included. The Desikan-Killiany cortical atlas (Desikan et al., 2006) was used to label the cortical regions, and FreeSurfer's (Fischl et al., 2002) subcortical segmentation was used for the subcortical regions. The volumes of the following cortical structures were chosen as ROIs: paracentral lobule, postcentral gyrus, posterior cingulate cortex, precentral gyrus, superior frontal gyrus, and lateral orbitofrontal cortex. In addition, the following three regions were calculated as a sum of two separate regions: anterior cingulate cortex (rostral anterior and caudal anterior divisions), middle frontal gyrus (rostral and caudal divisions), and medial orbitofrontal cortex (medial orbitofrontal cortex and frontal pole). The frontal pole was not treated as a single area as the reliability of the area was not measured in Desikan et al. (2006).

2.5.2 Diffusion tensor imaging (DTI)

The diffusion MRI has enabled a noninvasive method for exploring the connectivity of distinct anatomical networks within the brain. Diffusion refers to the random motion of molecules, and it describes the random motion from one spatial location to another over time. In fibrous tissues, such as the brain's white matter, the diffusion perpendicular to fiber orientation is significantly hindered when comparing diffusion along with the fiber orientation. The use of diffusion MRI allows indirect estimates of structural and geometric organization of the white matter (Le Bihan et al., 2001; Le Bihan & Johansen-Berg, 2012; Mori & Zhang, 2006).

DTI may be used to map and characterize white matter tracts. One commonly used DTI measure is FA. FA represents the degree of diffusion anisotropy and measures "the fraction of the magnitude of diffusion that can be related to anisotropic diffusion in a mean squared sense" (Papanikolaou et al., 2006). FA can be used to estimate the axonal organization because water diffuses more easily and thus more rapidly along axons than perpendicular to axons (Alexander et al., 2007; Mori & Zhang, 2006). Interpretation of the neurobiological background of FA, however, can be problematic because several factors, including myelination, extracellular water, cell membrane integrity, and the parallel arrangement of the fibers, have been proposed to explain FA (Le Bihan, 2003; Le Bihan & Johansen-Berg, 2012).

In addition to FA, three other DTI measures, namely mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were used in the current research. MD relates to the magnitude of diffusion in a voxel and describes "the overall mean-squared displacement of molecules" (Le Bihan et al., 2001). It can be calculated as a sum of the three eigenvalues divided by three (Alexander et al., 2007). The physiological diffusion processes behind MD occur on a micrometer scale. Cellular components, such as organelles, protein filaments, and membranes, hinder diffusion and therefore also reduce MD. More specifically, membrane permeability and the geometry of the membrane may have an impact on MD. In addition to these, MD is suggested to reflect extracellular space, when obtained with b of values 1000 s/mm^2 or lower (Le Bihan, 2013; Mori & Zhang, 2006).

RD refers to the average value of two perpendicular eigenvalues. Thus, it is the average of two smaller eigenvalues. RD is interpreted to indicate water diffusion perpendicular to the fibers. In the presence of fiber crossings, this interpretation could be misleading (O'Donnell & Westin, 2011). RD has been hypothesized to reflect changes in white matter pathology, and it has been proposed to demonstrate myelination. Several animal experiments indicate that RD could be used to detect myelin loss in the brain (S. Song et al., 2012; S. K. Song et al., 2002, 2003; Sun et al., 2006). However, myelination might not be the only factor that contributes to RD; other factors such as axonal density and fiber coherence (crossing fibers) may also affect RD (Budde et al., 2007; Klawiter et al., 2011; Wei et al., 2013).

AD is equal to the largest eigenvalue and it is thought to reflect the water diffusivity parallel to the axonal fiber tracts. It has been proposed that AD is a sensitive measure of white matter pathology, and changes in AD may indicate an axonal injury (Budde et al., 2007; S. K. Song et al., 2002, 2003; Sun et al., 2006). Experiments with transgenic mice have supported this view by showing that AD is sensitive to axonal integrity, compaction, and intra-axonal viscosity (Harsan et al., 2006). However, the interpretation concerning the relationship between AD and white matter pathology is somewhat complicated. In cases where the area of interest is not homogenous, crossing fibers can affect AD (Wheeler-Kingshott & Cercignani, 2009).

When interpreting the results of DTI analysis, it must be noted that the diffusion in axons occurs at the cellular level. However, in DTI, the information about diffusion is averaged over a voxel volume. In a single voxel, there may be several different fiber populations with different orientations. Thus, DTI presents only the average diffusion in a voxel (Mori & Zhang, 2006).

2.5.3 Functional connectivity

The brain is organized into connected networks and by using the resting state fMRI, which utilizes spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal, it is possible to study connectivity between spatially distinct but functionally connected brain regions. This functional connectivity refers to the statistical relationship between neurophysiological events occurring in different regions (Friston, 2011). The BOLD signal that is utilized in the functional connectivity measurements reflects changes in blood oxygenation levels. While it does not directly reflect neural activity, it has been a valuable method to explore the function and functional connectivity (Mark et al., 2015). Many different methods can be used to quantify functional connectivity. In the current research, we chose two different methods that use voxel-wise functional connectivity measures: homotopic connectivity measures and regional homogeneity.

Homotopic connectivity (also called voxel-mirrored homotopic connectivity) can be used to study functional connectivity between each voxel and its mirrored counterpart on the opposite hemisphere (Zuo et al., 2010). The corpus callosum is the main white matter structure that connects the hemispheres and the homotopic brain regions. Based on the results of **Study II**, which showed that corpus callosum white matter properties are related to aerobic fitness, we chose to study connectivity between hemispheres and, more specifically, homotopic connectivity.

In contrast to the connectivity between hemispheres, the second measure used in **Study III** was regional homogeneity. Regional homogeneity measures the statistical relationship between neighbor voxels. Thus, it measures the local functional interactions (Zang et al., 2004). Here, we measured the relationship between physical activity and aerobic fitness with regional homogeneity, using Kendall's coefficient of concordance value between each voxel's time series and those of its 26 neighbor voxels (Zang et al., 2004). This method allows measuring functional interactions between spatially nearest neighbors and is robust against noise (Jiang & Zuo, 2016).

2.6 MRI acquisition

Brain imaging data for all the studies in this research were collected at Aalto NeuroImaging, Aalto University School of Science, Finland on a 3-T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil. Total scanning time was approximately 45 min, and it included structural MRI, diffusion MRI, resting state fMRI, field mapping, and perfusion MRI scans. All scans, except perfusion MRI, were acquired using Auto Align to minimize the variation in slice positioning (van der Kouwe et al., 2005). Prior to imaging, the participants were familiarized with the measurement protocol. All participants were instructed to keep their head still during the scanning, and pads were used to minimize head motion. In addition, the participants wore earplugs to reduce the considerable noise caused by the MRI scanner.

T1-weighted structural MRI images were used in **Study I** and **Study III**. They were acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) pulse sequence. The scanning time for this sequence was 6:02 min, and the protocol included 176 sagittal slices. The images were acquired with the following parameters: inversion time (TI) = 1100 ms, repetition time (TR) = 2530 ms, echo time (TE) = 3.3 ms, voxel size = 1.0 × 1.0 × 1.0 mm^3, flip angle = 7°, slice thickness = 1 mm, field of view (FOV) = 256 × 256 × 176 mm3, and bandwidth = 200 Hz/Px, using the GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) parallel imaging technique with an acceleration factor R = 2 and with 32 reference lines.

For the diffusion-weighted imaging (DWI) in **Study II**, a spin-echo based single-shot echo-planar imaging (EPI) sequence with fat saturation was used. 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 artifacts and artifacts caused by eye motion on the imaging slices. A total of 70 slices without a 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: TR = 11,100 ms, TE = 78 ms, FOV = 212 mm, matrix size = 106, voxel size = 2 × 2 × 2 mm^3, GRAPPA acceleration = 2 and phase partial Fourier = 6/8. The total scanning time for DWI series was 15:34 min (7:47 min for each series).

Study III included a resting state fMRI scan (7:05 min). During this scan, participants were instructed to keep their eyes open and fixate on a black cross on a gray background. The resting state fMRI data was acquired with an EPI sequence with the following parameters: TR = 2610 ms, TE = 30 ms, flip angle 75˚, FOV = 210 mm, 45 interleaved axial slices, GRAPPA acceleration = 2, phase partial Fourier = 7/8, and voxel size = 3.0 × 3.0 × 3.0 mm. The scan consisted of 160 EPI volumes.

2.7 MRI image analysis

Structural MRI. During scanning, the images were inspected for motion artifacts and in the case of a large motion artifacts, the second scan was done immediately. All the images were processed with FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu). Briefly, this included processes such as removal of non-brain tissue, Talairach transformation, segmentation of the subcortical white matter, and deep grey matter volumetric structures (Fischl et al., 2002, 2004), intensity normalization, tessellation of the grey matter white matter boundary, and automated topology correction. Following the automated FreeSurfer pipeline, all reconstructed volumes were visually inspected. First, all slices were manually inspected for errors in the skull stripping, and if errors occurred, either the watershed threshold was changed, or manual edits were carried out as part of the recommended workflow for FreeSurfer. Then, white matter segmentation and pial surface were inspected. Errors were manually corrected following FreeSurfer guidelines. Estimated intracranial volume (eTIV) was calculated based on the method described by Buckner et al. (2004).

Diffusion MRI. In **Study II**, diffusion-weighted images were processed using the FMRIB Software Library (FSL) version 5.0.11 (Jenkinson et al., 2012, www.fmrib.ox.ac.uk/fsl) (for details, please see Ruotsalainen et al., 2020). Briefly, voxel-wise maps of the FA, MD, RD, and AD were obtained, and statistical analysis was carried out with Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). To test the association between both physical activity and aerobic fitness with white matter tract measures, FSL's randomise tool with 10,000 permutations was used (Winkler et al., 2014). The age, pubertal stage, and sex were used as covariates in the model. 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 $p < 0.05$. For the TBSS analysis, we used the average values of the imputed datasets (for the physical activity, aerobic fitness, and pubertal stage). The analysis pipeline is available at Open Science Framework (https://osf.io/rg6zf/).

Resting state fMRI. The image analysis is briefly described here; for full details of the image analysis, please refer to original **Study III**. The resting-state fMRI data were preprocessed using fMRIPrep 1.4.1 (Esteban et al., 2019). Following the fMRIPrep preprocessing, the whole-brain masked resting state fMRI data were detrended, band-pass filtered (0.008–0.08 Hz), confounds regressed, and standardized with nilearn.image.clean_img (version 0.2.5). The participant was excluded from the analysis if there were less than four mins of data that had framewise displacement smaller than 0.5 mm or DVARS < 2 (Power et al., 2012). One subject was removed based on these criteria. Regional homogeneity was examined using Kendall's coefficient of concordance value between each voxel's time series with that of its 26 neighbor voxels using the 3dReho tool from the Analysis of Functional NeuroImages (AFNI) software suite (Cox, 1996; Zang et al., 2004). Subsequently, the individual ReHo maps were standardized into z-values and spatially smoothed with a 6 mm kernel. The voxel-mirrored homotopic connectivity (VMHC) was calculated according to the pipeline provided by The Configurable Pipeline for the Analysis of Connectomes (C-PAC) (Craddock et al., 2013; Zuo et al., 2010), excluding the preprocessing steps which were done as described above. Before the VMHC analysis, the resting state fMRI images were spatially smoothed with a 6 mm kernel. To test the relationship of both physical activity and aerobic fitness with regional homogeneity and VMHC, 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 TFCE and family-wise error correction – a threshold of $p < 0.05$. The code used for ReHo and VMHC analysis is available at https://osf.io/ydwhz/.

2.8 Regression and moderation analyses

In **Study I**, the associations between the brain's volumetric measures and both physical activity as well as aerobic fitness was assessed with multiple linear regression. The predictors, which were entered simultaneously into the model, were either physical activity or aerobic fitness and age, sex, pubertal stage, and estimated intracranial volume. BMI was not included as a covariate as there were no associations between BMI and any of the ROIs, and adding BMI as an additional covariate did not affect the results. Assumptions of linearity, normality, homoscedasticity, and multicollinearity were checked. Due to the restrictions imposed by the use of multiple imputation, instead of whole-brain analysis, we used ROI-based analysis. The relationship between either physical activity or aerobic fitness and grey matter volumes has not been previously studied in this age group. Therefore, we included a more comprehensive set of brain regions in the analysis. To balance between false positives and false negatives, a false discovery rate (FDR) threshold of 0.1 was considered noteworthy (Yekutieli & Benjamini, 1999).

In **Study II,** we used multiple linear regression to analyze the associations of core executive functions (inhibition, working memory, sustained attention) with both physical activity and aerobic fitness. The regression model used to predict performance in core executive functions was the same as in **Study I**, excluding the intracranial volume. Thus, predictors were physical activity or aerobic fitness, age, sex, and pubertal stage. Assumptions of linearity, homoscedasticity, normality, and multicollinearity were tested. To correct for multiple comparisons, FDR was used and results with an alpha level smaller than 0.05 after the FDR adjustment was considered noteworthy.

In **Study II**, we conducted an exploratory analysis to test whether the FA of predetermined white matter tracts moderated the association of either physical activity or aerobic fitness with core executive functions. Based on previous literature that had investigated the relationship between either aerobic fitness or physical activity with white matter FA in young participants, we used the following white matter tracts as ROIs: the body and genu of the corpus callosum, the bilateral superior corona radiata, the bilateral superior longitudinal fasciculus, and the bilateral uncinate fasciculus (Chaddock-Heyman et al., 2014, 2018; Schaeffer et al., 2014). 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 ROI. For the moderation analysis, we used the same model for assessing the associations between core executive functions and physical activity/aerobic fitness; however, the main effect of the FA and an interaction term (FA*MVPA or FA*aerobic fitness) was added to the model. 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. The results with an alpha level smaller than 0.05 were considered noteworthy.

3 OVERVIEW OF THE RESULTS OF THE ORIGINAL STUDIES

3.1 Study I: Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents

The aim of this **Study I** was to investigate the relationship of the brain's gray matter volumes with both aerobic fitness and physical activity in adolescents. The association between specific ROIs and both physical activity and aerobic fitness was explored using multiple linear regression controlling for sex, age, pubertal stage, and eTIV. Analysis revealed two ROIs that showed a noteworthy association with aerobic fitness (Figure 1). First, aerobic fitness was negatively associated with the volume of left superior frontal gyrus volume (FDR-adjusted $p = 0.020$). The regression model predicted a 500 mm^3 decrease in volume for each extra min in the 20-m shuttle run test (formula: 22.3 − 0.5 [shuttle run in min] − 0.83 [age in years] + 2.35 [gender; 0 = female, 1 = male] − 0.07 [pubertal stage; Tanner score from 1−5] + 0.013 [eTIV in cm^3]). Second, aerobic fitness was positively associated with left pallidum volume (FDR-adjusted $p = 0.069$). For the left pallidum volume, the regression model predicted a 48 mm^3 increase in volume for each extra minute in shuttle run test (formula: 1.87 + 0.05 [shuttle run] − 0.11 [age] − 0.03 [gender] + 0.02 [pubertal stage] + 0.001 [eTIV]). We did not find evidence of an association between MVPA and any ROI. The correlation between the 20-m shuttle run and MVPA was $r = 0.45$ ($p = 0.001$). These results indicate that, even though aerobic fitness and physical activity are related to each other, they show a differential association with brain volumes.

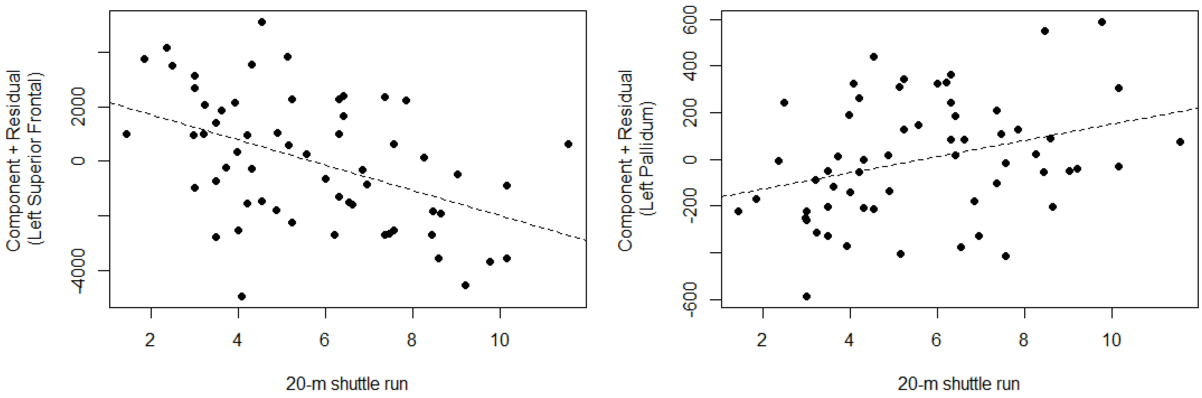

FIGURE 1 Partial residual plots for the relationship between the left superior frontal gyrus volume and the 20-m shuttle run (left graph) and the left pallidum volume and the 20-m shuttle run (right graph) (from Ruotsalainen et al., 2019).

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

The main objective of **Study II** was to investigate the relationship of aerobic fitness and physical activity with the brain's white matter. The first aim was to study how different white matter measures (FA, MD, RD, and AD) are related to aerobic fitness and physical activity. Furthermore, this research examined whether white matter FA moderated the relationship between physical activity and aerobic fitness with core executive functions. This second investigation sought to obtain data that would help to understand variability in research concerning the relationship between aerobic fitness and physical activity with core executive functions.

The TBSS analysis revealed a positive association between aerobic fitness and several white matter tracts (Figure 2, Table 7). Higher aerobic fitness was associated with larger FA in eight clusters of which the centers of mass localized to the left and right superior corona radiata and the body of the corpus callosum (Table 7). In addition, higher aerobic fitness was related to smaller MD, RD, and AD in several white matter areas, such as the corpus callosum and the bilateral superior corona radiata (see Table 7 for details on all the clusters and tracts associated with FA, MD, RD, and AD). We did not find noteworthy correlations between physical activity and white matter properties. The correlation between the 20-m shuttle run and MVPA was r(57) = 0.48, p = 0.0001. All statistical maps can be found in our Neurovault collection at https://neurovault.org/collections/5206/ (Gorgolewski et al., 2015).

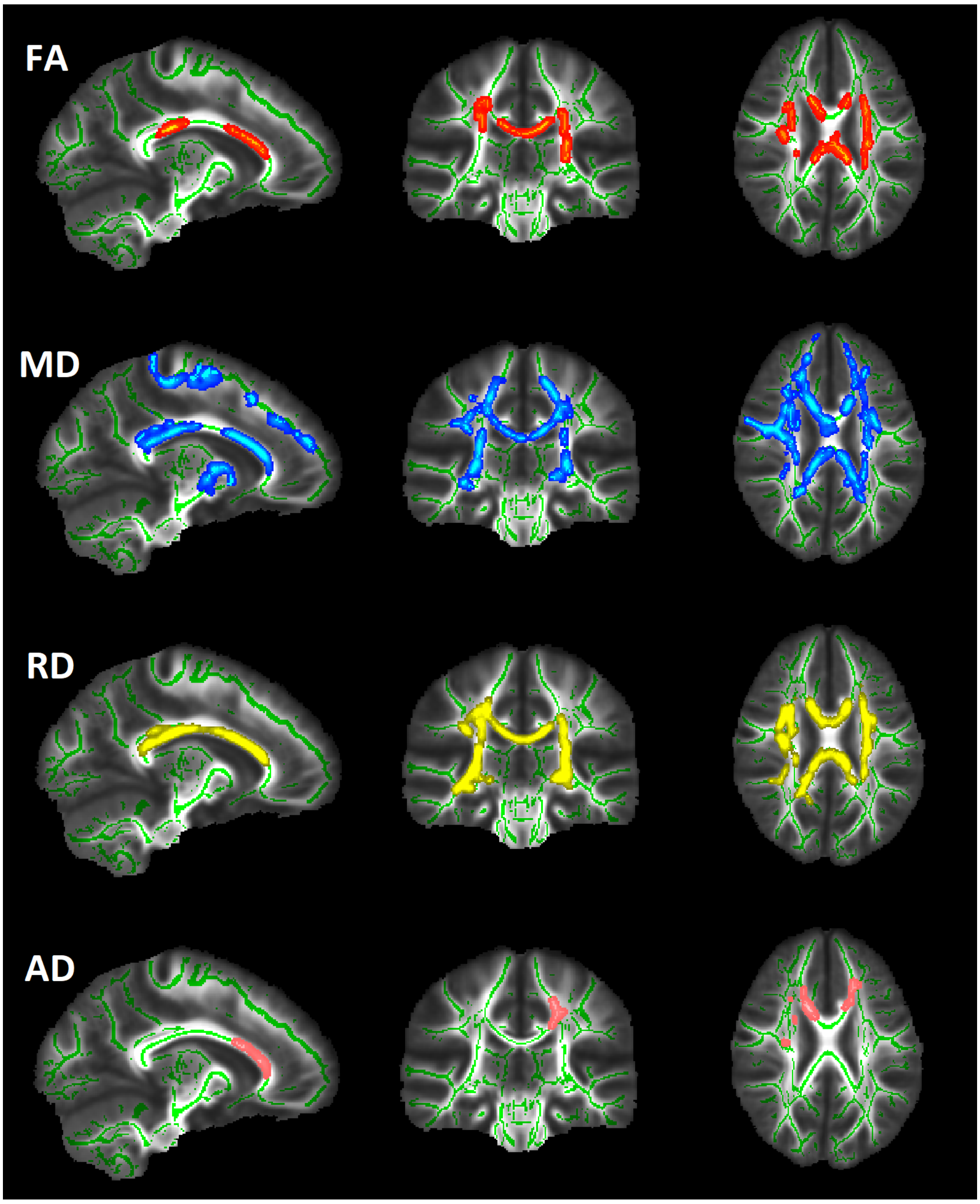

FIGURE 2 Correlations ($p < 0.05$, family-wise error and TFCE corrected) between aerobic fitness and FA (red), MD (blue), RD (yellow), and AD (pink). The results are overlaid on an MNI152 1-mm template (coordinates: –12, –24, and 25). The correlation between aerobic fitness and FA was positive and it was negative between aerobic fitness and MD, RD, and AD. The significant regions are thickened for illustrative purposes. AD: axial diffusivity, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity (from Ruotsalainen et al., 2020).

TABLE 6 Characteristics of white matter clusters correlated with aerobic fitness (modified from Ruotsalainen et al. 2020).

Measure	Cluster size (voxels)	Anatomica location of clusters (center of mass)	t	p-value	MNI coordinates		
					X	Y	Z
FA	801	SCR L[A]	2.39	0.025	−25.4	−12.1	26.5
FA	563	SCR R[B]	2.34	0.037	27.6	−17.2	32.2
FA	431	SCR[C]	2.36	0.039	−1.5	14.9	20.4
FA	319	Body of CC[D]	2.34	0.044	−4.15	−24	26.7
FA	83	SCR R[E]	2.51	0.047	24.3	11.2	30.6
FA	25	Unclassified[F]	2.09	0.05	30.5	6.84	25.6
FA	2	SCR R	3.29	0.05	22.5	−14.5	35.5
FA	1	SCR R	3.43	0.05	21	−13	35
MD	15494	Body of CC[G]	1.99	0.03	1.92	−4.17	28.4
RD	7674	Unclassified[H]	2.02	0.032	9.33	−15.6	25.6
AD	2117	ALIC R[I]	1.85	0.026	21.9	20.3	10.1
	980	Body of CC[J]	1.85	0.031	−17.8	5.9	32.5
	67	Unclassified	3.02	0.046	33.9	21.6	19.3
	34	Unclassified	3.14	0.047	16.6	21.1	38.9

JHU ICBM-DTI-81 tracts (% of voxels)

[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)

The MNI coordinates indicate the anatomical location of the center of mass for each cluster. The p-values were derived from the clusters and are TFCE and family-wise error rate corrected. 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 with which 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.

ACR: anterior corona radiata, AD: axial diffusivity, ALIC: anterior limb of internal capsule, CC: corpus callosum, FA: fractional anisotropy, L: left, MD: mean diffusivity, PCR: posterior corona radiata, PLIC: posterior limb of internal capsule, PTR: posterior thalamic radiation, R: right, RD: radial diffusivity, RLIC: retrolenticular part of internal capsule, SCR: superior corona radiata, SFOF: superior fronto-occipital fasciculus, and SLF: superior longitudinal fasciculus.

Concerning correlations between aerobic fitness and physical activity with core executive functions, we did not find significant correlations after correcting for multiple comparisons.

The exploratory moderation analysis revealed that white matter FA in the body of the corpus callosum and the right superior corona radiata moderated the relationship between the 20-m shuttle run performance and spatial working memory. 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. A follow-up simple slope analysis showed that with FA values in the body of the corpus callosum, aerobic fitness was negatively associated with working memory (Figure 3), whereas, with low FA values, there were no significant associations between aerobic fitness and working memory. Regarding physical activity, with low FA values in the body and genu of the corpus callosum, physical activity was positively related to working memory. However, physical activity was not associated with working memory with high FA values. We did not find evidence of white matter moderation on the connection between other core executive functions and either physical activity or aerobic fitness.

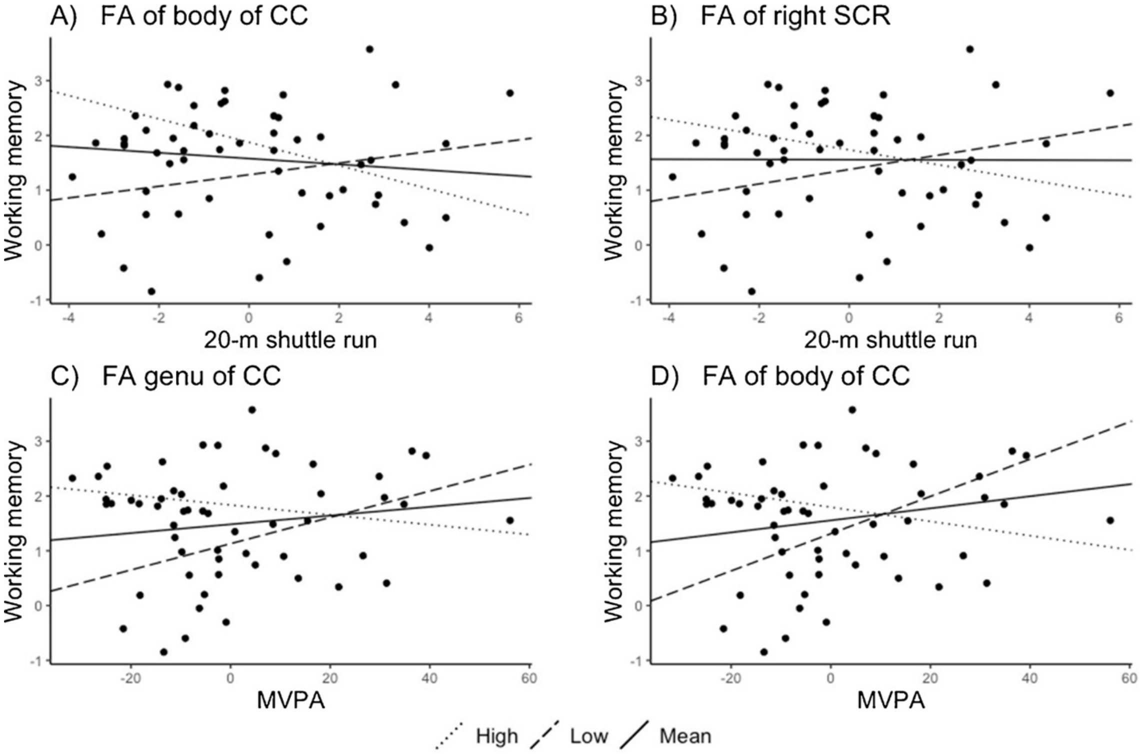

FIGURE 3 The moderating effect of FA of (High: ± 1 SD, Low: ± 1 SD) (A) the body of CC, and (B) the SCR regarding the relationship between working memory and the 20-m shuttle run performance. The moderating effect of FA of (C) the genu and (D) the body of CC regarding the relationship between working memory and the MVPA. CC: corpus callosum, FA: fractional anisotropy, MVPA: moderate-to-vigorous physical activity, SCR: superior corona radiata, and SD: standard deviation (from Ruotsalainen et al., 2020).

3.3 Study III: Physical activity relates to increased local functional connectivity in adolescents

Study III examined the connection between physical activity and aerobic fitness with both local and interhemispheric functional connectivity, measured with regional homogeneity and VMHC, respectively. Regional homogeneity analysis showed that a higher level of MVPA was correlated to increased regional homogeneity in a cluster located mainly in the right supramarginal gyrus, after TFCE and family-wise error correction (Figure 4, Table 8). We did not find a significant association between aerobic fitness and regional homogeneity (Figure 5). Concerning interhemispheric functional connectivity, we did not find strong evidence of the association between VMHC and either physical activity or aerobic fitness.

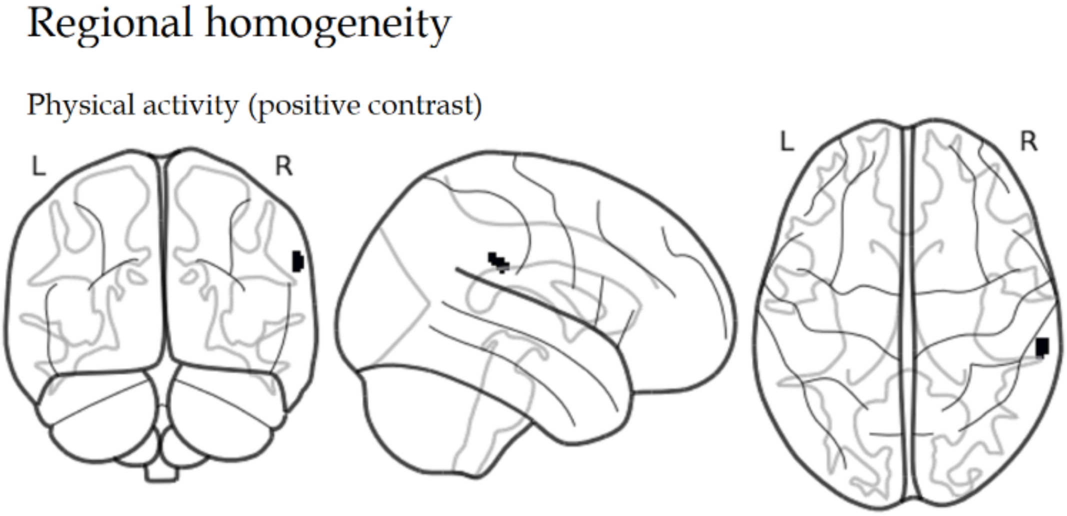

FIGURE 4 Group-level thresholded map of the positive correlation between MVPA and ReHo ($p < 0.05$, TFCE and family-wise error corrected). L= left, R= right. The colored region represents the region significantly correlated with physical activity.

TABLE 7 Cluster details for the positive correlation between physical activity and ReHo.

Cluster size (voxels)	Structures to which the cluster belongs to (% of voxels)	p-value	MNI coordinates		
			X	Y	Z
33	Supramarginal gyrus (51.8), planum temporale (10.0), superior temporal gyrus (7.8), parietal operculum cortex (6.6), angular gyrus (0.2)	0.035	65.2	–32	30.8

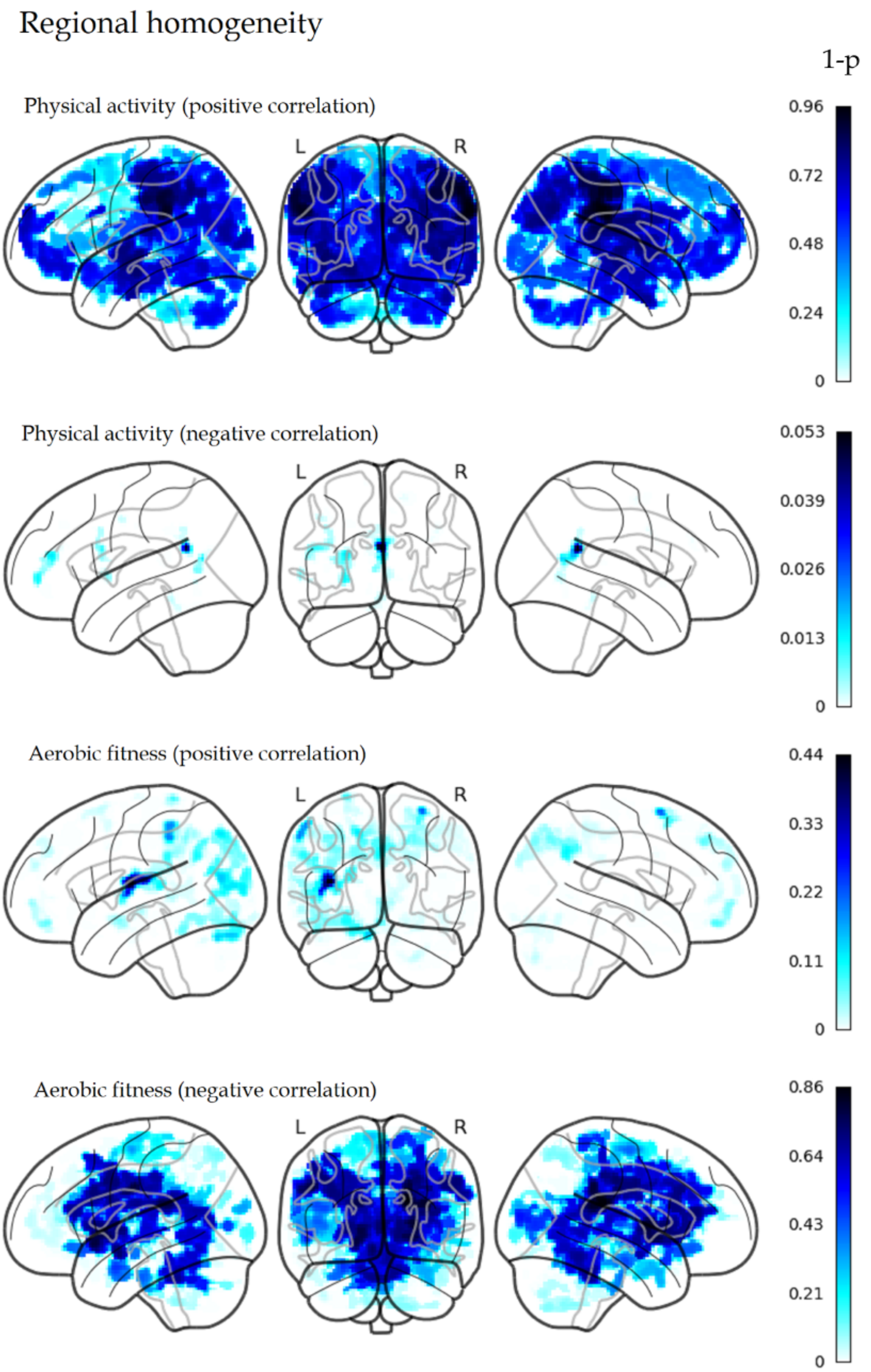

FIGURE 5 Group-level 1-p-value maps (unthresholded) of positive and negative contrasts (correlations) between physical activity and aerobic fitness with ReHo. The colorbar indicates the 1-p-value. Thus, darker values are the smaller p-values, and lighter values indicate larger p-values. L = left, R =right.

4 DISCUSSION

4.1 Study I: Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents

In **Study I,** we examined the association between physical activity and aerobic fitness with *a priori* defined cortical and subcortical volumes in adolescents. We found a negative correlation between aerobic fitness and the left superior frontal gyrus volume and a positive correlation between aerobic fitness and the left pallidum volume. We did not find evidence of the relationship between physical activity and any ROI. Overall, these findings imply that, although aerobic fitness and physical activity are related to each other, they show a differential association with the brain's regional volumes in adolescents.

Relatively few studies have investigated the association between either physical activity or aerobic fitness with gray matter volumes in youth. Our finding regarding the negative correlation between aerobic fitness and the left superior frontal cortex volume is partly in line with previous studies concerning young participants. Chaddock-Heyman et al. (2015) found a similar association between aerobic fitness and the thickness of this area in preadolescent children. However, 15–18-year-old males showed a positive association between aerobic fitness and both the left rostral middle frontal cortex and bilateral hippocampus (Herting et al., 2016; Herting & Nagel, 2012). Taken together, these earlier investigations and our results imply that the association between aerobic fitness and superior frontal cortex exists only in childhood to middle adolescence, but it may not be so prominent in late adolescence.

Frontal brain regions are suggested to develop relatively late and undergo decreases in volume and thickness during adolescence (Giedd et al., 1999; Gogtay et al., 2004). Interestingly, recent findings indicate that the largest decreases in cortical thickness during adolescence take place in the superior frontal cortex (Teeuw, Brouwer, Koenis, et al., 2019). Furthermore, it was reported that the changes in the superior frontal cortex in 12–17-year old participants were under strong genetic control (Teeuw, Brouwer, Koenis, et al., 2019). Moreover, while it has been proposed that aerobic fitness is also under strong genetic control (Bouchard et al., 2011; R. Ross et al., 2019), shared genetic factors underlying aerobic fitness and superior frontal cortex development, could at least partly explain the current finding.

In addition to the negative correlation with the left superior frontal cortex, aerobic fitness was positively correlated with the left pallidum volume in this study. The pallidum is part of the basal ganglia and it is involved in regulating motor activity. Aerobic fitness has been previously associated with the shape (Ortega et al., 2019) and the volume of the pallidum (Chaddock et al. 2012) in preadolescent children. The results of this study indicate that this association also occurs in adolescents.

We could not find evidence of the relationship between MVPA and brain volumes in any ROI. This is in agreement with findings from Herting et al. (2016), who did not find an association between self-reported physical activity and either surface area or volume in any region included in the current study.

Our results show that physical activity and aerobic fitness are differently related to regional brain volumes in adolescents. This differential association in adolescents could reflect a role of genetic factors, as mentioned above. Furthermore, individual differences in responses to physical activity could also explain why we did not see an association regarding physical activity. It is well known that individuals differ in their responses to exercise or physical activity. Thus, even though the intensity, frequency, and duration of exercise are the same, the individuals may have different physiological responses to the exercise (Bonafiglia et al., 2016; Bouchard et al., 1999; Bouchard & Rankinen, 2001; Montero & Lundby, 2017). Aerobic fitness is, at least partly, an outcome of long-term physical activity or exercise, and it is therefore influenced by individual responsiveness. On the contrary, the level of physical activity does not provide information about the responsiveness. It is plausible that the long-term brain responses to physical activity also show this individual responsiveness, implying that even though the level of physical activity is the same, the possible effects to the brain might differ between individuals.

The results of this study revealed that physical activity and aerobic fitness show differential associations with brain regional volumes, highlighting the importance of measuring these both to demonstrate the relationship of physical behavior vs. physical capacity with brain properties. Furthermore, previous studies concerning young participants have concentrated on the preadolescent children and males during late adolescence. Thus, this study provides new evidence concerning a previously understudied age group of both females and males during early and middle adolescence.

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

Study II aimed to investigate 1) the association between physical activity and aerobic fitness with white matter properties, and 2) whether the white matter FA moderates the connection between physical activity and aerobic fitness with core executive functions. We found that aerobic fitness was positively correlated with the white matter FA most robustly in the body of the corpus callosum and the superior corona radiata. Furthermore, aerobic fitness was negatively associated with white matter MD, RD, and AD. The association concerning MD and RD was more widespread than for FA and included several white matter tracts. We did not find evidence of the association of physical activity and any white matter measure. However, the exploratory moderation analysis suggests that white matter properties of specific tracts moderate the relationship between physical activity and aerobic fitness with working memory.

The association between either physical activity or aerobic fitness and white matter properties have been investigated in only a few studies (Table 3 and Table 4). The results regarding aerobic fitness are mostly in accordance with the results by Chaddock-Heyman et al. (2014), who found that higher-fit preadolescent children had greater FA in the superior corona radiata, the body of the corpus callosum, and the superior longitudinal fasciculus. The authors also reported that higher-fit children had lower RD in the superior corona radiata and superior longitudinal fasciculus, but the AD of any of the measured tracts did not differ between the groups. The current study found an association with the same tracts as had Chaddock-Heyman et al. (2014), although we also found more widespread associations (regarding MD and RD). This difference could be explained by the choice of the analysis approach, as the TBSS analysis enables showing associations with parts of the tracts, while the whole tract is considered when using ROI-based analysis. In adolescents, contrary to the current results, Herting et al. (2014) did not find evidence of an association between aerobic fitness and white matter FA in 15–18-year old males. This discrepancy may be explained by methodological or sample-related differences, such as age and sex of the participants. Furthermore, the method to assess the level of aerobic fitness differed between the studies.

White matter tracts associated with aerobic fitness in the present study mostly mature at an early age and are under genetic control during adolescence. Developmental studies found that tracts which were most robustly correlated with aerobic fitness in the current study (corpus callosum, superior corona radiata), develop relatively early and do not change to a large extent during adolescence (Lebel et al., 2008; Simmonds et al., 2014). Associations concerning MD and RD were more widespread and also included tracts that are still suggested to undergo changes during adolescence (such as the superior longitudinal fasciculus). However, also for MD and RD, the majority of the tracts that are associated with aerobic fitness are tracts that mature relatively early. The FA variability of these tracts appears to be under a relatively strong genetic influence during adolescence (M.-C. Chiang et al., 2011). While previous literature has demonstrated that aerobic fitness and response to exercise are partly predicted by genetic factors (Bouchard et al., 2011; R. Ross et al., 2019), a common genetic pathway might underlie aerobic fitness and white matter FA in adolescents.

The results of the current study showing no evidence of the association between physical activity and white matter properties of the brain are in agreement with previous studies in 15–18-year-old male adolescents (Herting et al., 2014) and preadolescent children (Krafft, Schaeffer, et al., 2014). Yet, contrary to our results, Chaddock-Heyman et al. (2018) reported an increase in FA of the genu of the corpus callosum after exercise intervention. However, the exercise did not affect white matter in any of the other tracts. Also, in contrast to the current results, a large cross-sectional study (n=2532) reported that self-reported physical activity was associated with the MD of several white matter tracts in 10-year-old children (Rodriguez-Ayllon, Derks, et al., 2020). Furthermore, in accordance with some earlier findings (Chaddock-Heyman et al., 2018; Herting et al., 2014), we did not find evidence of the association between physical activity and FA of the uncinate fasciculus, as suggested by Schaeffer et al. (2014) in a study with 10-year-old children. Overall, the earlier results suggest that physical activity is related to specific white matter properties during childhood; however, studies in adolescents have not found evidence of this association.

We did not find strong evidence of the association between core executive functions and either physical activity or aerobic fitness. The earlier literature concerning this relationship is contradictory (Álvarez-Bueno et al., 2017; Chaddock, Erickson, Prakash, Kim, et al., 2010; de Greeff et al., 2016; Huang et al., 2015; Stroth et al., 2009; Westfall et al., 2018) and this still remains debatable (Diamond & Ling, 2016, 2019; Hillman et al., 2018). Due to these contradictions, we conducted an exploratory moderation analysis to examine whether white matter influences the strength or the direction of the association between aerobic fitness or physical activity with core executive functions. The connection between both physical activity and aerobic fitness with working memory was moderated by white matter FA. This suggests that individual variation in the white matter FA might be a factor behind some of the earlier contradictory findings.

To investigate the moderation effect in more detail, a simple slopes analysis was conducted. It revealed that higher levels of physical activity are associated with better working memory performance only at low levels of FA in the body and the genu of the corpus callosum. However, the association at high levels of FA was nonsignificant. Regarding aerobic fitness, we found that, at high FA in the body of the corpus callosum, aerobic fitness is negatively associated with working memory. Based on these findings, the corpus callosum seems to affect the direction of the connection between working memory and both physical activity and aerobic fitness.

It is uncertain what exact mechanisms are behind the moderation effect. One possibility is synchrony-related mechanisms. Earlier findings show that brain electrophysiological synchrony is important for working memory (Miller et al., 2018) and that even small changes in white matter microstructure can influence brain synchrony (Pajevic et al., 2014). Furthermore, it is known that the corpus callosum, which is crucial in interhemispheric communication, is also important for brain synchrony (Ellis et al., 2016; Engel et al., 1991). Thus, small changes in the corpus callosum microstructure could possibly influence synchrony, which could have implications for working memory. Secondly, animal models have revealed that experience-related increases in myelination may both stabilize the connections in the brain and suppress plasticity (McGee et al., 2005). It has also been proposed that FA values in regions of coherent fiber directions (such as parts of corpus callosum) are sensitive to myelination (Chang et al., 2017).

This could imply that the higher FA values found in human studies, could potentially indicate a lower level of plasticity in regions of coherent fiber directions. It could be hypothesized, in light of the present results, that physical activity and aerobic fitness positively influence working memory only when plasticity in the corpus callosum is higher. However, this highly speculative conclusion remains to be elucidated.

Based on the current findings, physical activity does not seem to influence the brain's white matter in adolescence (or vice versa). However, higher aerobic fitness is associated with the white matter microstructure. This finding suggests that physical behavior is not important for the structural connections of the brain, but the capacity to perform physical activities appears to be. Exploratory moderation analysis revealed that the white matter moderates the connection between physical activity and aerobic fitness with working memory, suggesting that individual variation in white matter properties might affect the strength or direction of these connections. However, more studies are needed to confirm these preliminary findings, especially intervention studies to elucidate the influence of white matter to the connection between physical activity/aerobic fitness and working memory.

4.3 Study III: Physical activity is positively associated with local functional connectivity in adolescents' brains

The purpose of **Study III** was to determine associations between both MVPA and aerobic fitness with local and interhemispheric functional connectivity indicated by regional homogeneity and VMHC, respectively. Our analysis showed that physical activity, but not aerobic fitness, is correlated with regional homogeneity. The correlation was found in a small area located mainly in the right supramarginal gyrus. Surprisingly, we did not find evidence of the correlation between homotopic connectivity and either physical activity or aerobic fitness.

Previous literature shows that the execution of motor tasks is related to changes in regional homogeneity in sensorimotor brain regions (Deng et al., 2016; Lv et al., 2013). These acute associations do not, however, reveal whether continued physical performance has effects on local functional connectivity at rest. This question was recently approached in a study using an animal model for depression, which showed that physical activity (wheel running) increased regional homogeneity in several brain regions in young mice with mild stress (Dong et al., 2020). While we also found an association between physical activity and regional homogeneity, this association was not widespread. On the contrary, the current findings show that physical activity is related to local functional connectivity in a small cluster located in the right supramarginal gyrus.

In addition to involvement in higher cognitive functions such as language (Oberhuber et al., 2016; Stoeckel et al., 2009) and empathy (Silani et al., 2013), the supramarginal gyrus is also involved in proprioception (Ben-Shabat et al., 2015; Kheradmand et al., 2015), motor planning, and motor attention (Barbaro et al., 2019; Burke et al., 2013; McDowell et al., 2018; Rushworth et al., 1997). For physical activity, motor planning and attention are obviously important. During physical activity, it is also crucial to be able to sense one's own body and movement. These results could indicate that physical activity increases local functional connectivity in brain areas important for sensing and planning movements. However, to confirm the causal relationship, intervention studies are needed.

Contrary to our expectations, we did not find evidence of the correlation between homotopic functional connectivity and either aerobic fitness or physical activity. Our expectations were based on the earlier results in this same sample of adolescents showing an association between aerobic fitness and white matter microstructure in the corpus callosum. The corpus callosum's properties have been found to relate to homotopic connectivity (De Benedictis et al., 2016; Mancuso et al., 2019; Tobyne et al., 2016). However, in addition to white matter microstructure, other factors also influence homotopic connectivity. Recently, it was found that the white matter microstructure only explained at best 13 % of the variance in homotopic connectivity (Mollink et al., 2019). Furthermore, the connection between functional connectivity and white matter structural connectivity increases with age (Betzel et al., 2014), suggesting that, in later life, this connection might be stronger.

Very few studies have examined the association between either physical activity or aerobic fitness with interhemispheric functional connectivity. Our results are in agreement with a study showing no significant association between physical activity and interhemispheric connectivity in older adults (Veldsman et al., 2017). Our study is, however, not completely comparable to this earlier study, as there are several methodological and sample related differences. Nevertheless, the results of both studies indicate that there is a lack of evidence of the connection between physical activity and interhemispheric connectivity. Interhemispheric connectivity or, more precisely, homotopic connectivity was studied in relation to aerobic fitness in middle-aged participants in a recent study (Ikuta & Loprinzi, 2019). The results showed that in this age group, parahippocampal, but not hippocampal homotopic connectivity is related to aerobic fitness. We could not replicate the finding regarding parahippocampal homotopic connectivity, which might be explained by smaller sample size in the present study or that this connection is more prominent in adults than in adolescents.

Overall, our findings indicate that adolescents' physical behavior is connected with local functional connectivity in an area involved in sensorimotor functions. The lack of a noteworthy connections between aerobic fitness and either measure of functional connectivity suggests that the capacity to perform an exercise or physical activity might not be important for these types of functional communication, but behavior is. Future studies should elucidate whether there is a causal relationship between physical activity or exercise and local functional connectivity in adolescents.

4.4 Methodological considerations and limitations

Overall, the studies included in this dissertation have some limitations that need to be addressed. Some of the limitations are study-specific, while other limitations arise from the common methodological choices and sample used in this dissertation.

Firstly, in **Study I**, we used the Desikan-Killiany atlas (Desikan et al., 2006) to define the regions used in the analysis. Even though parcellations based on this atlas are relatively small, even smaller parcellations could have been more sensitive in detecting locally more precise associations. This approach, however, would have required more participants. Furthermore, the Desikan-Killiany atlas parcellations have been used relatively often in this field, and using the same parcellations enhances comparisons between studies. Secondly, in **Study II**, we utilized DTI to study white matter properties. DTI has some limitations, such as it does not take into account the possibility of crossing fibers, and by using DTI, it is difficult to make interpretations concerning underlying white matter microstructure. Nevertheless, it is a commonly used method to study white matter properties, and using it enables comparison to earlier studies in this field. Thirdly, in **Study II** and **Study III**, we used the mean of the imputed values in the analysis. It is recommended that the imputed parameters and their standard errors should be combined using Rubin's rules (Van Buuren, 2012, p. 37–38). However, due to computational restrictions imposed by DTI and functional connectivity analysis methods, we used averages of the imputed values in our analyses.

There are also a few general limitations that can be identified. Firstly, these studies estimated the level of aerobic fitness using indirect measurement (20-m shuttle run test). Recently, some questions have been raised on its validity (Armstrong & Welsman, 2019). On the other hand, earlier investigations suggest that the reliability and correlation of 20-m shuttle run test with maximal oxygen consumption is relatively high when compared with direct measurements (Castro-Pinero et al., 2010; Liu et al., 1992; Mayorga-Vega et al., 2015). Secondly, we did not include BMI as an additional covariate in the analyses. BMI is related to performance in the 20-m shuttle run test, but it seems to have a minimal effect on the correlation between shuttle run test performance and maximal oxygen consumption (Mahar et al., 2018). In addition, in **Study I**, adding BMI as an additional covariate did not change the results, and to keep the same model between the studies, BMI was not added to the models in **Study II** and **Study III**. However, when interpreting the results of this dissertation, it should be noted that our indirect measurement might yield different results than cardiorespiratory fitness estimated by dividing maximal oxygen consumption with lean body mass. Thirdly, concerning the measurement of physical activity, using different cut-points to define physical activity may yield different estimates of the amount of MVPA and limit the comparability between studies. Despite various possible cut-points, Evenson cut-points have been recommended (Trost et al., 2011). In addition, although accelerometers provide an objective measure of physical activity and are widely used, the same amount of objectively measured physical activity may produce different physiological responses for each individual. Finally, the sample size (n=58–61) may not be large enough to detect weak associations and the cross-sectional nature of the current studies does not allow us to make interpretations concerning causal relationships.

4.5 General discussion

This doctoral dissertation consists of three studies examining the association of both physical activity and aerobic fitness with the structural and functional properties of the adolescents' brains. Furthermore, the moderating effect of white matter on the associations between physical activity and aerobic fitness with core executive functions were studied. Overall, the studies show that aerobic fitness is related to the brain's structural properties, while physical activity is associated with brain function measured at rest. More specifically, aerobic fitness was related to gray matter in the left superior frontal cortex and in the pallidum, and also with the microstructure of several white matter tracts (most robustly with superior corona radiata and corpus callosum). On the contrary, we did not find evidence of the connection between physical activity and either gray or white matter measures, but it was positively related to local functional connectivity in the right supramarginal gyrus. Regarding the connection between either physical activity or aerobic fitness with core executive functions, the white matter was found to moderate the connection between both physical activity and aerobic fitness with working memory. This result implies that the level of the brain's white matter FA might explain some of the earlier contradictory findings regarding the association between physical activity and aerobic fitness with working memory.

It could be assumed that physical activity and aerobic fitness would show similar associations with brain measures, as they are connected with each other. In order to improve aerobic fitness, an individual needs to do physical activity or exercise with long enough duration, high enough intensity, and high enough frequency. In accordance with this, also in the current study, there was a moderate association between MVPA and aerobic fitness. Despite the connection between these measures, a large part of the variability in aerobic fitness is not accounted for by physical activity. It has been proposed that the differences between physical activity and aerobic fitness in adolescence could be explained by physical and behavioral changes occurring during growth and maturation as well as social and environmental factors (Cheng et al., 2014; Malina, 2001; Rhodes et al., 2018). Interestingly, earlier literature indicates that physical activity and fitness during adolescence are also differently associated with several physiological measures as well as with health risk factors (Boreham et al., 2002; Hurtig-Wennlöf et al., 2007). These earlier results and the current findings emphasize the differences in physical activity and aerobic fitness, and how these differences have a significant impact when examining the association with brain measures.

In the articles included in this dissertation, we speculated the role of genetic factors in the associations between physical activity and aerobic fitness with brain's structure and function. In the present studies, aerobic fitness was most robustly associated with those gray matter regions and white matter tracts that have been found to be under strong genetic control (M.-C. Chiang et al., 2011; Rentería et al., 2014; Teeuw, Brouwer, Koenis, et al., 2019). Furthermore, aerobic fitness measured with maximal oxygen consumption (Schutte et al., 2016) as well as trainability of aerobic fitness (Bouchard et al., 1999, 2011; Williams et al., 2017) has been proposed to be largely explained by genetic factors. Thus, how much exercise improves aerobic fitness is under genetic control. As both aerobic fitness and the structural brain regions associated with fitness in the present studies are under strong genetic influence, the existence of shared genetic factors is possible.

In **Study III**, we did not find evidence of an association between aerobic fitness and functional connectivity, but physical activity was correlated with local functional connectivity. When compared with the brain's structural measures, it appears that the genetic influences on gray and white matter structures might be higher than on functional connectivity (M.-C. Chiang et al., 2011; Colclough et al., 2017; Reineberg et al., 2020; Teeuw, Brouwer, Guimarães, et al., 2019; Teeuw, Brouwer, Koenis, et al., 2019). In addition, local functional connectivity properties measured with local clustering in 12-year-old participants were not significantly influenced by genes in contrast to global properties that were under genetic control (van den Heuvel et al., 2013), thus, suggesting that local functional connectivity could potentially be more readily influenced by behavior such as physical activity.

Interestingly, the developmental studies indicate that most of the regions and tracts associated with aerobic fitness, such as the corpus callosum and the superior corona radiata, develop relatively early and do not change to a large extent in adolescence (Gogtay et al., 2004; Lebel et al., 2008). On the other hand, the superior frontal gyrus and the superior longitudinal fasciculus are still undergoing changes during adolescence (Lebel et al., 2008; Teeuw, Brouwer, Koenis, et al., 2019). Thus, the results imply that, even though most regions and tracts associated with aerobic fitness develop rather early, there is no clear pattern that aerobic fitness is related to brain areas only at a specific stage of development.

The brain regions and tracts associated with physical activity and aerobic fitness in the current studies have a significant role in motor behavior (e.g., globus pallidus, superior frontal gyrus, corpus callous, corona radiata, superior longitudinal fasciculus, internal capsule, and supramarginal gyrus). Despite this, they also have an important role in many other functions such as higher-order cognitive functions (e.g., the superior frontal gyrus) and language (e.g., the supramarginal gyrus). It could be tempting to speculate that physical activity and aerobic fitness influence cognition through these brain regions. However, as the earlier evidence concerning the connection between physical activity and aerobic fitness with cognition in youth is contradictory, such a speculation could be problematic.

The **Study II** did not reveal significant correlations between either physical activity or aerobic fitness with core executive functions, and as mentioned above, the earlier evidence concerning this relationship is contradictory. The results, however, suggest that the white matter FA of specific tracts interacts with the relationship between physical activity and aerobic fitness with working memory. These exploratory cross-sectional results imply that, when studying the effect of physical activity or aerobic fitness on working memory, the level or condition of the white matter could influence the results of the exercise intervention. Thus, when conducting an exercise intervention study targeted to improve working memory, these current results highlight the importance of taking into account the individual brain measures. Although physical activity levels and working memory levels of participants might be similar, there can be substantial differences in properties of the brain regions crucial for the working memory. It should be noted, however, that here the moderating effect was rather small.

The results of this dissertation advance our understanding concerning the connection between physical activity and aerobic fitness with the adolescent brain. The findings will especially help to understand the differential connection that physical activity and aerobic fitness have with brain properties during adolescence. Earlier studies have mainly focused on other age groups, and the knowledge concerning this stage on development when significant changes occur in the adolescent's body and the brain is lacking. Our results show that aerobic fitness has an important connection with the brain structure and physical activity with the functional connectivity at rest in adolescents. Future studies are needed to determine the causal relationship between these connections. Furthermore, future studies should also investigate possible shared genetic factors between physical activity and aerobic fitness with brain development during adolescence.

YHTEENVETO (SUMMARY)

Nuoruuden aikaisen fyysisen aktiivisuuden ja aerobisen kunnon yhteys aivojen rakenteisiin ja toiminnallisiin yhteyksiin

Viimeisten vuosikymmenten aikana murrosikäisten nuorten kestävyyskunto on laskenut ja fyysisen aktiivisuuden määrä on suurella osalla nuoria alle suositusten. Tämä suuntaus on herättänyt huolta, koska vähäinen liikunnan määrä ja runsas paikallaolo voivat olla haitallisia nuorten terveydelle ja hyvinvoinnille. Näistä tiedoista huolimatta, tutkimustietoa fyysisen aktiivisuuden määrän ja kestävyyskunnon yhteydestä nuorten aivoihin ei juurikaan ole. Vaikka aiemmat tutkimukset ovat havainneet yhteyden liikunnan ja aivojen rakenteiden sekä toiminnan välillä muissa ikäryhmissä, on näiden tulosten yleistäminen murrosikäisiin nuoriin ongelmallista. Murrosiän aikana nuoren kehossa sekä aivoissa tapahtuu merkittäviä muutoksia. Osa muutoksista on uniikkeja, vain murrosiän aikana tapahtuvia muutoksia. Lisäksi on myös usein ehdotettu, että nuorten aivot muovautuvat helpommin kuin aikuisten aivot. Näin ollen nuoruuden aikaisella liikunnalla saattaa olla jopa korostunut merkitys aivoille. Tämän väitöskirjatyön päätarkoituksena on tarkastella fyysisen aktiivisuuden ja kestävyyskunnon yhteyttä murrosikäisten nuorten aivoihin. Toisena tarkoituksena on tarkastella aivojen valkean aineen osuutta fyysisen aktiivisuuden/kestävyyskunnon ja kognition (toiminnanohjaus) väliseen suhteeseen.

Tämä väitöskirja koostuu kolmesta tutkimuksesta, joissa kaikissa tutkittavat olivat pääosin samoja 12,7–16,2-vuotiaita nuoria (n=58–61). Tämän lisäksi fyysisen aktiivisuuden ja kestävyyskunnon mittarit olivat samoja kaikissa tutkimuksissa. Keskiraskas ja raskas fyysinen aktiivisuus mitattiin kiihtyvyysanturimittareilla viikon ajalta ja kestävyyskunnon taso arvioitiin 20 m sukkulajuoksutestillä. Aivokuvantaminen suoritettiin magneettikuvauksella (MRI) ja näissä tutkimuksissa aivojen ominaisuuksia mitattiin kolmella eri menetelmällä: rakenteellinen MRI (Tutkimus I), diffuusiokuvantaminen (Tutkimus II) ja lepotilan toiminnallinen MRI (Tutkimus III).

Väitöskirjan ensimmäisessä tutkimuksessa selvitettiin nuorten fyysisen aktiivisuuden ja kestävyyskunnon yhteyttä aivojen harmaaseen aineeseen. Aivojen harmaa aine koostuu pääosin hermosolujen solukeskuksista ja tuojahaarakkeista. Aivokuvantamismenetelmiä hyödyntäen on havaittu, että eri alueiden harmaan aineen tilavuudet ovat liittyvät merkitsevästi mm. kognitiivisiin toimintoihin ja aivosairauksiin. Tässä tutkimuksessa korkeamman kestävyyskunnon havaittiin olevan yhteydessä vasemman yläetupoimun pienempään tilavuuteen sekä vasemman linssitumakkeen pallon suurempaan tilavuuteen, kun ikä, sukupuoli, puberteetin vaihe ja aivojen kokonaistilavuus otettiin huomioon. Molemmat näistä alueista osallistuvat motorisiin toimintoihin, mutta erityisesti yläetupoimulla on merkittävä rooli monissa kognitiivisissa toiminnoissa. Tässä tutkimuksessa ei löydetty selkeää kytköstä fyysisen aktiivisuuden ja aivojen harmaan aineen välillä. Nämä tulokset osoittavat, että kestävyyskunto ja fyysinen aktiivisuus ovat eri lailla yhteydessä nuorten aivoihin, kun tarkastellaan harmaan aineen tilavuuksia. Yhteys on merkittävä kestävyyskuntoon, mutta ei fyysiseen aktiivisuuteen.

Toisessa tutkimuksessa selvitettiin nuorten fyysisen aktiivisuuden ja kestävyyskunnon yhteyttä aivojen valkean aineen ratojen ominaisuuksiin sekä valkean aineen moderaatio-vaikutusta fyysisen aktiivisuuden/kestävyyskunnon ja toiminnanohjauksen väliseen yhteyteen. Aivojen valkean aineen ratoja pitkin välittyy viestejä eri aivoalueiden välillä ja tämä mahdollistaa aivojen sisäisen kommunikaation, jota tarvitsemme jokapäiväisessä elämässä. Aivokuvantamistutkimuksissa valkean aineen ominaisuuksien on havaittu olevan merkityksellisiä monille toiminnoille, kuten toiminnanohjaukselle. Tämän tutkimuksen toisena tarkoituksena oli selvittää valkean aineen tason yhteys fyysisen aktiivisuuden/kestävyyskunnon ja toiminnanohjauksen välillä havaittuun yhteyteen. Toiminnanohjauksen tutkimus keskittyi erityisesti tarkkaavuuteen, inhibitioon ja työmuistiin. Tulokset osoittavat, että nuorten kestävyyskunto on yhteydessä useisiin valkean aineen ominaisuuksiin monilla eri valkean aineen radoilla. Selkeimmin yhteys näkyy kunnon sekä aivokurkiaisen ja ylemmän corona radiatan välillä. Tämän lisäksi myös mm. sisäkotelon ja superior longitudinal fasciculus:n ominaisuudet ovat yhteydessä kestävyyskuntoon. Fyysisen aktiivisuuden ja valkean aineen ominaisuuksien välillä ei havaittu olevan merkittävää yhteyttä. Eksploratiivisessa moderaatio-analyysissa havaittiin, erityisesti aivokurkiaisen valkean aineen tason olevan yhteydessä fyysisen aktiivisuuden/kestävyyskunnon ja työmuistin väliseen kytkökseen. Kuten ensimmäisessäkin osatutkimuksessa, myös tässäkin tutkimuksessa nuorten kestävyyskunnon havaittiin olevan yhteydessä aivojen rakenteisiin, mutta todisteita fyysisen aktiivisuuden ja aivojen valkean aineen rakenteiden välisestä yhteydestä ei löydetty. Lisäksi tulokset viittaavat siihen, että tiettyjen aivoratojen valkean aineen taso voi vaikuttaa sekä fyysisen aktiivisuuden ja työmuistin että kestävyyskunnon ja työmuistin välillä havaitun yhteyden suuntaan ja voimakkuuteen.

Väitöskirjan kolmas tutkimus keskittyi tarkastelemaan aivojen lepotilan toimintaa. Toisessa tutkimuksessa aivokurkiaisen valkean aineen havaittiin olevan yhteydessä kestävyyskuntoon. Aivokurkiaisella on myös tärkeä rooli aivopuoliskojen välisessä kommunikaatiossa, koska se on suurin aivopuoliskoja yhdistävä rakenne. Tämän havainnon pohjalta, kolmannessa tutkimuksessa tutkittiin miten sekä kestävyyskunto että fyysinen aktiivisuus ovat kytköksissä aivopuoliskojen väliseen lepotilan kommunikaatioon tai tarkemmin toiminnalliseen konnektiviteettiin homologisilla aivojen alueilla. Aivopuoliskojen välisten yhteyksien lisäksi tutkimme myös aivojen paikallista kommunikaatiota (regional homogeneity). Päinvastoin kuin kahdessa aiemmassa tutkimuksessa, fyysisen aktiivisuuden, mutta ei kestävyyskunnon, havaittiin olevan yhteydessä aivojen paikalliseen kommunikaatioon pääosin oikean puoleisessa supramarginaalisessa poimussa. Tutkimuksessa ei havaittu merkittävää yhteyttä aivopuoliskojen välisen toiminnallisen konnektiviteetin ja fyysisen aktiivisuuden tai kestävyyskunnon välillä.

Kokonaisuutena tämän väitöskirjan tulokset osoittavat sekä fyysisen aktiivisuuden että kestävyyskunnon liittyvän nuorten aivojen ominaisuuksiin. Yhteydet näiden kahden liikuntamittarin ja aivojen ominaisuuksien välillä eroavat kuitenkin huomattavasti. Kestävyyskunto on yhteydessä erityisesti aivojen rakenteisiin, kun taas fyysinen aktiivisuus on yhteydessä lepotilan toimintaan vain pienellä motoristen toimintojen kannalta tärkeällä alueella. Yleisesti ottaen havaitut yhteydet sekä molempien liikuntamittareiden että aivojen välillä painottuvat alueisiin, joilla on motoristen toimintojen kannalta oleellinen merkitys. Lisäksi yhteydet rajoittuivat suhteellisen pienille alueille, pois lukien yhteydet valkean aineeseen, jossa kestävyyskunnon merkitsevä yhteys aivoihin on laajalle levittynyttä. Nämä tutkimustulokset viittaavat siihen, että nuorten vähentyneellä liikunnalla ja erityisesti huonontuneella kestävyyskunnolla voi olla vaikutuksia aivoihin. Syy-seuraussuhdetta tämä tutkimus ei kuitenkaan pysty vahvistamaan ja tämän tulkinnan todentamiseen tarvitaankin pitkittäistutkimuksia.

REFERENCES

Abreu-Mendoza, R. A., Chamorro, Y., Garcia-Barrera, M. A., & Matute, E. (2018). The contributions of executive functions to mathematical learning difficulties and mathematical talent during adolescence. *PLoS ONE*, *13*(12), e0209267. https://doi.org/10.1371/journal.pone.0209267

Alarcón, G., Cservenka, A., Rudolph, M. D., Fair, D. A., & Nagel, B. J. (2015). Developmental sex differences in resting state functional connectivity of amygdala sub-regions. *NeuroImage*, *115*, 235–244. https://doi.org/10.1016/j.neuroimage.2015.04.013

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion Tensor Imaging of the Brain. *Neurotherapeutics*, *4*(3), 316–329. https://doi.org/10.1016/j.nurt.2007.05.011

Allan, J. L., McMinn, D., & Daly, M. (2016). A Bidirectional Relationship between Executive Function and Health Behavior: Evidence, Implications, and Future Directions. *Frontiers in Neuroscience*, *10*, 386. https://doi.org/10.3389/fnins.2016.00386

Álvarez-Bueno, C., Pesce, C., Cavero-Redondo, I., Sánchez-López, M., Martínez-Hortelano, J. A., & Martínez-Vizcaíno, V. (2017). The Effect of Physical Activity Interventions on Children's Cognition and Metacognition: A Systematic Review and Meta-Analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(9), 729–738. https://doi.org/10.1016/J.JAAC.2017.06.012

Amad, A., Seidman, J., Draper, S. B., Bruchhage, M. M. K., Lowry, R. G., Wheeler, J., Robertson, A., Williams, S. C. R., & Smith, M. S. (2017). Motor Learning Induces Plasticity in the Resting Brain-Drumming Up a Connection. *Cerebral Cortex*, *27*(3), 2010–2021. https://doi.org/10.1093/cercor/bhw048

Anderson, J. S., Druzgal, T. J., Froehlich, A., Dubray, M. B., Lange, N., Alexander, A. L., Abildskov, T., Nielsen, J. A., Cariello, A. N., Cooperrider, J. R., Bigler, E. D., & Lainhart, J. E. (2011). Decreased interhemispheric functional connectivity in autism. *Cerebral Cortex*, *21*(5), 1134–1146. https://doi.org/10.1093/cercor/bhq190

Armstrong, N., & Welsman, J. (2019). Youth cardiorespiratory fitness: Evidence, myths and misconceptions. *Bulletin of the World Health Organization*, *97*(11). https://doi.org/10.2471/BLT.18.227546

Asato, M. R., Terwilliger, R., Woo, J., & Luna, B. (2010). White matter development in adolescence: A DTI study. *Cerebral Cortex*, *20*(9), 2122–2131. https://doi.org/10.1093/cercor/bhp282

Awh, E., Vogel, E. K., & Oh, S. H. (2006). Interactions between attention and working memory. *Neuroscience*, *139*(1), 201–208. https://doi.org/10.1016/j.neuroscience.2005.08.023

Baddeley, A. D., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation - Advances in Research and Theory*, *8*(C), 47–89. https://doi.org/10.1016/S0079-7421(08)60452-1

Barbaro, M. F., Kramer, D. R., Nune, G., Lee, M. B., Peng, T., Liu, C. Y., Kellis, S., & Lee, B. (2019). Directional tuning during reach planning in the supramarginal gyrus using local field potentials. *Journal of Clinical Neuroscience*, *64*, 214–219. https://doi.org/10.1016/j.jocn.2019.03.061

Bathelt, J., Gathercole, S. E., Johnson, A., & Astle, D. E. (2018). Differences in brain morphology and working memory capacity across childhood. *Developmental Science*, *21*(3), e12579. https://doi.org/10.1111/desc.12579

Baum, G. L., Ciric, R., Roalf, D. R., Betzel, R. F., Moore, T. M., Shinohara, R. T., Kahn, A. E., Vandekar, S. N., Rupert, P. E., Quarmley, M., Cook, P. A., Elliott, M. A., Ruparel, K., Gur, R. E., Gur, R. C., Bassett, D. S., & Satterthwaite, T. D. (2017). Modular Segregation of Structural Brain Networks Supports the Development of Executive Function in Youth. *Current Biology*, *27*(11), 1561–1572. https://doi.org/10.1016/J.CUB.2017.04.051

Bava, S., Jacobus, J., Thayer, R. E., & Tapert, S. F. (2013). Longitudinal Changes in White Matter Integrity Among Adolescent Substance Users. *Alcoholism: Clinical and Experimental Research*, *37*(S1), E181-189. https://doi.org/10.1111/j.1530-0277.2012.01920.x

Bava, S., Thayer, R., Jacobus, J., Ward, M., Jernigan, T. L., & Tapert, S. F. (2010). Longitudinal characterization of white matter maturation during adolescence. *Brain Research*, *1327*, 38–46. https://doi.org/10.1016/j.brainres.2010.02.066

Ben-Shabat, E., Matyas, T. A., Pell, G. S., Brodtmann, A., & Carey, L. M. (2015). The right supramarginal gyrus is important for proprioception in healthy and stroke-affected participants: A functional MRI study. *Frontiers in Neurology*, *6*, 248. https://doi.org/10.3389/fneur.2015.00248

Benes, F. M., Turtle, M., Khan, Y., & Farol, P. (1994). Myelination of a Key Relay Zone in the Hippocampal Formation Occurs in the Human Brain during Childhood, Adolescence, and Adulthood. *Archives of General Psychiatry*, *51*(6), 477–484. https://doi.org/10.1001/archpsyc.1994.03950060041004

Berlucchi, G. (2002). The origin of the term plasticity in the neurosciences: Ernesto Lugaro and chemical synaptic transmission. *Journal of the History of the Neurosciences*, *11*(3), 305–309. https://doi.org/10.1076/jhin.11.3.305.10396

Best, J. R., Miller, P. H., & Naglieri, J. A. (2011). Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. *Learning and Individual Differences*, *21*(4), 327–336. https://doi.org/10.1016/J.LINDIF.2011.01.007

Betzel, R. F., Byrge, L., He, Y., Goñi, J., Zuo, X. N., & Sporns, O. (2014). Changes in structural and functional connectivity among resting-state networks across the human lifespan. *NeuroImage*, *102*, 345–357. https://doi.org/10.1016/j.neuroimage.2014.07.067

Bherer, L. (2015). Cognitive plasticity in older adults: Effects of cognitive training and physical exercise. *Annals of the New York Academy of Sciences*, *1337*, 1–6. https://doi.org/10.1111/nyas.12682

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *Journal of Aging Research*, *2013*, 657508. https://doi.org/10.1155/2013/657508

Bjork, J. M., Smith, A. R., Chen, G., & Hommer, D. W. (2010). Adolescents, adults and rewards: Comparing motivational neurocircuitry recruitment using fMRI. *PLoS ONE*, *5*(7), e11440. https://doi.org/10.1371/journal.pone.0011440

Blakemore, S. J. (2012). Imaging brain development: The adolescent brain. *NeuroImage*, *61*(2), 397–406. https://doi.org/10.1016/j.neuroimage.2011.11.080

Blakemore, S. J., Burnett, S., & Dahl, R. E. (2010). The role of puberty in the developing adolescent brain. *Human Brain Mapping*, *31*(6), 926–933. https://doi.org/10.1002/hbm.21052

Blanton, R. E., Cooney, R. E., Joormann, J., Eugène, F., Glover, G. H., & Gotlib, I. H. (2012). Pubertal stage and brain anatomy in girls. *Neuroscience*, *217*, 105–112. https://doi.org/10.1016/j.neuroscience.2012.04.059

Bodmer, B., Friedrich, J., Roessner, V., & Beste, C. (2018). Differences in response inhibition processes between adolescents and adults are modulated by sensory processes. *Developmental Cognitive Neuroscience*, *31*, 35–45. https://doi.org/10.1016/j.dcn.2018.04.008

Boelema, S. R., Harakeh, Z., Ormel, J., Hartman, C. A., Vollebergh, W. A. M., & van Zandvoort, M. J. E. (2014). Executive functioning shows differential maturation from early to late adolescence: Longitudinal findings from a TRAILS study. *Neuropsychology*, *28*(2), 177–187. https://doi.org/10.1037/neu0000049

Bonafiglia, J. T., Rotundo, M. P., Whittall, J. P., Scribbans, T. D., Graham, R. B., & Gurd, B. J. (2016). Inter-Individual Variability in the Adaptive Responses to Endurance and Sprint Interval Training: A Randomized Crossover Study. *PLOS ONE*, *11*(12), e0167790. https://doi.org/10.1371/journal.pone.0167790

Boraxbekk, C. J., Salami, A., Wåhlin, A., & Nyberg, L. (2016). 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*, 133–141. https://doi.org/10.1016/j.neuroimage.2015.12.010

Boreham, C., Twisk, J., Neville, C., Savage, M., Murray, L., & Gallagher, A. (2002). Associations between physical fitness and activity patterns during adolescence and cardiovascular risk factors in young adulthood: The Northern Ireland Young Hearts Project. *International Journal of Sports Medicine, Supplement*, *23*(S1), 22–26. https://doi.org/10.1055/s-2002-28457

Bossong, M. G., & Niesink, R. J. M. (2010). Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Progress in Neurobiology*, *92*(3), 370–385. https://doi.org/10.1016/j.pneurobio.2010.06.010

Bouchard, C., An, P., Rice, T., Skinner, J. S., Wilmore, J. H., Gagnon, J., Pérusse, L., Leon, A. S., & Rao, D. C. (1999). Familial aggregation of VO2max response to exercise training: results from the HERITAGE Family Study.

Journal of Applied Physiology, *87*(3), 1003–1008. https://doi.org/10.1055/s-2000-12983

Bouchard, C., & Rankinen, T. (2001). Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise*, *33*(6 Suppl), S446-51; discussion S452-3. http://www.ncbi.nlm.nih.gov/pubmed/11427769

Bouchard, C., Sarzynski, M. A., Rice, T. K., Kraus, W. E., Church, T. S., Sung, Y. J., Rao, D. C., & Rankinen, T. (2011). Genomic predictors of the maximal O 2 uptake response to standardized exercise training programs. *Journal of Applied Physiology*, *110*(5), 1160–1170. https://doi.org/10.1152/japplphysiol.00973.2010

Bramen, J. E., Hranilovich, J. A., Dahl, R. E., Forbes, E. E., Chen, J., Toga, A. W., Dinov, I. D., Worthman, C. M., & Sowell, E. R. (2011). Puberty influences medial temporal lobe and cortical gray matter maturation differently in boys than girls matched for sexual maturity. *Cerebral Cortex*, *21*(3). https://doi.org/10.1093/cercor/bhq137

Brehmer, Y., Rieckmann, A., Bellander, M., Westerberg, H., Fischer, H., & Bäckman, L. (2011). Neural correlates of training-related working-memory gains in old age. *NeuroImage*, *58*(4), 1110–1120. https://doi.org/10.1016/j.neuroimage.2011.06.079

Broadwater, M. A., Liu, W., Crews, F. T., & Spear, L. P. (2014). Persistent loss of hippocampal neurogenesis and increased cell death following adolescent, but not adult, chronic ethanol exposure. *Developmental Neuroscience*, *36*(3–4), 297–305. https://doi.org/10.1159/000362874

Brookman-Byrne, A., Mareschal, D., Tolmie, A. K., & Dumontheil, I. (2018). Inhibitory control and counterintuitive science and maths reasoning in adolescence. *PLoS ONE*, *13*(6), e0198973. https://doi.org/10.1371/journal.pone.0198973

Brouwer, R. M., Panizzon, M. S., Glahn, D. C., Hibar, D. P., Hua, X., Jahanshad, N., Abramovic, L., de Zubicaray, G. I., Franz, C. E., Hansell, N. K., Hickie, I. B., Koenis, M. M. G., Martin, N. G., Mather, K. A., McMahon, K. L., Schnack, H. G., Strike, L. T., Swagerman, S. C., Thalamuthu, A., … Hulshoff Pol, H. E. (2017). Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: Results of the ENIGMA plasticity working group. *Human Brain Mapping*, *38*(9), 4444–4458. https://doi.org/10.1002/hbm.23672

Buckner, R. L., Head, D., Parker, J., Fotenos, A. F., Marcus, D., Morris, J. C., & Snyder, A. Z. (2004). A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *NeuroImage*, *23*(2), 724–738. https://doi.org/10.1016/J.NEUROIMAGE.2004.06.018

Budde, M. D., Kim, J. H., Liang, H.-F., Schmidt, R. E., Russell, J. H., Cross, A. H., & Song, S.-K. (2007). Toward accurate diagnosis of white matter pathology using diffusion tensor imaging. *Magnetic Resonance in Medicine*, *57*(4), 688–695. https://doi.org/10.1002/mrm.21200

Burke, M. R., Bramley, P., Gonzalez, C. C., & McKeefry, D. J. (2013). The contribution of the right supra-marginal gyrus to sequence learning in eye movements. *Neuropsychologia*, *51*(14), 3048–3056. https://doi.org/10.1016/j.neuropsychologia.2013.10.007

Burzynska, A. Z., Chaddock-Heyman, L., Voss, M. W., Wong, C. N., Gothe, N. P., Olson, E. A., Knecht, A., Lewis, A., Monti, J. M., Cooke, G. E., Wojcicki, T. R., Fanning, J., Chung, H. D., Awick, E., McAuley, E., & Kramer, A. F. (2014). Physical Activity and Cardiorespiratory Fitness Are Beneficial for White Matter in Low-Fit Older Adults. *PLoS ONE*, *9*(9), e107413. https://doi.org/10.1371/journal.pone.0107413

Cancela, J., Burgo, H., & Sande, E. (2019). Physical fitness and executive functions in adolescents: cross-sectional associations with academic achievement. *Journal of Physical Therapy Science*, *31*(7), 556–562. https://doi.org/10.1589/jpts.31.556

Casey, B. J. (2015). Beyond Simple Models of Self-Control to Circuit-Based Accounts of Adolescent Behavior. *Annual Review of Psychology*, *66*(1), 295–319. https://doi.org/10.1146/annurev-psych-010814-015156

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Reports*, *100*(2), 126–131. https://doi.org/10.2307/20056429

Castro-Pinero, J., Artero, E. G., Espana-Romero, V., Ortega, F. B., Sjostrom, M., Suni, J., & Ruiz, J. R. (2010). Criterion-related validity of field-based fitness tests in youth: a systematic review. *British Journal of Sports Medicine*, *44*(13), 934–943. https://doi.org/10.1136/bjsm.2009.058321

Chaddock-Heyman, L., Erickson, K. I., Holtrop, J. L., Voss, M. W., Pontifex, M. B., Raine, L. B., Hillman, C. H., & Kramer, A. F. (2014). Aerobic fitness is associated with greater white matter integrity in children. *Frontiers in Human Neuroscience*, *8*, 584. https://doi.org/10.3389/fnhum.2014.00584

Chaddock-Heyman, L., Erickson, K. I., Kienzler, C., Drollette, E. S., Raine, L. B., Kao, S.-C., Bensken, J., Weisshappel, R., Castelli, D. M., Hillman, C. H., & Kramer, A. F. (2018). Physical Activity Increases White Matter Microstructure in Children. *Frontiers in Neuroscience*, *12*, 950. https://doi.org/10.3389/fnins.2018.00950

Chaddock-Heyman, L., Erickson, K. I., Kienzler, C., King, M., Pontifex, M. B., Raine, L. B., Hillman, C. H., & Kramer, A. F. (2015). The Role of Aerobic Fitness in Cortical Thickness and Mathematics Achievement in Preadolescent Children. *PLOS ONE*, *10*(8), e0134115. https://doi.org/10.1371/journal.pone.0134115

Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., VanPatter, M., Pontifex, M. B., Raine, L. B., Konkel, A., Hillman, C. H., Cohen, N. J., & Kramer, A. F. (2010). A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Research*, *1358*, 172–183. https://doi.org/10.1016/J.BRAINRES.2010.08.049

Chaddock, L., Erickson, K. I., Prakash, R. S., VanPatter, M., Voss, M. W., Pontifex, M. B., Raine, L. B., Hillman, C. H., & Kramer, A. F. (2010). Basal ganglia volume is associated with aerobic fitness in preadolescent children. *Developmental Neuroscience*, *32*(3), 249–256. https://doi.org/10.1159/000316648

Chaddock, L., Hillman, C. H., Pontifex, M. B., Johnson, C. R., Raine, L. B., & Kramer, A. F. (2012). Childhood aerobic fitness predicts cognitive performance one year later. *Journal of Sports Sciences*, *30*(5), 421–430. https://doi.org/10.1080/02640414.2011.647706

Chahal, R., Vilgis, V., Grimm, K. J., Hipwell, A. E., Forbes, E. E., Keenan, K., & Guyer, A. E. (2018). Girls' pubertal development is associated with white matter microstructure in late adolescence. *NeuroImage*, *181*, 659–669. https://doi.org/10.1016/j.neuroimage.2018.07.050

Chang, E. H., Argyelan, M., Aggarwal, M., Chandon, T.-S. S., Karlsgodt, K. H., Mori, S., & Malhotra, A. K. (2017). The role of myelination in measures of white matter integrity: Combination of diffusion tensor imaging and two-photon microscopy of CLARITY intact brains. *NeuroImage*, *147*, 253–261. https://doi.org/10.1016/j.neuroimage.2016.11.068

Cheng, L. A., Mendonça, G., & Farias Júnior, J. C. De. (2014). Physical activity in adolescents: Analysis of the social influence of parents and friends. *Jornal de Pediatria*, *90*(1), 35–41. https://doi.org/10.1016/j.jped.2013.05.006

Chiang, H. L., Chen, Y. J., Lo, Y. C., Tseng, W. Y. I., & Gau, S. S. F. (2015). Altered white matter tract property related to impaired focused attention, sustained attention, cognitive impulsivity and vigilance in attention-deficit/hyperactivity disorder. *Journal of Psychiatry and Neuroscience*, *40*(5), 325–335. https://doi.org/10.1503/jpn.140106

Chiang, M.-C., McMahon, K. L., de Zubicaray, G. I., Martin, N. G., Hickie, I., Toga, A. W., Wright, M. J., & Thompson, P. M. (2011). Genetics of white matter development: A DTI study of 705 twins and their siblings aged 12 to 29. *NeuroImage*, *54*(3), 2308–2317. https://doi.org/10.1016/j.neuroimage.2010.10.015

Chuderski, A., & Jastrzebski, J. (2018). Much ado about aha!: Insight problem solving is strongly related to working memory capacity and reasoning ability. *Journal of Experimental Psychology: General*, *147*(2), 257–281. https://doi.org/10.1037/xge0000378

Colby, J. B., Van Horn, J. D., & Sowell, E. R. (2011). Quantitative in vivo evidence for broad regional gradients in the timing of white matter maturation during adolescence. *NeuroImage*, *54*(1), 25–31. https://doi.org/10.1016/j.neuroimage.2010.08.014

Colclough, G. L., Smith, S. M., Nichols, T. E., Winkler, A. M., Sotiropoulos, S. N., Glasser, M. F., Van Essen, D. C., & Woolrich, M. W. (2017). The heritability of multi-modal connectivity in human brain activity. *ELife*, *6*, e20178. https://doi.org/10.7554/eLife.20178

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *58*(2), 176–180. https://doi.org/10.1093/gerona/58.2.m176

Compas, B. E., Jaser, S. S., Bettis, A. H., Watson, K. H., Gruhn, M. A., Dunbar, J. P., Williams, E., & Thigpen, J. C. (2017). Coping, emotion regulation, and psychopathology in childhood and adolescence: A meta-analysis and narrative review. *Psychological Bulletin*, *143*(9), 939–991. https://doi.org/10.1037/bul0000110

Constantinidis, C., & Klingberg, T. (2016). The neuroscience of working memory capacity and training. *Nature Reviews Neuroscience*, *17*(7), 438–449. https://doi.org/10.1038/nrn.2016.43

Constantinidis, C., & Luna, B. (2019). Neural Substrates of Inhibitory Control Maturation in Adolescence. *Trends in Neurosciences*, *42*(9), 604–616. https://doi.org/10.1016/j.tins.2019.07.004

Costigan, S. A., Eather, N., Plotnikoff, R. C., Hillman, C. H., & Lubans, D. R. (2016). High-Intensity Interval Training for Cognitive and Mental Health in Adolescents. *Medicine and Science in Sports and Exercise*, *48*(10), 1985–1993. https://doi.org/10.1249/MSS.0000000000000993

Cowan, N. (2016). Working Memory Maturation: Can We Get at the Essence of Cognitive Growth? *Perspectives on Psychological Science*, *11*(2), 239–264. https://doi.org/10.1177/1745691615621279

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, *29*(3), 162–173. https://doi.org/10.1006/cbmr.1996.0014

Craddock, C., Sikka, S., Cheung, B., Khanuja, R., Ghosh, S., Yan, C., Li, Q., Lurie, D., Vogelstein, J., Burns, R., Colcombe, S., Mennes, M., Kelly, C., Di Martino, A., Castellanos, F., & Milham, M. (2013). Towards Automated Analysis of Connectomes: The Configurable Pipeline for the Analysis of Connectomes (C-PAC). *Frontiers in Neuroinformatics*, *7*. https://doi.org/10.3389/conf.fninf.2013.09.00042

Cragg, L., & Nation, K. (2008). Go or no-go? Developmental improvements in the efficiency of response inhibition in mid-childhood. *Developmental Science*, *11*(6), 819–827. https://doi.org/10.1111/j.1467-7687.2008.00730.x

Da Silva, I. C. M., Hino, A. A., Lopes, A., Ekelund, U., Brage, S., Gonçalves, H., Menezes, A. B., Reis, R. S., & Hallal, P. C. (2017). Built environment and physical activity: Domain-and activity-specific associations among Brazilian adolescents. *BMC Public Health*, *17*(1), 616. https://doi.org/10.1186/s12889-017-4538-7

Dajani, D. R., & Uddin, L. Q. (2016). Local brain connectivity across development in autism spectrum disorder: A cross-sectional investigation. *Autism Research*, *9*(1), 43–54. https://doi.org/10.1002/aur.1494

Darki, F., & Klingberg, T. (2015). The role of fronto-parietal and fronto-striatal networks in the development of working memory: A longitudinal study. *Cerebral Cortex*, *25*(6), 1587–1595. https://doi.org/10.1093/cercor/bht352

De Bellis, M. D., Keshavan, M. S., Beers, S. R., Hall, J., Frustaci, K., Masalehdan, A., Noll, J., & Boring, A. M. (2001). Sex Differences in Brain Maturation during Childhood and Adolescence. *Cerebral Cortex*, *11*(6), 552–557. https://doi.org/10.1093/cercor/11.6.552

De Benedictis, A., Petit, L., Descoteaux, M., Marras, C. E., Barbareschi, M., Corsini, F., Dallabona, M., Chioffi, F., & Sarubbo, S. (2016). New insights in the homotopic and heterotopic connectivity of the frontal portion of the human corpus callosum revealed by microdissection and diffusion tractography. *Human Brain Mapping*, *37*(12), 4718–4735. https://doi.org/10.1002/hbm.23339

de Greeff, J. W., Hartman, E., Mullender-Wijnsma, M. J., Bosker, R. J., Doolaard, S., & Visscher, C. (2016). Long-term effects of physically active academic lessons on physical fitness and executive functions in primary school children. *Health Education Research*, *31*(2), 185–194. https://doi.org/10.1093/her/cyv102

De Villers-Sidani, E., Chang, E. F., Bao, S., & Merzenich, M. M. (2007). Critical period window for spectral tuning defined in the primary auditory cortex (A1) in the rat. *Journal of Neuroscience*, *27*(1), 180–189. https://doi.org/10.1523/JNEUROSCI.3227-06.2007

Dehn, M. J. (2017). How working memory enables fluid reasoning. *Applied Neuropsychology: Child*, *6*(3), 245–247. https://doi.org/10.1080/21622965.2017.1317490

Deng, L., Sun, J., Cheng, L., & Tong, S. (2016). Characterizing dynamic local functional connectivity in the human brain. *Scientific Reports*, *6*(1), 1–13. https://doi.org/10.1038/srep26976

Denson, T. F., Pedersen, W. C., Friese, M., Hahm, A., & Roberts, L. (2011). Understanding Impulsive Aggression: Angry Rumination and Reduced Self-Control Capacity Are Mechanisms Underlying the Provocation-Aggression Relationship. *Personality and Social Psychology Bulletin*, *37*(6), 850–862. https://doi.org/10.1177/0146167211401420

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology*, *64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Diamond, A., & Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science*, *333*(6045), 959–964. https://doi.org/10.1126/science.1204529

Diamond, A., & Ling, D. S. (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. *Developmental Cognitive Neuroscience*, *18*, 34–48. https://doi.org/10.1016/J.DCN.2015.11.005

Diamond, A., & Ling, D. S. (2019). Aerobic-Exercise and resistance-training interventions have been among the least effective ways to improve executive functions of any method tried thus far. *Developmental Cognitive Neuroscience*, *37*, 100572. https://doi.org/10.1016/J.DCN.2018.05.001

Dong, Z., Liu, Z., Liu, Y., Zhang, R., Mo, H., Gao, L., & Shi, Y. (2020). Physical exercise rectifies CUMS-induced aberrant regional homogeneity in mice accompanied by the adjustment of skeletal muscle PGC-1a/IDO1 signals and hippocampal function. *Behavioural Brain Research*, *383*. https://doi.org/10.1016/j.bbr.2020.112516

Donnelly, J. E., Hillman, C. H., Castelli, D., Etnier, J. L., Lee, S., Tomporowski, P., Lambourne, K., & Szabo-Reed, A. N. (2016). Physical Activity, Fitness, Cognitive Function, and Academic Achievement in Children. *Medicine & Science in Sports & Exercise*, *48*(6), 1197–1222. https://doi.org/10.1249/MSS.0000000000000901

Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., Lessov-Schlaggar, C. N., Barnes, K. A., Dubis, J. W., Feczko, E., Coalson, R. S., Pruett, J. R., Barch, D. M., Petersen, S. E., & Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science*, *329*(5997), 1358–1361. https://doi.org/10.1126/science.1194144

Dow-Edwards, D., MacMaster, F. P., Peterson, B. S., Niesink, R., Andersen, S., & Braams, B. R. (2019). Experience during adolescence shapes brain development: From synapses and networks to normal and pathological behavior. *Neurotoxicology and Teratology*, *76*, 106834. https://doi.org/10.1016/j.ntt.2019.106834

Dutil, C., Walsh, J. J., Featherstone, R. B., Gunnell, K. E., Tremblay, M. S., Gruber, R., Weiss, S. K., Cote, K. A., Sampson, M., & Chaput, J. P. (2018). Influence of sleep on developing brain functions and structures in children and adolescents: A systematic review. *Sleep Medicine Reviews*, *42*, 184–201. https://doi.org/10.1016/j.smrv.2018.08.003

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The Medial Temporal Lobe and Recognition Memory. *Annual Review of Neuroscience*, *30*, 123–152. https://doi.org/10.1146/annurev.neuro.30.051606.094328

Ellis, M. U., DeBoard Marion, S., McArthur, D. L., Babikian, T., Giza, C., Kernan, C. L., Newman, N., Moran, L., Akarakian, R., Houshiarnejad, A., Mink, R., Johnson, J., Babbitt, C. J., Olsen, A., & Asarnow, R. F. (2016). The UCLA Study of Children with Moderate-to-Severe Traumatic Brain Injury: Event-Related Potential Measure of Interhemispheric Transfer Time. *Journal of Neurotrauma*, *33*(11), 990–996. https://doi.org/10.1089/neu.2015.4023

Engel, A., Konig, P., Kreiter, A., & Singer, W. (1991). Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science*, *252*(5009), 1177–1179. https://doi.org/10.1126/science.252.5009.1177

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, Ø., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A Longitudinal Diffusion Tensor Imaging Study. *Human Brain Mapping*, *33*(10), 2390–2406. https://doi.org/10.1002/hbm.21370

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the*

United States of America, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Erickson, L. C., Thiessen, E. D., Godwin, K. E., Dickerson, J. P., & Fisher, A. V. (2015). Endogenously and exogenously driven selective sustained attention: Contributions to learning in kindergarten children. *Journal of Experimental Child Psychology*, *138*, 126–134. https://doi.org/10.1016/j.jecp.2015.04.011

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, *16*(1), 143–149. https://doi.org/10.3758/BF03203267

Ernst, M., Torrisi, S., Balderston, N., Grillon, C., & Hale, E. A. (2015). fMRI Functional Connectivity Applied to Adolescent Neurodevelopment. *Annual Review of Clinical Psychology*, *11*(1), 361–377. https://doi.org/10.1146/annurev-clinpsy-032814-112753

Esteban-Cornejo, I., Cadenas-Sanchez, C., Contreras-Rodriguez, O., Verdejo-Roman, J., Mora-Gonzalez, J., Migueles, J. H., Henriksson, P., Davis, C. L., Verdejo-Garcia, A., Catena, A., & Ortega, F. B. (2017). A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. *NeuroImage*, *159*, 346–354. https://doi.org/10.1016/J.NEUROIMAGE.2017.08.011

Esteban-Cornejo, I., Mora-Gonzalez, J., Cadenas-Sanchez, C., Contreras-Rodriguez, O., Verdejo-Román, J., Henriksson, P., Migueles, J. H., Rodriguez-Ayllon, M., Molina-García, P., Suo, C., Hillman, C. H., Kramer, A. F., Erickson, K. I., Catena, A., Verdejo-García, A., & Ortega, F. B. (2019). Fitness, cortical thickness and surface area in overweight/obese children: The mediating role of body composition and relationship with intelligence. *NeuroImage*, *186*, 771–781. https://doi.org/10.1016/j.neuroimage.2018.11.047

Esteban-Cornejo, I., Rodriguez-Ayllon, M., Verdejo-Roman, J., Cadenas-Sanchez, C., Mora-Gonzalez, J., Chaddock-Heyman, L., Raine, L. B., Stillman, C. M., Kramer, A. F., Erickson, K. I., Catena, A., Ortega, F. B., & Hillman, C. H. (2019). Physical Fitness, White Matter Volume and Academic Performance in Children: Findings From the ActiveBrains and FITKids2 Projects. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.00208

Esteban-Cornejo, I., Tejero-Gonzalez, C. M., Sallis, J. F., & Veiga, O. L. (2015). Physical activity and cognition in adolescents: A systematic review. *Journal of Science and Medicine in Sport*, *18*(5), 534–539. https://doi.org/10.1016/j.jsams.2014.07.007

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4

Evenson, K. R., Catellier, D. J., Gill, K., Ondrak, K. S., & McMurray, R. G. (2008). Calibration of two objective measures of physical activity for children.

Journal of Sports Sciences, *26*(14), 1557–1565. https://doi.org/10.1080/02640410802334196

Fair, D. A., Cohen, A. L., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., & Schlaggar, B. L. (2008). The maturing architecture of the brain's default network. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(10), 4028–4032. https://doi.org/10.1073/pnas.0800376105

Fair, D. A., Dosenbach, N. U. F., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., Raichle, M. E., Petersen, S. E., & Schlaggar, B. L. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(33), 13507–11352. https://doi.org/10.1073/pnas.0705843104

Fairchild, G., van Goozen, S. H. M., Stollery, S. J., Aitken, M. R. F., Savage, J., Moore, S. C., & Goodyer, I. M. (2009). Decision Making and Executive Function in Male Adolescents with Early-Onset or Adolescence-Onset Conduct Disorder and Control Subjects. *Biological Psychiatry*, *66*(2), 162–168. https://doi.org/10.1016/j.biopsych.2009.02.024

Fields, R. D. (2010). Change in the brain's white matter. *Science*, *330*(6005), 768–769. https://doi.org/10.1126/science.1199139

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Fischl, B., Salat, D. H., van der Kouwe, A. J. W., Makris, N., Ségonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage*, *23*, S69–S84. https://doi.org/10.1016/J.NEUROIMAGE.2004.07.016

Fjell, A. M., Walhovd, K. B., Brown, T. T., Kuperman, J. M., Chung, Y., Hagler, D. J., Venkatraman, V., Roddey, J. C., Erhart, M., McCabe, C., Akshoomoff, N., Amaral, D. G., Bloss, C. S., Libiger, O., Darst, B. F., Schork, N. J., Casey, B. J., Chang, L., Ernst, T. M., … Gruen, J. (2012). Multimodal imaging of the self-regulating developing brain. *Proceedings of the National Academy of Sciences*, *109*(48), 19620–19625. https://doi.org/10.1073/pnas.1208243109

Fortenbaugh, F. C., Degutis, J., Germine, L., Wilmer, J. B., Grosso, M., Russo, K., & Esterman, M. (2015). Sustained attention across the life span in a sample of 10,000: Dissociating ability and strategy. *Psychological Science*, *26*(9), 1497–1510. https://doi.org/10.1177/0956797615594896

Friston, K. J. (2011). Functional and Effective Connectivity: A Review. *Brain Connectivity*, *1*(1), 13–36. https://doi.org/10.1089/brain.2011.0008

Fuhrmann, D., Knoll, L. J., & Blakemore, S. J. (2015). Adolescence as a Sensitive Period of Brain Development. *Trends in Cognitive Sciences*, *19*(10), 558–566. https://doi.org/10.1016/j.tics.2015.07.008

Fung, W., & Swanson, H. L. (2017). Working memory components that predict word problem solving: Is it merely a function of reading, calculation, and fluid intelligence? *Memory and Cognition*, *45*(5), 804–823. https://doi.org/10.3758/s13421-017-0697-0

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *Journal of Neuroscience*, *26*(25), 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

García-Madruga, J. A., Gómez-Veiga, I., & Vila, J. (2016). Executive functions and the improvement of thinking abilities: The intervention in reading comprehension. *Frontiers in Psychology*, *7*, 58. https://doi.org/10.3389/fpsyg.2016.00058

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1), 1–16. https://doi.org/10.1002/acp.934

Geier, C. F., Terwilliger, R., Teslovich, T., Velanova, K., & Luna, B. (2010). Immaturities in reward processing and its influence on inhibitory control in adolescence. *Cerebral Cortex*, *20*(7), 1613–1629. https://doi.org/10.1093/cercor/bhp225

Genc, S., Malpas, C. B., Ball, G., Silk, T. J., & Seal, M. L. (2018). Age, sex, and puberty related development of the corpus callosum: a multi-technique diffusion MRI study. *Brain Structure and Function*, *223*(6), 2753–2765. https://doi.org/10.1007/s00429-018-1658-5

Genc, S., Smith, R. E., Malpas, C. B., Anderson, V., Nicholson, J. M., Efron, D., Sciberras, E., Seal, M. L., & Silk, T. J. (2018). Development of white matter fibre density and morphology over childhood: A longitudinal fixel-based analysis. *NeuroImage*, *183*, 666–676. https://doi.org/10.1016/j.neuroimage.2018.08.043

Gennatas, E. D., Avants, B. B., Wolf, D. H., Satterthwaite, T. D., Ruparel, K., Ciric, R., Hakonarson, H., Gur, R. E., & Gur, R. C. (2017). Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. *Journal of Neuroscience*, *37*(20), 5065–5073. https://doi.org/10.1523/JNEUROSCI.3550-16.2017

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Nature Neuroscience*, *2*(10), 861–863. https://doi.org/10.1038/13158

Giorgio, A., Watkins, K. E., Chadwick, M., James, S., Winmill, L., Douaud, G., De Stefano, N., Matthews, P. M., Smith, S. M., Johansen-Berg, H., & James, A. C. (2010). Longitudinal changes in grey and white matter during adolescence. *NeuroImage*, *49*(1), 94–103. https://doi.org/10.1016/j.neuroimage.2009.08.003

Goddings, A. L., Mills, K. L., Clasen, L. S., Giedd, J. N., Viner, R. M., & Blakemore, S. J. (2014). The influence of puberty on subcortical brain development. *NeuroImage*, *88*, 242–251. https://doi.org/10.1016/j.neuroimage.2013.09.073

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., Nugent, T. F., Herman, D. H., Clasen, L. S., Toga, A. W., Rapoport, J. L., & Thompson, P. M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(21), 8174–8179. https://doi.org/10.1073/pnas.0402680101

Gogtay, N., & Thompson, P. M. (2010). Mapping gray matter development: Implications for typical development and vulnerability to psychopathology. *Brain and Cognition*, *72*(1), 6–15. https://doi.org/10.1016/j.bandc.2009.08.009

Gómez-Pinilla, F., So, V., & Kesslak, J. P. (1998). Spatial learning and physical activity contribute to the induction of fibroblast growth factor: Neural substrates for increased cognition associated with exercise. *Neuroscience*, *85*(1), 53–61. https://doi.org/10.1016/S0306-4522(97)00576-9

Gómez, C. M., Barriga-Paulino, C. I., Rodríguez-Martínez, E. I., Rojas-Benjumea, M. Á., Arjona, A., & Gómez-González, J. (2018). The neurophysiology of working memory development: From childhood to adolescence and young adulthood. *Reviews in the Neurosciences*, *29*(3), 261–282. https://doi.org/10.1515/revneuro-2017-0073

Gorgolewski, K. J., Varoquaux, G., Rivera, G., Schwarz, Y., Ghosh, S. S., Maumet, C., Sochat, V. V., Nichols, T. E., Poldrack, R. A., Poline, J.-B., Yarkoni, T., & Margulies, D. S. (2015). NeuroVault.org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. *Frontiers in Neuroinformatics*, *9*, 8. https://doi.org/10.3389/fninf.2015.00008

Gorham, L. S., Jernigan, T., Hudziak, J., & Barch, D. M. (2019). Involvement in Sports, Hippocampal Volume, and Depressive Symptoms in Children. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *4*(5), 484–492. https://doi.org/10.1016/j.bpsc.2019.01.011

Grayson, D. S., & Fair, D. A. (2017). Development of large-scale functional networks from birth to adulthood: A guide to the neuroimaging literature. *NeuroImage*, *160*, 15–31. https://doi.org/10.1016/j.neuroimage.2017.01.079

Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Development*, *58*(3), 539–559. https://doi.org/10.1111/j.1467-8624.1987.tb01400.x

Gur, R. E., & Gur, R. C. (2016). Sex differences in brain and behavior in adolescence: Findings from the Philadelphia Neurodevelopmental Cohort. *Neuroscience and Biobehavioral Reviews*, *70*, 159–170. https://doi.org/10.1016/j.neubiorev.2016.07.035

Gutin, B., Yin, Z., Humphries, M. C., & Barbeau, P. (2005). Relations of moderate and vigorous physical activity to fitness and fatness in adolescents. *American Journal of Clinical Nutrition*, *81*(4), 746–750. https://doi.org/10.1093/ajcn/81.4.746

Hallal, P. C., Andersen, L. B., Bull, F. C., Guthold, R., Haskell, W., Ekelund, U., Alkandari, J. R., Bauman, A. E., Blair, S. N., Brownson, R. C., Craig, C. L., Goenka, S., Heath, G. W., Inoue, S., Kahlmeier, S., Katzmarzyk, P. T., Kohl, H. W., Lambert, E. V., Lee, I. M., … Wells, J. C. (2012). Global physical activity levels: Surveillance progress, pitfalls, and prospects. *The Lancet, 380*(9838), 247–257. https://doi.org/10.1016/S0140-6736(12)60646-1

Hallal, P. C., Victora, C. G., Azevedo, M. R., & Wells, J. C. K. (2006). Adolescent physical activity and health: A systematic review. *Sports Medicine*, *36*(12), 1019–1030. https://doi.org/10.2165/00007256-200636120-00003

Harsan, L. A., Poulet, P., Guignard, B., Steibel, J., Parizel, N., Loureiro de Sousa, P., Boehm, N., Grucker, D., & Ghandour, M. S. (2006). Brain dysmyelination and recovery assessment by noninvasive in vivo diffusion tensor magnetic resonance imaging. *Journal of Neuroscience Research*, *83*(3), 392–402. https://doi.org/10.1002/jnr.20742

Hatta, A., Nishihira, Y., Kim, S. R., Kaneda, T., Kida, T., Kamijo, K., Sasahara, M., & Haga, S. (2005). Effects of habitual moderate exercise on response processing and cognitive processing in older adults. *Japanese Journal of Physiology*, *55*(1), 29–36. https://doi.org/10.2170/jjphysiol.R2068

He, J., & Crews, F. T. (2007). Neurogenesis decreases during brain maturation from adolescence to adulthood. *Pharmacology Biochemistry and Behavior*, *86*(2), 327–333. https://doi.org/10.1016/j.pbb.2006.11.003

Herting, M. M., Colby, J. B., Sowell, E. R., & Nagel, B. J. (2014). White matter connectivity and aerobic fitness in male adolescents. *Developmental Cognitive Neuroscience*, *7*, 65–75. https://doi.org/10.1016/J.DCN.2013.11.003

Herting, M. M., Johnson, C., Mills, K. L., Vijayakumar, N., Dennison, M., Liu, C., Goddings, A. L., Dahl, R. E., Sowell, E. R., Whittle, S., Allen, N. B., & Tamnes, C. K. (2018). Development of subcortical volumes across adolescence in males and females: A multisample study of longitudinal changes. *NeuroImage*, *172*, 194–205. https://doi.org/10.1016/j.neuroimage.2018.01.020

Herting, M. M., Keenan, M. F., & Nagel, B. J. (2016). Aerobic Fitness Linked to Cortical Brain Development in Adolescent Males: Preliminary Findings Suggest a Possible Role of BDNF Genotype. *Frontiers in Human Neuroscience*, *10*, 327. https://doi.org/10.3389/fnhum.2016.00327

Herting, M. M., Kim, R., Uban, K. A., Kan, E., Binley, A., & Sowell, E. R. (2017). Longitudinal changes in pubertal maturation and white matter microstructure. *Psychoneuroendocrinology*, *81*, 70–79. https://doi.org/10.1016/j.psyneuen.2017.03.017

Herting, M. M., Maxwell, E. C., Irvine, C., & Nagel, B. J. (2012). The impact of sex, puberty, and hormones on white matter microstructure in adolescents. *Cerebral Cortex*, *22*(9), 1979–1992. https://doi.org/10.1093/cercor/bhr246

Herting, M. M., & Nagel, B. J. (2012). Aerobic fitness relates to learning on a virtual Morris Water Task and hippocampal volume in adolescents. *Behavioural Brain Research*, *233*(2), 517–525. https://doi.org/10.1016/J.BBR.2012.05.012

Herting, M. M., & Sowell, E. R. (2017). Puberty and structural brain development in humans. *Frontiers in Neuroendocrinology*, *44*, 122–137. https://doi.org/10.1016/j.yfrne.2016.12.003

Hillman, C. H., McAuley, E., Erickson, K. I., Liu-Ambrose, T., & Kramer, A. F. (2018). On mindful and mindless physical activity and executive function: A response to Diamond and Ling (2016). *Developmental Cognitive Neuroscience*, *37*, 100529. https://doi.org/10.1016/J.DCN.2018.01.006

Hilton, D. C., Jarrett, M. A., McDonald, K. L., & Ollendick, T. H. (2017). Attention Problems as a Mediator of the Relation between Executive Function and Social Problems in a Child and Adolescent Outpatient Sample. *Journal of Abnormal Child Psychology*, *45*(4), 777–788. https://doi.org/10.1007/s10802-016-0200-6

Holmes, C. J., Kim-Spoon, J., & Deater-Deckard, K. (2016). Linking Executive Function and Peer Problems from Early Childhood Through Middle Adolescence. *Journal of Abnormal Child Psychology*, *44*(1), 31–42. https://doi.org/10.1007/s10802-015-0044-5

Hopkins, M. E., Nitecki, R., & Bucci, D. J. (2011). Physical exercise during adolescence versus adulthood: differential effects on object recognition memory and brain-derived neurotrophic factor levels. *Neuroscience*, *194*, 84–94. https://doi.org/10.1016/J.NEUROSCIENCE.2011.07.071

Huang, T., Tarp, J., Domazet, S. L., Thorsen, A. K., Froberg, K., Andersen, L. B., & Bugge, A. (2015). Associations of Adiposity and Aerobic Fitness with Executive Function and Math Performance in Danish Adolescents. *The Journal of Pediatrics*, *167*(4), 810–815. https://doi.org/10.1016/j.jpeds.2015.07.009

Hudziak, J. J., Albaugh, M. D., Ducharme, S., Karama, S., Spottswood, M., Crehan, E., Evans, A. C., & Botteron, K. N. (2014). Cortical thickness maturation and duration of music training: Health-promoting activities shape brain development. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(11), 1153–1161. https://doi.org/10.1016/j.jaac.2014.06.015

Hurtig-Wennlöf, A., Ruiz, J. R., Harro, M., & Sjöström, M. (2007). Cardiorespiratory fitness relates more strongly than physical activity to cardiovascular disease risk factors in healthy children and adolescents: The European Youth Heart Study. *European Journal of Cardiovascular Prevention and Rehabilitation*, *14*(4), 575–581. https://doi.org/10.1097/HJR.0b013e32808c67e3

Ikuta, T., & Loprinzi, P. D. (2019). Association of cardiorespiratory fitness on interhemispheric hippocampal and parahippocampal functional connectivity. *European Journal of Neuroscience*, *50*(2), 1871–1877. https://doi.org/10.1111/ejn.14366

Jacobus, J., Thayer, R. E., Trim, R. S., Bava, S., Frank, L. R., & Tapert, S. F. (2013). White matter integrity, substance use, and risk taking in adolescence. *Psychology of Addictive Behaviors*, *27*(2), 431–442. https://doi.org/10.1037/a0028235

Janssen, I., & LeBlanc, A. G. (2010). Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *International Journal of Behavioral Nutrition and Physical Activity*, *7*, 40. https://doi.org/10.1186/1479-5868-7-40

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). Review FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jiang, L., & Zuo, X. N. (2016). Regional Homogeneity: A Multimodal, Multiscale Neuroimaging Marker of the Human Connectome. *Neuroscientist*, *22*(5), 486–505. https://doi.org/10.1177/1073858415595004

Joensuu, L., Syväoja, H., Kallio, J., Kulmala, J., Kujala, U. M., & Tammelin, T. H. (2018). Objectively measured physical activity, body composition and physical fitness: Cross-sectional associations in 9- to 15-year-old children. *European Journal of Sport Science*, *18*(6), 882–892. https://doi.org/10.1080/17461391.2018.1457081

Johnson, N. F., Kim, C., Clasey, J. L., Bailey, A., & Gold, B. T. (2012). Cardiorespiratory fitness is positively correlated with cerebral white matter integrity in healthy seniors. *NeuroImage*, *59*(2), 1514–1523. https://doi.org/10.1016/J.NEUROIMAGE.2011.08.032

Kamijo, K., Nishihira, Y., Hatta, A., Kaneda, T., Wasaka, T., Kida, T., & Kuroiwa, K. (2004). Differential influences of exercise intensity on information processing in the central nervous system. *European Journal of Applied Physiology*, *92*(3), 305–311. https://doi.org/10.1007/s00421-004-1097-2

Karbach, J., & Unger, K. (2014). Executive control training from middle childhood to adolescence. *Frontiers in Psychology*, *5*, 390. https://doi.org/10.3389/fpsyg.2014.00390

Karni, A., Meyer, G., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*, *377*(6545), 155–158. https://doi.org/10.1038/377155a0

Kelly, A. M. C., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., Margulies, D. S., Castellanos, F. X., & Milham, M. P. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex*, *19*(3), 640–657. https://doi.org/10.1093/cercor/bhn117

Kheradmand, A., Lasker, A., & Zee, D. S. (2015). Transcranial magnetic stimulation (TMS) of the supramarginal gyrus: A window to perception of upright. *Cerebral Cortex*, *25*(3), 765–771. https://doi.org/10.1093/cercor/bht267

Kieffer, M. J., Vukovic, R. K., & Berry, D. (2013). Roles of attention shifting and inhibitory control in fourth-grade reading comprehension. *Reading Research Quarterly*, *48*(4), 333–348. https://doi.org/10.1002/rrq.54

Kim, J. H. Y., & Juraska, J. M. (1997). Sex difference in the development of axon number in the splenium of the rat corpus callosum from postnatal day 15 through 60. *Developmental Brain Research*, *102*(1), 77–85. https://doi.org/10.1016/S0165-3806(97)00080-1

Kim, Y. J., Cha, E. J., Kim, S. M., Kang, K. D., & Han, D. H. (2015). The effects of taekwondo training on brain connectivity and body intelligence. *Psychiatry Investigation*, *12*(3), 335–340. https://doi.org/10.4306/pi.2015.12.3.335

Kinney, H. C., Brody, B. A., Kloman, A. S., & Gilles, F. H. (1988). Sequence of central nervous system myelination in human infancy: II. Patterns of myelination in autopsied infants. *Journal of Neuropathology and Experimental Neurology*, *47*(3), 217–234. https://doi.org/10.1097/00005072-198805000-00003

Kirk-Sanchez, N. J., & McGough, E. L. (2013). Physical exercise and cognitive performance in the elderly: Current perspectives. *Clinical Interventions in Aging*, *9*, 51–62. https://doi.org/10.2147/CIA.S39506

Klawiter, E. C., Schmidt, R. E., Trinkaus, K., Liang, H. F., Budde, M. D., Naismith, R. T., Song, S. K., Cross, A. H., & Benzinger, T. L. (2011). Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords. *NeuroImage*, *55*(4), 1454–1460. https://doi.org/10.1016/j.neuroimage.2011.01.007

Knoll, L. J., Fuhrmann, D., Sakhardande, A. L., Stamp, F., Speekenbrink, M., & Blakemore, S. J. (2016). A Window of Opportunity for Cognitive Training in Adolescence. *Psychological Science*, *27*(12), 1620–1631. https://doi.org/10.1177/0956797616671327

Koenis, M. M. G., Brouwer, R. M., van den Heuvel, M. P., Mandl, R. C. W., van Soelen, I. L. C., Kahn, R. S., Boomsma, D. I., & Hulshoff Pol, H. E. (2015). Development of the brain's structural network efficiency in early adolescence: A longitudinal DTI twin study. *Human Brain Mapping*, *36*(12), 4938–4953. https://doi.org/10.1002/hbm.22988

Kolb, B., & Gibb, R. (2014). Searching for the principles of brain plasticity and behavior. *Cortex*, *58*, 251–260. https://doi.org/10.1016/j.cortex.2013.11.012

Kolb, B., Harker, A., & Gibb, R. (2017). Principles of plasticity in the developing brain. *Developmental Medicine and Child Neurology*, *59*(12), 1218–1223. https://doi.org/10.1111/dmcn.13546

Kolb, B., Mychasiuk, R., Muhammad, A., & Gibb, R. (2013). Brain plasticity in the developing brain. *Progress in Brain Research*, *207*, 35–64. https://doi.org/10.1016/B978-0-444-63327-9.00005-9

Koolschijn, P. C. M. P., & Crone, E. A. (2013). Sex differences and structural brain maturation from childhood to early adulthood. *Developmental Cognitive Neuroscience*, *5*, 106–118. https://doi.org/10.1016/j.dcn.2013.02.003

Krafft, C. E., Pierce, J. E., Schwarz, N. F., Chi, L., Weinberger, A. L., Schaeffer, D. J., Rodrigue, A. L., Camchong, J., Allison, J. D., Yanasak, N. E., Liu, T., Davis, C. L., & McDowell, J. E. (2014). An eight month randomized controlled exercise intervention alters resting state synchrony in overweight children. *Neuroscience*, *256*, 445–455. https://doi.org/10.1016/j.neuroscience.2013.09.052

Krafft, C. E., Schaeffer, D. J., Schwarz, N. F., Chi, L., Weinberger, A. L., Pierce, J. E., Rodrigue, A. L., Allison, J. D., Yanasak, N. E., Liu, T., Davis, C. L., & McDowell, J. E. (2014). Improved Frontoparietal White Matter Integrity in Overweight Children Is Associated with Attendance at an After-School Exercise Program. *Developmental Neuroscience*, *36*(1), 1–9. https://doi.org/10.1159/000356219

Krogsrud, S. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Due-Tønnessen, P., Bjørnerud, A., Sampaio-Baptista, C., Andersson, J., Johansen-Berg, H., & Walhovd, K. B. (2018). Development of white matter microstructure in relation to verbal and visuospatial working memory—A longitudinal study. *PLoS ONE*, *13*(4), e0195540. https://doi.org/10.1371/journal.pone.0195540

Krogsrud, S. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Mork, L., Due-Tønnessen, P., Bjørnerud, A., Sampaio-Baptista, C., Andersson, J., Johansen-Berg, H., & Walhovd, K. B. (2016). Changes in white matter microstructure in the developing brain-A longitudinal diffusion tensor imaging study of children from 4 to 11years of age. *NeuroImage*, *124*(Pt A), 473–486. https://doi.org/10.1016/j.neuroimage.2015.09.017

Kwan, M. Y., Cairney, J., Faulkner, G. E., & Pullenayegum, E. E. (2012). Physical activity and other health-risk behaviors during the transition into early adulthood: A longitudinal cohort study. *American Journal of Preventive Medicine*, *42*(1), 14–20. https://doi.org/10.1016/j.amepre.2011.08.026

Larsen, B., & Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. *Neuroscience & Biobehavioral Reviews*, *94*, 179–195. https://doi.org/10.1016/J.NEUBIOREV.2018.09.005

Le Bihan, D. (2003). Looking into the functional architecture of the brain with diffusion MRI. *Nature Reviews Neuroscience*, *4*(6), 469–480. https://doi.org/10.1038/nrn1119

Le Bihan, D. (2013). Apparent diffusion coefficient and beyond : What diffusion mr imaging can tell us about tissue structure. *Radiology*, *268*(2), 318–322. https://doi.org/10.1148/radiol.13130420

Le Bihan, D., & Johansen-Berg, H. (2012). Diffusion MRI at 25: Exploring brain tissue structure and function. *NeuroImage*, *61*(2), 324–341. https://doi.org/10.1016/j.neuroimage.2011.11.006

Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, *13*(4), 534–546. https://doi.org/10.1002/jmri.1076

Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *Journal of Neuroscience*, *31*(30), 10937–10947. https://doi.org/10.1523/JNEUROSCI.5302-10.2011

Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *NeuroImage*, *182*, 207–218. https://doi.org/10.1016/J.NEUROIMAGE.2017.12.097

Lebel, C., Treit, S., & Beaulieu, C. (2019). A review of diffusion MRI of typical white matter development from early childhood to young adulthood. *NMR in Biomedicine*, *32*(4), e3778. https://doi.org/10.1002/nbm.3778

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*(3), 1044–1055. https://doi.org/10.1016/J.NEUROIMAGE.2007.12.053

Lee, T. M. C., Wong, M. L., Lau, B. W. M., Lee, J. C. Di, Yau, S. Y., & So, K. F. (2014). Aerobic exercise interacts with neurotrophic factors to predict cognitive functioning in adolescents. *Psychoneuroendocrinology*, *39*, 214–224. https://doi.org/10.1016/j.psyneuen.2013.09.019

Lehman, E. B., Naglieri, J. A., & Aquilino, S. A. (2010). A national study on the development of visual attention using the cognitive assessment system. *Journal of Attention Disorders*, *14*(1), 15–24. https://doi.org/10.1177/1087054709332473

Leppert, I. R., Almli, C. R., McKinstry, R. C., Mulkern, R. V., Pierpaoli, C., Rivkin, M. J., & Pike, G. B. (2009). T2 relaxometry of normal pediatric brain development. *Journal of Magnetic Resonance Imaging*, *29*(2), 258–267. https://doi.org/10.1002/jmri.21646

Libedinsky, C. D., & Fernandez, P. F. (2019). Graded memory: A cognitive category to replace spatial sustained attention and working memory. *Yale Journal of Biology and Medicine*, *92*(1), 121–125.

Liston, C., Watts, R., Tottenham, N., Davidson, M. C., Niogi, S., Ulug, A. M., & Casey, B. J. (2006). Frontostriatal microstructure modulates efficient recruitment of cognitive control. *Cerebral Cortex*, *16*(4), 553–560. https://doi.org/10.1093/cercor/bhj003

Liu, N. Y. S., Plowman, S. A., & Looney, M. A. (1992). The reliability and validity of the 20-meter shuttle test in american students 12 to 15 years old. *Research Quarterly for Exercise and Sport*, *63*(4), 360–365. https://doi.org/10.1080/02701367.1992.10608757

Lopez-Larson, M. P., Anderson, J. S., Ferguson, M. A., & Yurgelun-Todd, D. (2011). Local brain connectivity and associations with gender and age. *Developmental Cognitive Neuroscience*, *1*(2), 187–197. https://doi.org/10.1016/j.dcn.2010.10.001

López-Vicente, M., Tiemeier, H., Wildeboer, A., Muetzel, R. L., Verhulst, F. C., Jaddoe, V. W. V., Sunyer, J., & White, T. (2017). Cortical Structures Associated With Sports Participation in Children: A Population-Based Study. *Developmental Neuropsychology*, *42*(2), 58–69. https://doi.org/10.1080/87565641.2017.1309654

Lövdén, M., Wenger, E., Mårtensson, J., Lindenberger, U., & Bäckman, L. (2013). Structural brain plasticity in adult learning and development. *Neuroscience and Biobehavioral Reviews*, *37*(9 Pt B), 2296–2310. https://doi.org/10.1016/j.neubiorev.2013.02.014

Ludyga, S., Gerber, M., Kamijo, K., Brand, S., & Pühse, U. (2018). The effects of a school-based exercise program on neurophysiological indices of working memory operations in adolescents. *Journal of Science and Medicine in Sport*, *21*(8), 833–838. https://doi.org/10.1016/j.jsams.2018.01.001

Luna, B. (2009). Developmental Changes in Cognitive Control through Adolescence. *Advances in Child Development and Behavior*, *37*, 233–278. https://doi.org/10.1016/S0065-2407(09)03706-9

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development*, *75*(5), 1357–1372. https://doi.org/10.1111/j.1467-8624.2004.00745.x

Luna, B., Padmanabhan, A., & O'Hearn, K. (2010). What has fMRI told us about the Development of Cognitive Control through Adolescence? *Brain and Cognition*, *72*(1), 101–113. https://doi.org/10.1016/j.bandc.2009.08.005

Lv, Y., Margulies, D. S., Villringer, A., & Zang, Y.-F. (2013). Effects of Finger Tapping Frequency on Regional Homogeneity of Sensorimotor Cortex. *PLoS ONE*, *8*(5), e64115. https://doi.org/10.1371/journal.pone.0064115

Ma, Z., Ma, Y., & Zhang, N. (2018). Development of brain-wide connectivity architecture in awake rats. *NeuroImage*, *176*, 380–389. https://doi.org/10.1016/j.neuroimage.2018.05.009

Mabbott, D. J., Noseworthy, M., Bouffet, E., Laughlin, S., & Rockel, C. (2006). White matter growth as a mechanism of cognitive development in children. *NeuroImage*, *33*(3), 936–946. https://doi.org/10.1016/J.NEUROIMAGE.2006.07.024

MacLean, K. A., Ferrer, E., Aichele, S. R., Bridwell, D. A., Zanesco, A. P., Jacobs, T. L., King, B. G., Rosenberg, E. L., Sahdra, B. K., Shaver, P. R., Wallace, B. A., Mangun, G. R., & Saron, C. D. (2010). Intensive meditation training improves perceptual discrimination and sustained attention. *Psychological Science : A Journal of the American Psychological Society / APS*, *21*(6), 829–839. https://doi.org/10.1177/0956797610371339

Madsen, K. S., Baaré, W. F. C., Vestergaard, M., Skimminge, A., Ejersbo, L. R., Ramsøy, T. Z., Gerlach, C., Åkeson, P., Paulson, O. B., & Jernigan, T. L. (2010). Response inhibition is associated with white matter microstructure in children. *Neuropsychologia*, *48*(4), 854–862. https://doi.org/10.1016/j.neuropsychologia.2009.11.001

Mah, A., Geeraert, B., & Lebel, C. (2017). Detailing neuroanatomical development in late childhood and early adolescence using NODDI. *PLoS ONE*, *12*(8), e0182340. https://doi.org/10.1371/journal.pone.0182340

Mahar, M. T., Welk, G. J., & Rowe, D. A. (2018). Estimation of aerobic fitness from PACER performance with and without body mass index. *Measurement in Physical Education and Exercise Science*, *22*(3), 239–249. https://doi.org/10.1080/1091367X.2018.1427590

Malina, R. M. (2001). Physical activity and fitness: Pathways from childhood to adulthood. *American Journal of Human Biology*, *13*(2), 162–172. https://doi.org/10.1002/1520-6300(200102/03)13:2<162::AID-AJHB1025>3.0.CO;2-T

Mancuso, L., Uddin, L. Q., Nani, A., Costa, T., & Cauda, F. (2019). Brain functional connectivity in individuals with callosotomy and agenesis of the corpus callosum: A systematic review. *Neuroscience and Biobehavioral Reviews*, *105*, 231–248. https://doi.org/10.1016/j.neubiorev.2019.07.004

Mark, C. I., Mazerolle, E. L., & Chen, J. J. (2015). Metabolic and vascular origins of the BOLD effect: Implications for imaging pathology and resting-state brain function. *Journal of Magnetic Resonance Imaging*, *42*(2), 231–246. https://doi.org/10.1002/jmri.24786

Marshall, W. A., & Tanner, J. M. (1969). Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, *44*(235), 291–303. http://www.ncbi.nlm.nih.gov/pubmed/5785179

Marshall, W. A., & Tanner, J. M. (1970). Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood*, *45*(239), 13–23. http://www.ncbi.nlm.nih.gov/pubmed/5440182

Marwha, D., Halari, M., & Eliot, L. (2017). Meta-analysis reveals a lack of sexual dimorphism in human amygdala volume. *NeuroImage*, *147*, 282–294. https://doi.org/10.1016/j.neuroimage.2016.12.021

Mayorga-Vega, D., Aguilar-Soto, P., & Viciana, J. (2015). Criterion-related validity of the 20-m shuttle run test for estimating cardiorespiratory fitness: A meta-analysis. *Journal of Sports Science and Medicine*, *14*(3), 536–547.

McDowell, T., Holmes, N. P., Sunderland, A., & Schürmann, M. (2018). TMS over the supramarginal gyrus delays selection of appropriate grasp orientation during reaching and grasping tools for use. *Cortex*, *103*, 117–129. https://doi.org/10.1016/j.cortex.2018.03.002

McGee, A. W., Yang, Y., Fischer, Q. S., Daw, N. W., & Strittmatter, S. M. (2005). Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science (New York, N.Y.)*, *309*(5744), 2222–2226. https://doi.org/10.1126/science.1114362

Melby-Lervåg, M., & Hulme, C. (2013). Is working memory training effective? A meta-analytic review. *Developmental Psychology*, *49*(2), 270–291. https://doi.org/10.1037/a0028228

Menon, V. (2013). Developmental pathways to functional brain networks: Emerging principles. *Trends in Cognitive Sciences*, *17*(12), 627–640. https://doi.org/10.1016/j.tics.2013.09.015

Menzies, L., Goddings, A. L., Whitaker, K. J., Blakemore, S. J., & Viner, R. M. (2015). The effects of puberty on white matter development in boys. *Developmental Cognitive Neuroscience*, *11*, 116–128. https://doi.org/10.1016/j.dcn.2014.10.002

Meruelo, A. D., Castro, N., Cota, C. I., & Tapert, S. F. (2017). Cannabis and alcohol use, and the developing brain. *Behavioural Brain Research*, *325*(Pt A), 44–50. https://doi.org/10.1016/j.bbr.2017.02.025

Miller, E. K., Lundqvist, M., & Bastos, A. M. (2018). Working Memory 2.0. *Neuron*, *100*(2), 463–475. https://doi.org/10.1016/j.neuron.2018.09.023

Mills, K. L., Goddings, A.-L., Herting, M. M., Meuwese, R., Blakemore, S.-J., Crone, E. A., Dahl, R. E., Güroğlu, B., Raznahan, A., Sowell, E. R., & Tamnes, C. K. (2016). Structural brain development between childhood and adulthood: Convergence across four longitudinal samples. *NeuroImage*, *141*, 273–281. https://doi.org/10.1016/J.NEUROIMAGE.2016.07.044

Mills, K. L., Goddings, A. L., Clasen, L. S., Giedd, J. N., & Blakemore, S. J. (2014). The developmental mismatch in structural brain maturation during adolescence. *Developmental Neuroscience*, *36*(3–4), 147–160. https://doi.org/10.1159/000362328

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H. L., Houts, R., Poulton, R., Roberts, B. W., Ross, S., Sears, M. R., Thomson, W. M., & Caspi, A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National*

Academy of Sciences of the United States of America, *108*(7), 2693–2698. https://doi.org/10.1073/pnas.1010076108

Mollink, J., Smith, S. M., Elliott, L. T., Kleinnijenhuis, M., Hiemstra, M., Alfaro-Almagro, F., Marchini, J., van Cappellen van Walsum, A. M., Jbabdi, S., & Miller, K. L. (2019). The spatial correspondence and genetic influence of interhemispheric connectivity with white matter microstructure. *Nature Neuroscience*, *22*(5), 809–819. https://doi.org/10.1038/s41593-019-0379-2

Montero, D., & Lundby, C. (2017). Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. *The Journal of Physiology*, *595*(11), 3377–3387. https://doi.org/10.1113/JP273480

Mori, S., & Zhang, J. (2006). Principles of Diffusion Tensor Imaging and Its Applications to Basic Neuroscience Research. *Neuron*, *51*(5), 527–539. https://doi.org/10.1016/j.neuron.2006.08.012

Moura, L. M., Kempton, M., Barker, G., Salum, G., Gadelha, A., Pan, P. M., Hoexter, M., Del Aquilla, M. A. G., Picon, F. A., Anés, M., Otaduy, M. C. G., Amaro, E., Rohde, L. A., McGuire, P., Bressan, R. A., Sato, J. R., & Jackowski, A. P. (2016). Age-effects in white matter using associated diffusion tensor imaging and magnetization transfer ratio during late childhood and early adolescence. *Magnetic Resonance Imaging*, *34*(4), 529–534. https://doi.org/10.1016/j.mri.2015.12.021

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of White Matter is Associated with the Development of Cognitive Functions during Childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233. https://doi.org/10.1162/0898929041920441

Narvacan, K., Treit, S., Camicioli, R., Martin, W., & Beaulieu, C. (2017). Evolution of deep gray matter volume across the human lifespan. *Human Brain Mapping*, *38*(8), 3771–3790. https://doi.org/10.1002/hbm.23604

Neeper, S. A., Góauctemez-Pinilla, F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature*, *373*(6510), 109. https://doi.org/10.1038/373109a0

Nemati, F., & Kolb, B. (2010). Motor cortex injury has different behavioral and anatomical effects in early and late adolescence. *Behavioral Neuroscience*, *124*(5), 612–622. https://doi.org/10.1037/a0020911

Neufang, S., Specht, K., Hausmann, M., Güntürkün, O., Herpertz-Dahlmann, B., Fink, G. R., & Konrad, K. (2009). Sex differences and the impact of steroid hormones on the developing human brain. *Cerebral Cortex*, *19*(2). https://doi.org/10.1093/cercor/bhn100

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *58*(4), 361–383. https://doi.org/10.1111/jcpp.12675

Nokia, M. S., Lensu, S., Ahtiainen, J. P., Johansson, P. P., Koch, L. G., Britton, S. L., & Kainulainen, H. (2016). Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained. *The Journal of Physiology*, *594*(7), 1855–1873. https://doi.org/10.1113/JP271552

Nupponen, H., Soini, H., & Telama, R. (1999). *Koululaisten kunnon ja liikehallinnan mittaaminen [Test manual of motor fitness and abilities for schools]* (2nd ed.). Likes.

O'Connell, R. G., Bellgrove, M. A., Dockree, P. M., Lau, A., Fitzgerald, M., & Robertson, I. H. (2008). Self-Alert Training: Volitional modulation of autonomic arousal improves sustained attention. *Neuropsychologia*, *46*(5), 1379–13790. https://doi.org/10.1016/j.neuropsychologia.2007.12.018

O'Donnell, L. J., & Westin, C. F. (2011). An introduction to diffusion tensor image analysis. *Neurosurgery Clinics of North America*, *22*(2), 185–196. https://doi.org/10.1016/j.nec.2010.12.004

O'Leary, J. D., Hoban, A. E., Cryan, J. F., O'Leary, O. F., & Nolan, Y. M. (2019). Differential effects of adolescent and adult-initiated voluntary exercise on context and cued fear conditioning. *Neuropharmacology*, *145*, 49–58. https://doi.org/10.1016/j.neuropharm.2018.05.007

O'Leary, J. D., Hoban, A. E., Murphy, A., O'Leary, O. F., Cryan, J. F., & Nolan, Y. M. (2019). Differential effects of adolescent and adult-initiated exercise on cognition and hippocampal neurogenesis. *Hippocampus*, *29*(4), 352–365. https://doi.org/10.1002/hipo.23032

Oberhuber, M., Hope, T. M. H., Seghier, M. L., Parker Jones, O., Prejawa, S., Green, D. W., & Price, C. J. (2016). Four Functionally Distinct Regions in the Left Supramarginal Gyrus Support Word Processing. *Cerebral Cortex*, *26*(11), 4212–4226. https://doi.org/10.1093/cercor/bhw251

Oberlin, L. E., Verstynen, T. D., Burzynska, A. Z., Voss, M. W., Prakash, R. S., Chaddock-Heyman, L., Wong, C., Fanning, J., Awick, E., Gothe, N., Phillips, S. M., Mailey, E., Ehlers, D., Olson, E., Wojcicki, T., McAuley, E., Kramer, A. F., & Erickson, K. I. (2016). White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. *NeuroImage*, *131*, 91–101. https://doi.org/10.1016/J.NEUROIMAGE.2015.09.053

Ortega, F. B., Campos, D., Cadenas-Sanchez, C., Altmäe, S., Martínez-Zaldívar, C., Martín-Matillas, M., Catena, A., & Campoy, C. (2019). Physical fitness and shapes of subcortical brain structures in children. *British Journal of Nutrition*, *122*, S49–S58. https://doi.org/10.1017/S0007114516001239

Ortega, F. B., Ruiz, J. R., Castillo, M. J., & Sjöström, M. (2008). Physical fitness in childhood and adolescence: A powerful marker of health. *International Journal of Obesity*, *32*(1), 1–11. https://doi.org/10.1038/sj.ijo.0803774

Østby, Y., Tamnes, C. K., Fjell, A. M., & Walhovd, K. B. (2011). Morphometry and connectivity of the fronto-parietal verbal working memory network in development. *Neuropsychologia*, *49*(14), 3854–3862. https://doi.org/10.1016/j.neuropsychologia.2011.10.001

Østby, Y., Tamnes, C. K., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., & Walhovd, K. B. (2009). Heterogeneity in subcortical brain development: A structural magnetic resonance imaging study of brain maturation from 8 to 30 years. *Journal of Neuroscience*, *29*(38), 11772–11782. https://doi.org/10.1523/JNEUROSCI.1242-09.2009

Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1996). Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain : A Journal of Neurology*, *119 (Pt 5)*, 1597–1615. http://www.ncbi.nlm.nih.gov/pubmed/8931583

Owen, K. B., Smith, J., Lubans, D. R., Ng, J. Y. Y., & Lonsdale, C. (2014). Self-determined motivation and physical activity in children and adolescents: A systematic review and meta-analysis. *Preventive Medicine*, *67*, 270–279. https://doi.org/10.1016/j.ypmed.2014.07.033

Pajevic, S., Basser, P. J., & Fields, R. D. (2014). Role of myelin plasticity in oscillations and synchrony of neuronal activity. *Neuroscience*, *276*, 135–147. https://doi.org/10.1016/J.NEUROSCIENCE.2013.11.007

Papanikolaou, N., Karampekios, S., Papadaki, E., Malamas, M., Maris, T., & Gourtsoyiannis, N. (2006). Fractional anisotropy and mean diffusivity measurements on normal human brain: Comparison between low- and high-resolution diffusion tensor imaging sequences. *European Radiology*, *16*(1), 187–192. https://doi.org/10.1007/s00330-005-2833-7

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human cortex. *Annual Review of Neuroscience*, *28*, 377–401. https://doi.org/10.1146/annurev.neuro.27.070203.144216

Pattwell, S. S., Duhoux, S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D., Ruberry, E. J., Powers, A., Mehta, N., Yang, R. R., Soliman, F., Glatt, C. E., Casey, B. J., Ninan, I., & Lee, F. S. (2012). Altered fear learning across development in both mouse and human. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(40), 16318–16323. https://doi.org/10.1073/pnas.1206834109

Paus, T. (2010a). Growth of white matter in the adolescent brain: Myelin or axon? *Brain and Cognition*, *72*(1), 26–35. https://doi.org/10.1016/j.bandc.2009.06.002

Paus, T. (2010b). Sex differences in the human brain. A developmental perspective. *Progress in Brain Research*, *186*, 13–28. https://doi.org/10.1016/B978-0-444-53630-3.00002-6

Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, *9*(12), 947–957. https://doi.org/10.1038/nrn2513

Paus, T., Zijdenbos, A., Worsley, K., Collins, D., Blumenthal, J., Giedd, J. ., Rapoport, J. L., & Evans, A. C. (1999). Structural Maturation of Neural Pathways in Children and Adolescents : In Vivo Study. *Science*, *283*(5409), 1908–1911. https://doi.org/https://doi.org/10.1126/science.283.5409.1908

Peeters, M., Vollebergh, W. A. M., Wiers, R. W., & Field, M. (2014). Psychological changes and cognitive impairments in adolescent heavy drinkers. *Alcohol and Alcoholism*, *49*(2), 182–186. https://doi.org/10.1093/alcalc/agt162

Peper, J. S., Schnack, H. G., Brouwer, R. M., Van Baal, G. C. M., Pjetri, E., Székely, E., Van Leeuwen, M., Van Den Berg, S. M., Collins, D. L., Evans,

A. C., Boomsma, D. I., Kahn, R., & Hulshoff Pol, H. E. (2009). Heritability of regional and global brain structure at the onset of puberty: A magnetic resonance imaging study in 9-year-old twin pairs. *Human Brain Mapping*, *30*(7), 2184–2196. https://doi.org/10.1002/hbm.20660

Petanjek, Z., Judaš, M., Šimić, G., Rašin, M. R., Uylings, H. B. M., Rakic, P., & Kostović, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(32), 13281–13286. https://doi.org/10.1073/pnas.1105108108

Peters, B. D., Szeszko, P. R., Radua, J., Ikuta, T., Gruner, P., Derosse, P., Zhang, J. P., Giorgio, A., Qiu, D., Tapert, S. F., Brauer, J., Asato, M. R., Khong, P. L., James, A. C., Gallego, J. A., & Malhotra, A. K. (2012). White matter development in adolescence: Diffusion tensor imaging and meta-analytic results. *Schizophrenia Bulletin*, *38*(6), 1308–1317. https://doi.org/10.1093/schbul/sbs054

Pfefferbaum, A., Rohlfing, T., Pohl, K. M., Lane, B., Chu, W., Kwon, D., Nolan Nichols, B., Brown, S. A., Tapert, S. F., Cummins, K., Thompson, W. K., Brumback, T., Meloy, M. J., Jernigan, T. L., Dale, A., Colrain, I. M., Baker, F. C., Prouty, D., De Bellis, M. D., … Sullivan, E. V. (2016). Adolescent Development of Cortical and White Matter Structure in the NCANDA Sample: Role of Sex, Ethnicity, Puberty, and Alcohol Drinking. *Cerebral Cortex*, *26*(10), 4101–4121. https://doi.org/10.1093/cercor/bhv205

Piekarski, D. J., Johnson, C. M., Boivin, J. R., Thomas, A. W., Lin, W. C., Delevich, K., M Galarce, E., & Wilbrecht, L. (2017). Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex? *Brain Research*, *1654*(Pt B), 123–144. https://doi.org/10.1016/j.brainres.2016.08.042

Pindus, D. M., Davis, R. D. M., Hillman, C. H., Bandelow, S., Hogervorst, E., Biddle, S. J. H., & Sherar, L. B. (2015). The relationship of moderate-to-vigorous physical activity to cognitive processing in adolescents: findings from the ALSPAC birth cohort. *Psychological Research*, *79*(5), 715–728. https://doi.org/10.1007/s00426-014-0612-2

Poon, K. (2018). Hot and cool executive functions in adolescence: Development and contributions to important developmental outcomes. *Frontiers in Psychology*, *8*, 2311. https://doi.org/10.3389/fpsyg.2017.02311

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.10.018

R Core Team. (2018). *R: A Language and Environment for Statistical Computing* (3.4.0). R Foundation for Statistical Computing. https://www.r-project.org

Reineberg, A. E., Hatoum, A. S., Hewitt, J. K., Banich, M. T., & Friedman, N. P. (2020). Genetic and Environmental Influence on the Human Functional Connectome. *Cerebral Cortex*, *30*(4), 2099–2113. https://doi.org/10.1093/cercor/bhz225

Reiss, A. L., Abrams, M. T., Singer, H. S., Ross, J. L., & Denckla, M. B. (1996). Brain development, gender and IQ in children. A volumetric imaging study. *Brain*, *119*(Pt 5), 1763–1774. https://doi.org/10.1093/brain/119.5.1763

Rentería, M. E., Hansell, N. K., Strike, L. T., Mcmahon, K. L., de Zubicaray, G. I., Hickie, I. B., Thompson, P. M., Martin, N. G., Medland, S. E., & Wright, M. J. (2014). Genetic architecture of subcortical brain regions: Common and region-specific genetic contributions. *Genes, Brain and Behavior*, *13*(8), 821–830. https://doi.org/10.1111/gbb.12177

Rhodes, R. E., Saelens, B. E., & Sauvage-Mar, C. (2018). Understanding Physical Activity through Interactions Between the Built Environment and Social Cognition: A Systematic Review. *Sports Medicine*, *48*(8), 1893–1912. https://doi.org/10.1007/s40279-018-0934-0

Rice, F. L., & Van Der Loos, H. (1977). Development of the barrels and barrel field in the somatosensory cortex of the mouse. *Journal of Comparative Neurology*, *171*(4), 545–560. https://doi.org/10.1002/cne.901710408

Rodrigue, C., Gearhardt, A. N., & Bégin, C. (2019). Food Addiction in Adolescents: Exploration of psychological symptoms and executive functioning difficulties in a non-clinical sample. *Appetite*, *141*, 104303. https://doi.org/10.1016/j.appet.2019.05.034

Rodriguez-Ayllon, M., Derks, I. P. M., van den Dries, M. A., Esteban-Cornejo, I., Labrecque, J. A., Yang-Huang, J., Raat, H., Vernooij, M. W., White, T., Ortega, F. B., Tiemeier, H., & Muetzel, R. L. (2020). Associations of physical activity and screen time with white matter microstructure in children from the general population. *NeuroImage*, *205*, 116258. https://doi.org/10.1016/j.neuroimage.2019.116258

Rodriguez-Ayllon, M., Esteban-Cornejo, I., Verdejo-Román, J., Muetzel, R. L., Migueles, J. H., Mora-Gonzalez, J., Solis-Urra, P., Erickson, K. I., Hillman, C. H., Catena, A., Tiemeier, H., & Ortega, F. B. (2020). Physical Activity, Sedentary Behavior, and White Matter Microstructure in Children with Overweight or Obesity. *Medicine & Science in Sports & Exercise*, *52*(5), 1218–1226. https://doi.org/10.1249/mss.0000000000002233

Rogol, A. D., Roemmich, J. N., & Clark, P. A. (2002). Growth at puberty. *Journal of Adolescent Health*, *31*(S6), 192–200. https://doi.org/10.1016/S1054-139X(02)00485-8

Romeo, R. D. (2017). The impact of stress on the structure of the adolescent brain: Implications for adolescent mental health. *Brain Research*, *1654*, 185–191. https://doi.org/10.1016/j.brainres.2016.03.021

Rosenzweig, M. R. (1996). Aspects of the Search for Neural Mechanisms of Memory. *Annual Review of Psychology*, *47*, 1–32. https://doi.org/10.1146/annurev.psych.47.1.1

Ross, N., Yau, P. L., & Convit, A. (2015). Obesity, fitness, and brain integrity in adolescence. *Appetite*, *93*, 44–50. https://doi.org/10.1016/j.appet.2015.03.033

Ross, R., Goodpaster, B. H., Koch, L. G., Sarzynski, M. A., Kohrt, W. M., Johannsen, N. M., Skinner, J. S., Castro, A., Irving, B. A., Noland, R. C., Sparks, L. M., Spielmann, G., Day, A. G., Pitsch, W., Hopkins, W. G., & Bouchard, C. (2019). Precision exercise medicine: understanding exercise response variability. *British Journal of Sports Medicine*, *53*(18), 1141–1153. https://doi.org/10.1136/bjsports-2018-100328

Ruigrok, A. N. V., Salimi-Khorshidi, G., Lai, M. C., Baron-Cohen, S., Lombardo, M. V., Tait, R. J., & Suckling, J. (2014). A meta-analysis of sex differences in human brain structure. *Neuroscience and Biobehavioral Reviews*, *39*, 34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004

Ruiz, J. R., Rizzo, N. S., Hurtig-Wennlöf, A., Ortega, F. B., Wärnberg, J., & Sjöström, M. (2006). Relations of total physical activity and intensity to fitness and fatness in children: The European Youth Heart Study. *American Journal of Clinical Nutrition*, *84*(2), 299–303. https://doi.org/10.1093/ajcn/84.2.299

Ruotsalainen, I., Gorbach, T., Perkola, J., Renvall, V., Syväoja, H. J., Tammelin, T. H., Karvanen, J., & Parviainen, T. (2020). Physical activity, aerobic fitness, and brain white matter: Their role for executive functions in adolescence. *Developmental Cognitive Neuroscience*, *42*. https://doi.org/10.1016/j.dcn.2020.100765

Ruotsalainen, I., Renvall, V., Gorbach, T., Syväoja, H. J., Tammelin, T. H., Karvanen, J., & Parviainen, T. (2019). Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents. *Behavioural Brain Research*, *362*, 122–130. https://doi.org/10.1016/J.BBR.2018.12.041

Rushworth, M. F. S., Nixon, P. D., Renowden, S., Wade, D. T., & Passingham, R. E. (1997). The left parietal cortex and motor attention. *Neuropsychologia*, *35*(9), 1261–1273. https://doi.org/10.1016/S0028-3932(97)00050-X

Sala, G., & Gobet, F. (2020). Working memory training in typically developing children: A multilevel meta-analysis. *Psychonomic Bulletin and Review*, 1–12. https://doi.org/10.3758/s13423-019-01681-y

Sallis, J. F., Cerin, E., Conway, T. L., Adams, M. A., Frank, L. D., Pratt, M., Salvo, D., Schipperijn, J., Smith, G., Cain, K. L., Davey, R., Kerr, J., Lai, P. C., Mitáš, J., Reis, R., Sarmiento, O. L., Schofield, G., Troelsen, J., Van Dyck, D., … Owen, N. (2016). Physical activity in relation to urban environments in 14 cities worldwide: A cross-sectional study. *The Lancet*, *387*(10034), 2207–2217. https://doi.org/10.1016/S0140-6736(15)01284-2

Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. *Brain Research Reviews*, *35*(2), 146–160. https://doi.org/10.1016/S0165-0173(01)00044-3

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., Gur, R. C., & Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *NeuroImage*, *60*(1), 623–632. https://doi.org/10.1016/j.neuroimage.2011.12.063

Satterthwaite, T. D., Wolf, D. H., Ruparel, K., Erus, G., Elliott, M. A., Eickhoff, S. B., Gennatas, E. D., Jackson, C., Prabhakaran, K., Smith, A., Hakonarson, H., Verma, R., Davatzikos, C., Gur, R. E., & Gur, R. C. (2013). Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth. *NeuroImage*, *83*, 45–57. https://doi.org/10.1016/j.neuroimage.2013.06.045

Schaeffer, D. J., Krafft, C. E., Schwarz, N. F., Chi, L., Rodrigue, A. L., Pierce, J. E., Allison, J. D., Yanasak, N. E., Liu, T., Davis, C. L., & McDowell, J. E. (2014). An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. *Psychophysiology*, *51*(8), 728–733. https://doi.org/10.1111/psyp.12227

Schmithorst, V. J., & Yuan, W. (2010). White matter development during adolescence as shown by diffusion MRI. *Brain and Cognition*, *72*(1), 16–25. https://doi.org/10.1016/j.bandc.2009.06.005

Schutte, N. M., Nederend, I., Hudziak, J. J., Bartels, M., & de Geus, E. J. C. (2016). Twin-sibling study and meta-analysis on the heritability of maximal oxygen consumption. *Physiological Genomics*, *48*(3), 210–219. https://doi.org/10.1152/physiolgenomics.00117.2015

Scudder, M. R., Drollette, E. S., Szabo-Reed, A. N., Lambourne, K., Fenton, C. I., Donnelly, J. E., & Hillman, C. H. (2016). Tracking the relationship between children's aerobic fitness and cognitive control. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *35*(9), 967–978. https://doi.org/10.1037/hea0000343

Seghete, K. L. M., Herting, M. M., & Nagel, B. J. (2013). White matter microstructure correlates of inhibition and task-switching in adolescents. *Brain Research*, *1527*, 15–28. https://doi.org/10.1016/J.BRAINRES.2013.06.003

Seunarine, K. K., Clayden, J. D., Jentschke, S., Muñoz, M., Cooper, J. M., Chadwick, M. J., Banks, T., Vargha-Khadem, F., & Clark, C. A. (2016). Sexual Dimorphism in White Matter Developmental Trajectories Using Tract-Based Spatial Statistics. *Brain Connectivity*, *6*(1), 37–47. https://doi.org/10.1089/brain.2015.0340

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J. L., Giedd, J. N., & Wise, S. P. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience*, *28*(14), 3586–3594. https://doi.org/10.1523/JNEUROSCI.5309-07.2008

Shephard, R. J. (2003). Limits to the measurement of habitual physical activity by questionnaires. *British Journal of Sports Medicine*, *37*(3), 197–206; discussion 206. https://doi.org/10.1136/BJSM.37.3.197

Silani, G., Lamm, C., Ruff, C. C., & Singer, T. (2013). Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. *Journal of Neuroscience*, *33*(39), 15466–15476. https://doi.org/10.1523/JNEUROSCI.1488-13.2013

Silver, H., & Feldman, P. (2005). Evidence for Sustained Attention and Working Memory in Schizophrenia Sharing a Common Mechanism. *Journal of Neuropsychiatry*, *17*(3), 391–398. https://doi.org/10.1176/appi.neuropsych.17.3.391

Simmonds, D. J., Hallquist, M. N., Asato, M., & Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage*, *92*, 356–368. https://doi.org/10.1016/j.neuroimage.2013.12.044

Simms, N. K., Frausel, R. R., & Richland, L. E. (2018). Working memory predicts children's analogical reasoning. *Journal of Experimental Child Psychology, 166*, 160–177. https://doi.org/10.1016/j.jecp.2017.08.005

Singh, A. S., Saliasi, E., van den Berg, V., Uijtdewilligen, L., de Groot, R. H. M., Jolles, J., Andersen, L. B., Bailey, R., Chang, Y.-K., Diamond, A., Ericsson, I., Etnier, J. L., Fedewa, A. L., Hillman, C. H., McMorris, T., Pesce, C., Pühse, U., Tomporowski, P. D., & Chinapaw, M. J. M. (2019). Effects of physical activity interventions on cognitive and academic performance in children and adolescents: a novel combination of a systematic review and recommendations from an expert panel. *British Journal of Sports Medicine, 53*(10), 640–647. https://doi.org/10.1136/bjsports-2017-098136

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature Neuroscience, 7*(10), 1040–1047. https://doi.org/10.1038/nn1326

Sjöwall, D., Thorell, L. B., Mandic, M., & Westerståhl, M. (2019). No effects of a long-term physical activity intervention on executive functioning among adolescents. *SAGE Open Medicine, 7*. https://doi.org/10.1177/2050312119880734

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31*(4), 1487–1505. https://doi.org/10.1016/J.NEUROIMAGE.2006.02.024

Song, S. K., Sun, S. W., Ju, W. K., Lin, S. J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage, 20*(3), 1714–1722. https://doi.org/10.1016/j.neuroimage.2003.07.005

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage, 17*(3), 1429–1436. https://doi.org/10.1006/nimg.2002.1267

Song, S., Sharma, N., Buch, E. R., & Cohen, L. G. (2012). White matter microstructural correlates of superior long-term skill gained implicitly under randomized practice. *Cerebral Cortex, 22*(7). https://doi.org/10.1093/cercor/bhr247

Sowell, E. R., Delis, D., Stiles, J., & Jernigan, T. L. (2001). Improved memory functioning and frontal lobe maturation between childhood and adolescence: A structural MRI study. *Journal of the International Neuropsychological Society, 7*(3), 312–322. https://doi.org/10.1017/S135561770173305X

Sowell, E. R., Peterson, B. S., Kan, E., Woods, R. P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P. M., & Toga, A. W. (2007). Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cerebral Cortex, 17*(7), 1550–1560. https://doi.org/10.1093/cercor/bhl066

Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003). Mapping cortical change across the human life span. *Nature Neuroscience, 6*(3), 309–315. https://doi.org/10.1038/nn1008

Spear, L. P. (2013). Adolescent neurodevelopment. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, *52*(2 Suppl 2), S7-13. https://doi.org/10.1016/j.jadohealth.2012.05.006

Squeglia, L. M., & Gray, K. M. (2016). Alcohol and Drug Use and the Developing Brain. *Current Psychiatry Reports*, *5*, 46. https://doi.org/10.1007/s11920-016-0689-y

Stave, E. A., De Bellis, M. D., Hooper, S. R., Woolley, D. P., Chang, S. K., & Chen, S. D. (2017). Dimensions of attention associated with the microstructure of corona radiata white matter. *Journal of Child Neurology*, *32*(5), 458–466. https://doi.org/10.1177/0883073816685652

Steele, C. J., Bailey, J. A., Zatorre, R. J., & Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: Evidence for a sensitive period. *Journal of Neuroscience*, *33*(3), 1282–1290. https://doi.org/10.1523/JNEUROSCI.3578-12.2013

Stoeckel, C., Gough, P. M., Watkins, K. E., & Devlin, J. T. (2009). Supramarginal gyrus involvement in visual word recognition. *Cortex*, *45*(9), 1091–1096. https://doi.org/10.1016/j.cortex.2008.12.004

Strömmer, J. M., Davis, S. W., Henson, R. N., Tyler, L. K., Tyler, L. K., Brayne, C., Bullmore, E. T., Calder, A. C., Cusack, R., Dalgleish, T., Duncan, J., Henson, R. N., Matthews, F. E., Marslen-Wilson, W. D., Rowe, J. B., Shafto, M. A., Campbell, K., Cheung, T., Davis, S., … Campbell, K. L. (2020). Physical Activity Predicts Population-Level Age-Related Differences in Frontal White Matter. *The Journals of Gerontology: Series A*, *75*(2), 236–243. https://doi.org/10.1093/gerona/gly220

Stroth, S., Kubesch, S., Dieterle, K., Ruchsow, M., Heim, R., & Kiefer, M. (2009). Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. *Brain Research*, *1269*, 114–124. https://doi.org/10.1016/J.BRAINRES.2009.02.073

Sun, S. W., Liang, H. F., Le, T. Q., Armstrong, R. C., Cross, A. H., & Song, S. K. (2006). Differential sensitivity of in vivo and ex vivo diffusion tensor imaging to evolving optic nerve injury in mice with retinal ischemia. *NeuroImage*, *32*(3), 1195–1204. https://doi.org/10.1016/j.neuroimage.2006.04.212

Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biology*, *7*(7), e1000157. https://doi.org/10.1371/journal.pbio.1000157

Swagerman, S. C., Brouwer, R. M., de Geus, E. J. C., Hulshoff Pol, H. E., & Boomsma, D. I. (2014). Development and heritability of subcortical brain volumes at ages 9 and 12. *Genes, Brain and Behavior*, *13*(8), 733–742. https://doi.org/10.1111/gbb.12182

Syväoja, H. J., Tammelin, T. H., Ahonen, T., Kankaanpää̈, A., & Kantomaa, M. T. (2014). The associations of objectively measured physical activity and sedentary time with cognitive functions in school-aged children. *PLoS ONE*, *9*(7), e103559. https://doi.org/10.1371/journal.pone.0103559

Talukdar, T., Nikolaidis, A., Zwilling, C. E., Paul, E. J., Hillman, C. H., Cohen, N. J., Kramer, A. F., & Barbey, A. K. (2018). Aerobic Fitness Explains Individual Differences in the Functional Brain Connectome of Healthy

Young Adults. *Cerebral Cortex*, *28*(10), 3600–3609. https://doi.org/10.1093/cercor/bhx232

Tamnes, C. K., Bos, M. G. N., van de Kamp, F. C., Peters, S., & Crone, E. A. (2018). Longitudinal development of hippocampal subregions from childhood to adulthood. *Developmental Cognitive Neuroscience*, *30*, 212–222. https://doi.org/10.1016/j.dcn.2018.03.009

Tamnes, C. K., Fjell, A. M., Westlye, L. T., Østby, Y., & Walhovd, K. B. (2012). Becoming consistent: Developmental reductions in intraindividual variability in reaction time are related to white matter integrity. *Journal of Neuroscience*, *32*(3), 972–982. https://doi.org/10.1523/JNEUROSCI.4779-11.2012

Tamnes, C. K., Herting, M. M., Goddings, A.-L., Meuwese, R., Blakemore, S.-J., Dahl, R. E., Güroğlu, B., Raznahan, A., Sowell, E. R., Crone, E. A., & Mills, K. L. (2017). Development of the Cerebral Cortex across Adolescence: A Multisample Study of Inter-Related Longitudinal Changes in Cortical Volume, Surface Area, and Thickness. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *37*(12), 3402–3412. https://doi.org/10.1523/JNEUROSCI.3302-16.2017

Tamnes, C. K., Østby, Y., Fjell, A. M., Westlye, L. T., Due-Tønnessen, P., & Walhovd, K. B. (2010). Brain maturation in adolescence and young adulthood: Regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex*, *20*(3), 534–548. https://doi.org/10.1093/cercor/bhp118

Tamnes, C. K., Roalf, D. R., Goddings, A. L., & Lebel, C. (2018). Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. *Developmental Cognitive Neuroscience*, *33*, 161–175. https://doi.org/10.1016/j.dcn.2017.12.002

Tarp, J., Domazet, S. L., Froberg, K., Hillman, C. H., Andersen, L. B., & Bugge, A. (2016). Effectiveness of a School-Based Physical Activity Intervention on Cognitive Performance in Danish Adolescents: LCoMotion—Learning, Cognition and Motion – A Cluster Randomized Controlled Trial. *PLOS ONE*, *11*(6), e0158087. https://doi.org/10.1371/journal.pone.0158087

Teeuw, J., Brouwer, R. M., Guimarães, J. P. O. F. T., Brandner, P., Koenis, M. M. G., Swagerman, S. C., Verwoert, M., Boomsma, D. I., & Hulshoff Pol, H. E. (2019). Genetic and environmental influences on functional connectivity within and between canonical cortical resting-state networks throughout adolescent development in boys and girls. *NeuroImage*, *202*, 116073. https://doi.org/10.1016/j.neuroimage.2019.116073

Teeuw, J., Brouwer, R. M., Koenis, M. M. G., Swagerman, S. C., Boomsma, D. I., & Hulshoff Pol, H. E. (2019). Genetic Influences on the Development of Cerebral Cortical Thickness During Childhood and Adolescence in a Dutch Longitudinal Twin Sample: The Brainscale Study. *Cerebral Cortex*, *29*(3), 978–993. https://doi.org/10.1093/cercor/bhy005

Telzer, E. H., Goldenberg, D., Fuligni, A. J., Lieberman, M. D., & Gálvan, A. (2015). Sleep variability in adolescence is associated with altered brain development. *Developmental Cognitive Neuroscience*, *14*, 16–22. https://doi.org/10.1016/j.dcn.2015.05.007

Thillay, A., Roux, S., Gissot, V., Carteau-Martin, I., Knight, R. T., Bonnet-Brilhault, F., & Bidet-Caulet, A. (2015). Sustained attention and prediction: Distinct brain maturation trajectories during adolescence. *Frontiers in Human Neuroscience*, *9*, 519. https://doi.org/10.3389/fnhum.2015.00519

Tian, Q., Glynn, N. W., Erickson, K. I., Aizenstein, H. J., Simonsick, E. M., Yaffe, K., Harris, T. B., Kritchevsky, S. B., Boudreau, R. M., Newman, A. B., Lopez, O. L., Saxton, J., Rosano, C., & Health ABC Study. (2015). Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behavioural Brain Research*, *284*, 51–57. https://doi.org/10.1016/j.bbr.2015.01.045

Tierney, A. T., Krizman, J., Kraus, N., & Tallal, P. (2015). Music training alters the course of adolescent auditory development. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(32), 10062–10067. https://doi.org/10.1073/pnas.1505114112

Tobyne, S. M., Boratyn, D., Johnson, J. A., Greve, D. N., Mainero, C., & Klawiter, E. C. (2016). A surface-based technique for mapping homotopic interhemispheric connectivity: Development, characterization, and clinical application. *Human Brain Mapping*, *37*(8), 2849–2868. https://doi.org/10.1002/hbm.23214

Tozzi, L., Carballedo, A., Lavelle, G., Doolin, K., Doyle, M., Amico, F., Mccarthy, H., Gormley, J., Lord, A., O'Keane, V., & Frodl, T. (2016). Longitudinal functional connectivity changes correlate with mood improvement after regular exercise in a dose-dependent fashion. *European Journal of Neuroscience*, *43*(8), 1089–1096. https://doi.org/10.1111/ejn.13222

Treble, A., Hasan, K. M., Iftikhar, A., Stuebing, K. K., Kramer, L. A., Cox, C. S., Swank, P. R., & Ewing-Cobbs, L. (2013). Working memory and corpus callosum microstructural integrity after pediatric traumatic brain injury: A diffusion tensor tractography study. *Journal of Neurotrauma*, *30*(19), 1609–1619. https://doi.org/10.1089/neu.2013.2934

Treit, S., Chen, Z., Rasmussen, C., & Beaulieu, C. (2014). White matter correlates of cognitive inhibition during development: A diffusion tensor imaging study. *Neuroscience*, *276*, 87–97. https://doi.org/10.1016/j.neuroscience.2013.12.019

Trost, S. G., Loprinzi, P. D., Moore, R., Pfeiffer, K. A., Trost, A., Loprinzi, P. D., Moore, R., & Pfeiffer, K. A. (2011). Comparison of Accelerometer Cut Points for Predicting Activity Intensity in Youth. *Med. Sci. Sports Exerc*, *43*(7), 1360–1368. https://doi.org/10.1249/MSS.0b013e318206476e

Ullman, H., Almeida, R., & Klingberg, T. (2014). Structural maturation and brain activity predict future working memory capacity during childhood development. *Journal of Neuroscience*, *34*(5), 1592–1598. https://doi.org/10.1523/JNEUROSCI.0842-13.2014

Ullman, H., & Klingberg, T. (2017). Timing of white matter development determines cognitive abilities at school entry but not in late adolescence. *Cerebral Cortex*, *27*(9), 4516–4522. https://doi.org/10.1093/cercor/bhw256

Urrila, A. S., Artiges, E., Massicotte, J., Miranda, R., Vulser, H., Bézivin-Frere, P., Lapidaire, W., Lemaître, H., Penttilä, J., Conrod, P. J., Garavan, H., Martinot, M. L. P., & Martinot, J. L. (2017). Sleep habits, academic performance, and the adolescent brain structure. *Scientific Reports*, *7*, 41678. https://doi.org/10.1038/srep41678

Van Buuren, S. (2012). *Flexible imputation of missing data*. CRC Press.

Van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice : Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3), 1–67. https://doi.org/10.18637/jss.v045.i03

van den Heuvel, M. P., van Soelen, I. L. C., Stam, C. J., Kahn, R. S., Boomsma, D. I., & Hulshoff Pol, H. E. (2013). Genetic control of functional brain network efficiency in children. *European Neuropsychopharmacology*, *23*(1), 19–23. https://doi.org/10.1016/j.euroneuro.2012.06.007

van der Kouwe, A. J. W., Benner, T., Fischl, B., Schmitt, F., Salat, D. H., Harder, M., Sorensen, A. G., & Dale, A. M. (2005). On-line automatic slice positioning for brain MR imaging. *NeuroImage*, *27*(1), 222–230. https://doi.org/10.1016/J.NEUROIMAGE.2005.03.035

Van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(23), 13427–13431. https://doi.org/10.1073/pnas.96.23.13427

Van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience*, *2*(3), 266–270. https://doi.org/10.1038/6368

Vanes, L. D., Moutoussis, M., Ziegler, G., Goodyer, I. M., Fonagy, P., Jones, P. B., Bullmore, E. T., & Dolan, R. J. (2020). White matter tract myelin maturation and its association with general psychopathology in adolescence and early adulthood. *Human Brain Mapping*, *41*(3), 827–839. https://doi.org/10.1002/hbm.24842

Vanhelst, J., Béghin, L., Duhamel, A., Manios, Y., Molnar, D., De Henauw, S., Moreno, L. A., Ortega, F. B., Sjöström, M., Widhalm, K., Gottrand, F., Moreno, L. A., Moreno, L. A., Gottrand, F., De Henauw, S., González-Gross, M., Gilbert, C., Kafatos, A., Moreno, L. A., … Gómez Lorente, J. J. (2016). Physical Activity Is Associated with Attention Capacity in Adolescents. *The Journal of Pediatrics*, *168*, 126-131.e2. https://doi.org/10.1016/J.JPEDS.2015.09.029

Veldsman, M., Churilov, L., Werden, E., Li, Q., Cumming, T., & Brodtmann, A. (2017). Physical Activity after Stroke Is Associated with Increased Interhemispheric Connectivity of the Dorsal Attention Network. *Neurorehabilitation and Neural Repair*, *31*(2), 157–167. https://doi.org/10.1177/1545968316666958

Verburgh, L., Königs, M., Scherder, E. J. A., & Oosterlaan, J. (2014). Physical exercise and executive functions in preadolescent children, adolescents and young adults: A meta-analysis. *British Journal of Sports Medicine*, *48*(12), 973–979. https://doi.org/10.1136/bjsports-2012-091441

Vestergaard, M., Madsen, K. S., Baaré, W. F. C., Skimminge, A., Ejersbo, L. R., Ramsøy, T. Z., Gerlach, C., Åkeson, P., Paulson, O. B., & Jernigan, T. L. (2011). White Matter Microstructure in Superior Longitudinal Fasciculus Associated with Spatial Working Memory Performance in Children.

Journal of Cognitive Neuroscience, *23*(9), 2135–2146. https://doi.org/10.1162/jocn.2010.21592

Vijayakumar, N., Allen, N. B., Youssef, G., Dennison, M., Yücel, M., Simmons, J. G., & Whittle, S. (2016). Brain development during adolescence: A mixed-longitudinal investigation of cortical thickness, surface area, and volume. *Human Brain Mapping*, *37*(6), 2027–2038. https://doi.org/10.1002/hbm.23154

Vijayakumar, N., Op de Macks, Z., Shirtcliff, E. A., & Pfeifer, J. H. (2018). Puberty and the human brain: Insights into adolescent development. *Neuroscience and Biobehavioral Reviews*, *92*, 417–436. https://doi.org/10.1016/j.neubiorev.2018.06.004

Vollmer, B., Lundequist, A., Mårtensson, G., Nagy, Z., Lagercrantz, H., Smedler, A. C., & Forssberg, H. (2017). Correlation between white matter microstructure and executive functions suggests early developmental influence on long fibre tracts in preterm born adolescents. *PLoS ONE*, *12*(6), e0178893. https://doi.org/10.1371/journal.pone.0178893

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Kim, J. S., Alves, H., Szabo, A., Phillips, S. M., Wójcicki, T. R., Mailey, E. L., Olson, E. A., Gothe, N., Vieira-Potter, V. J., Martin, S. A., Pence, B. D., Cook, M. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2013). Neurobiological markers of exercise-related brain plasticity in older adults. *Brain, Behavior, and Immunity*, *28*, 90–99. https://doi.org/10.1016/j.bbi.2012.10.021

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., Alves, H., Heo, S., Szabo, A., White, S. M., Wojcicki, T. R., Mailey, E. L., Gothe, N., Olson, E. A., McAuley, E., & Kramer, A. F. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Frontiers in Aging Neuroscience*, *2*, 32. https://doi.org/10.3389/fnagi.2010.00032

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., Fanning, J., Awick, E., Gothe, N. P., Olson, E. A., McAuley, E., & Kramer, A. F. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage*, *131*, 113–125. https://doi.org/10.1016/J.NEUROIMAGE.2015.10.044

Wei, P., Leong, D., Calabrese, E., White, L., Pierce, T., Platt, S., & Provenzale, J. (2013). Diffusion Tensor Imaging of Neural Tissue Organization: Correlations between Radiologic and Histologic Parameters. *The Neuroradiology Journal*, *26*(5), 501–510. https://doi.org/10.1177/197140091302600502

Westfall, D. R., Gejl, A. K., Tarp, J., Wedderkopp, N., Kramer, A. F., Hillman, C. H., & Bugge, A. (2018). Associations Between Aerobic Fitness and Cognitive Control in Adolescents. *Frontiers in Psychology*, *9*, 1298. https://doi.org/10.3389/fpsyg.2018.01298

Wheeler-Kingshott, C. A. M., & Cercignani, M. (2009). About “axial” and “radial” diffusivities. *Magnetic Resonance in Medicine*, *61*(5), 1255–1260. https://doi.org/10.1002/mrm.21965

Wickel, E. E. (2017). Sedentary time, physical activity, and executive function in a longitudinal study of youth. *Journal of Physical Activity and Health*, *14*(3), 222–228. https://doi.org/10.1123/jpah.2016-0200

Wierenga, L. M., Bos, M. G. N., Schreuders, E., vd Kamp, F., Peper, J. S., Tamnes, C. K., & Crone, E. A. (2018). Unraveling age, puberty and testosterone effects on subcortical brain development across adolescence. *Psychoneuroendocrinology*, *91*, 105–114. https://doi.org/10.1016/j.psyneuen.2018.02.034

Wierenga, L. M., Sexton, J. A., Laake, P., Giedd, J. N., & Tamnes, C. K. (2018). A key characteristic of sex differences in the developing brain: Greater variability in brain structure of boys than girls. *Cerebral Cortex*, *28*(8), 2741–2751. https://doi.org/10.1093/cercor/bhx154

Wijndaele, K., Westgate, K., Stephens, S. K., Blair, S. N., Bull, F. C., Chastin, S. F. M., Dunstan, D. W., Ekelund, U., Esliger, D. W., Freedson, P. S., Granat, M. H., Matthews, C. E., Owen, N., Rowlands, A. V., Sherar, L. B., Tremblay, M. S., Troiano, R. P., Brage, Sø., & Healy, G. N. (2015). Utilization and Harmonization of Adult Accelerometry Data: Review and Expert Consensus. *Medicine and Science in Sports and Exercise*, *47*(10), 2129–2139. https://doi.org/10.1249/MSS.0000000000000661

Williams, C. J., Williams, M. G., Eynon, N., Ashton, K. J., Little, J. P., Wisloff, U., & Coombes, J. S. (2017). Genes to predict VO2max trainability: A systematic review. *BMC Genomics*, *18*(S8), 831. https://doi.org/10.1186/s12864-017-4192-6

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. https://doi.org/10.1016/J.NEUROIMAGE.2014.01.060

Woo, T. U. W. (2014). Neurobiology of schizophrenia onset. *Current Topics in Behavioral Neurosciences*, *16*, 267–295. https://doi.org/10.1007/7854_2013_243

Yakovlev, P. I., & Lecours, A.-R. (1967). The myelogenetic cycles of regional maturation of the brain. In Minkowski (Ed.), *Regional Development of Brain in Early Life* (pp. 3–70). Oxford: Blackwell.

Yekutieli, D., & Benjamini, Y. (1999). Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics. *Journal of Statistical Planning and Inference*, *82*(1–2), 171–196. https://doi.org/10.1016/S0378-3758(99)00041-5

Yli-Piipari, S., Leskinen, E., Jaakkola, T., & Liukkonen, J. (2012). Predictive role of physical education motivation: The developmental trajectories of physical activity during grades 7–9. *Research Quarterly for Exercise and Sport*, *83*(4), 560–569. https://doi.org/10.1080/02701367.2012.10599253

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *NeuroImage*, *22*(1), 394–400. https://doi.org/10.1016/j.neuroimage.2003.12.030

Zhang, R., Geng, X., & Lee, T. M. C. (2017). Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Structure and Function*, *222*(9), 3973–3990. https://doi.org/10.1007/s00429-017-1443-x

Ziegler, D. A., Simon, A. J., Gallen, C. L., Skinner, S., Janowich, J. R., Volponi, J. J., Rolle, C. E., Mishra, J., Kornfield, J., Anguera, J. A., & Gazzaley, A. (2019). Closed-loop digital meditation improves sustained attention in young adults. *Nature Human Behaviour*, *3*(7), 746–757. https://doi.org/10.1038/s41562-019-0611-9

Zuo, X. N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D. S., Bangaru, S., Grzadzinski, R., Evans, A. C., Zang, Y. F., Castellanos, F. X., & Milham, M. P. (2010). Growing together and growing apart: Regional and sex differences in the lifespan developmental trajectories of functional homotopy. *Journal of Neuroscience*, *30*(45), 15034–15043. https://doi.org/10.1523/JNEUROSCI.2612-10.2010

ORIGINAL PAPERS

I

AEROBIC FITNESS, BUT NOT PHYSICAL ACTIVITY, IS ASSOCIATED WITH GREY MATTER VOLUME IN ADOLESCENTS

by

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Research report

Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents

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ABSTRACT

Higher levels of aerobic fitness and physical activity are linked to beneficial effects on brain health, especially in older adults. The generalizability of these earlier results to young individuals is not straightforward, because physiological responses (such as cardiovascular responses) to exercise may depend on age. Earlier studies have mostly focused on the effects of either physical activity or aerobic fitness on the brain. Yet, while physical activity indicates the amount of activity, aerobic fitness is an adaptive state or attribute that an individual has or achieves. Here, by measuring both physical activity and aerobic fitness in the same study, we aimed to differentiate the association between these two measures and grey matter volume specifically. Magnetic resonance imaging scans were used to study volumes of 30 regions of interest located in the frontal, motor and subcortical areas of 60 adolescents (12.7–16.2 years old). Moderate-to-vigorous intensity physical activity (MVPA) was measured with hip-worn accelerometers and aerobic fitness was assessed with a 20-m shuttle run. Multiple regression analyses revealed a negative association between aerobic fitness and left superior frontal cortex volume and a positive association between aerobic fitness and the left pallidum volume. No associations were found between MVPA and any brain region of interest. These results demonstrate unequal contribution of physical activity and aerobic fitness on grey matter volumes, with inherent or achieved capacity (aerobic fitness) showing clearer associations than physical activity.

1. Introduction

Aerobic fitness, also referred to as cardiorespiratory fitness, and physical activity are factors that are known to be associated with brain health. Studies have demonstrated that physical activity and aerobic fitness levels are positively associated with several structural properties of grey matter e.g. [1–3]. However, the majority of the research in this field has focused on older adults, and the generalizability of these results to other age groups is not straightforward. The integrity of the neural network in later life is strongly influenced by the developmental processes during the first decades of life, highlighting the importance of exercise-related effects on the brain during this time period. Importantly, research so far has focused on the influence of *either* physical fitness *or* physical activity on brain measures rather than comparing the effects between them. In order to understand the role and significance of exercise-related measures on brain structure, it is crucial to compare the contribution of physical activity behaviour vs. the level of aerobic fitness to grey matter volumes in adolescents.

Physical activity and aerobic fitness are distinct concepts. Caspersen et al. [4] defined physical activity as “any bodily movement produced by skeletal muscles that results in energy expenditure” (p.126). On the other hand, physical fitness is a condition or adaptive state that an individual has or achieves. Aerobic fitness is typically measured either directly by measuring oxygen consumption during maximal exercise test or indirectly by using submaximal tests or field tests, such as the maximal 20-m shuttle run. Physical activity can be determined subjectively using questionnaires or objectively with measurement devices such as accelerometers. However, self-reported physical activity

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Abbreviations: eTIV, estimated intracranial volume; MVPA, moderate-to-vigorous intensity physical activity; ROI, region of interest

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assessments are considered less valid, because they are influenced by recall biases and other factors [5].

Even though measures of physical activity and aerobic fitness provide different information, they are related to each other to a certain extent. There seems to be a dose-response relationship between physical activity and aerobic fitness, concerning both the intensity and the amount of physical activity. In other words, the higher the intensity and amount of exercise training, the larger the improvements in aerobic fitness [6–8]. Importantly however, during adolescence the relationship between objectively measured physical activity and aerobic fitness is suggested to be only low to moderate [9–11]. Besides individual's own actions, aerobic fitness is influenced by inherent properties, the genotype. More than half of the individual differences in aerobic fitness could be explained by heritability [12,13]. Studying the independent associations of both physical activity and aerobic fitness on grey matter volumes, in the same individuals, will critically extend our understanding of the specific aspects of these measures.

In recent neuroimaging literature, aerobic fitness has been associated with grey matter properties in several brain regions. Surprisingly, only one group has investigated this association in adolescents. Herting et al. studied male adolescents (15–18 years old) and found that the level of aerobic fitness correlated with left hippocampus volume [14] and with right rostral middle frontal cortical volume [15]. In children, aerobic fitness has been demonstrated to associate with several subcortical regions, such as the hippocampus and basal ganglia [16–20]. In addition, exploratory analysis by Chaddock-Heyman et al. [21] proposes that more highly fit children may have decreased cortical thickness in superior frontal cortex, superior temporal areas, and lateral occipital cortex. To the best of our knowledge, only one study investigated the relationship between physical activity and grey matter volumes in youth. Based on self-reported, but not objectively measured physical activity, Herting et al. [15] found that male adolescents in high physical activity group demonstrated larger right medial pericalcarine and left precuneus surface areas than in low activity group.

Given these findings, it is problematic to determine whether it is the regular physical activity or the aerobic fitness level that is more important for brain structures in youth. Animal models using rats bred for their response to exercise training (high vs. low induced change in running capacity) have shed some light on this issue. Nokia et al. [22] observed that high-response rats exhibited larger increases in hippocampal neurogenesis than low-response rats after physical training. However, high-response rats also ran more, so the amount of physical training was not equal between groups. When controlling for amount of physical activity, female high-response rats still showed a higher rate of neurogenesis in hippocampus [23]. Moreover, the training at same intensity levels induced different responses in brain-derived neurotrophic factor (BDNF) in low- and high-response rats [24]. Thus, in animal models, inherent running capacity seemed to affect brain responses even though the exercise was similar between groups. Taken together, these results suggest that neither the amount of physical exercise nor the running capacity can independently explain differential responses to exercise.

Age has been suggested to influence the physiological responses to exercise. Several studies have reported age-related differences in exercise responses [25–28]. Supporting these human studies, animal models also indicate that age-related responses to exercise can be seen in cognition [29,30], in BDNF [30], and in microvascular function [31]. Although the main focus has been on the differences between young and old individuals, distinct responses to exercise have been also observed between adolescents and adults. Interestingly, Hopkins et al. [30] found that exercise enhanced relative levels of BDNF across brain regions and object recognition memory in adolescent rats 2–4 weeks after training intervention, but not in adult rats. Thus, brain responses to exercise can differ depending on age.

Despite the considerable number of studies concerning the effects of aerobic fitness or physical activity on grey matter volume in older adults, the evidence for this relationship in adolescence is inconclusive. To the best of our knowledge, no studies to date have compared objectively measured physical activity and fitness with grey matter volumes in adolescents. Therefore, we investigated how both physical activity and aerobic fitness associates with grey matter volumes in the adolescent brain. We measured physical activity objectively with accelerometers and aerobic fitness with a 20-m shuttle run. Magnetic resonance imaging (MRI) was applied to measure grey matter volumes. Based on the previous literature we hypothesized that both physical activity and aerobic fitness would show positive association with grey matter volumes in the basal ganglia and hippocampus.

2. Methods

2.1. Participants

Participants for this study were recruited from three schools in Central and Southern Finland. Potential participants were selected among volunteers participating in a larger longitudinal study (for more details see [32]). Cross-sectional data, collected at the end of the longitudinal study, was used in the current study. Potential participants were screened for exclusion criteria, which were: MRI contraindications, neurological disorders, use of medication that influences the central nervous system, major medical condition and left-handedness, which was assessed by the Edinburgh Handedness Inventory during the first research visit. Furthermore, in order to evaluate pubertal development, participants self-reported their stage of puberty by using the Tanner scale [33,34]. Sixty-one right-handed participants were scanned. One participant was removed from the analysis owing to excessive motion artefacts in the MRI. Thus, 60 adolescents were included in the analysis. The Central Finland Healthcare District Ethical Committee accepted the study. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and all participants and their legal guardian provided written informed consent. The participants were compensated with a 30-euro gift card for the participation in the brain scans.

2.2. Physical activity and aerobic fitness

Physical activity was objectively measured using a triaxial ActiGraph (Pensacola, FL, USA) GT3X + and wGT3X + accelerometers (for full details see Joensuu et al. [32]). Subjects were instructed to wear accelerometers on their right hip during waking hours for seven consecutive days, except during water-related activities. 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 analysis as such. For those subjects, that did not meet this criterion, a multiple imputation method (explained in more detail later) was employed to fill in the missing data. Activity counts were collected in 15 s epochs. If there was a period of at least 30 min of consecutive zero counts, it was considered as a non-wear time. A customized Visual Basic macro for Excel software was used for data reduction. 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). Data was collected at a sampling frequency of 60 Hz and standardly filtered. The cut points of Evenson et al. were utilised in the analysis [35,36].

Aerobic fitness was assessed with the maximal 20-m shuttle run test. The test was performed as described by Nupponen et al. [37]. Each participant ran between two lines 20-m apart at accelerating pace, which was indicated with an audio signal. The time participants ran until they failed to reach the end lines in two consecutive tones indicated the 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, speed was increased 0.5 km/h per level. The duration of each level was one minute. Participants were encouraged to keep running throughout the test.

In addition to physical activity and aerobic fitness tests, participants completed sets of tests on muscular fitness (push-up and curl-up), flexibility (four different measurements), and fundamental movement skills (5-leap test, throwing-catching combination test), which are not included in the current study article [32]. Of these tests, only the results of the throw-catch combination were used in multiple imputations, as explained in more detail later.

2.3. Magnetic resonance imaging acquisition

Images were acquired on a 3 T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) using a 32-channel head coil at the Aalto Neuroimaging unit, Aalto University, Espoo, Finland. Total scanning time was approximately 45 min and it included structural, diffusion, functional, field mapping, and perfusion MRI scans. All scans except perfusion MRI were acquired using "Auto Align" to minimize variation in slice positioning [38]. Prior to imaging, participants were familiarized with the measurement protocol. All participants were instructed to keep their head still during the scanning and pads were used to minimize head motion. In addition, the participants wore earplugs to compensate for the noisy environment.

T1-weighted structural images were acquired in the sagittal plane using the MPRAGE pulse sequence. The protocol included 176 sagittal slices and the scanning time was 6:02 min. The acquisition parameters were set as follows: TI = 1100 ms, TR = 2530 ms, TE = 3.3 ms, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3, flip angle = 7°, slice thickness = 1 mm, FOV = $256 \times 256 \times 176$ mm^3, bandwidth = 200 Hz/Px, and using the GRAPPA parallel imaging technique with an acceleration factor R = 2 and with 32 reference lines.

2.4. Image analysis

Images were visually inspected for motion artefacts during scanning. Six participants had large motion artefacts, warranting a second T1-weighted scan immediately after the first T1-weighted scan. Image analysis suite, FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu), was used for cortical surface reconstruction and volumetric segmentation [39]. Briefly, this analysis includes processes such as removal of non-brain tissue, Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures [40,41], intensity normalization, tessellation of the grey matter white matter boundary, and automated topology correction. Following the automated FreeSurfer pipeline, all reconstructed volumes were visually inspected. First, all slices were manually inspected for errors in skull-stripping, if errors occurred either watershed threshold was changed or manual edits were carried out as part of the recommended workflow for FreeSurfer. Then white matter segmentation and pial surface were inspected. Errors were manually corrected following FreeSurfer guidelines. Estimated intracranial volume (eTIV) was calculated based on the method described by Buckner et al. [42]. Subcortical region volumes were calculated using FreeSurfer's automatic whole brain segmentation [40]. Following subcortical volumes were chosen for regions of interests (ROIs): putamen, pallidum, caudate, nucleus accumbens, thalamus and hippocampus. Cortical regions were labelled according to the Desikan-Killiany cortical atlas [43]. The volumes of the following cortical structures were chosen as ROIs: paracentral lobule, postcentral gyrus, posterior cingulate cortex, precentral gyrus, superior frontal gyrus, and lateral orbitofrontal cortex. In addition, the following three regions were calculated as a sum of two separate regions: anterior cingulate cortex (rostral anterior and caudal anterior division), middle frontal gyrus (rostral and caudal divisions), and medial orbitofrontal cortex (medial orbitofrontal cortex and frontal pole) (Fig. 1). The frontal pole was not treated as a single area as the reliability of the area was not measured in Desikan et al. [43]. We used following rationale to choose ROIs for the analysis. Those subcortical areas that are known to be involved in motor behaviour (such as putamen and thalamus) were selected. In addition, hippocampus was selected as a ROI, since it has been shown to relate to aerobic fitness by several animal and human studies [14,17,44]. Several studies suggest that either aerobic fitness or physical activity are related to cognitive skills and especially to executive functions in youth [e.g. 45–47]. Frontal brain areas have a critical contribution especially in executive functions [e.g. 48]. Therefore, we included those frontal brain areas that have been shown to relate to either physical activity or aerobic fitness.

2.5. Statistical analyses

We assessed the associations between volumetric measures of brain structure and physical activity as well as aerobic fitness with multiple regression model:

$$GM_i = \beta_0 + \beta_1 X_i + \beta_2 Age_i + \beta_3 Gender_i + \beta_4 PS_i + \beta_5 eTIV_i + \varepsilon_i,$$

where GM_i is the grey matter volume of a ROI for subject i, X_i is physical activity or aerobic fitness, Age_i, $Gender_i$, PS_i and $eTIV_i$ are age, gender, pubertal stage and estimated intracranial volume, respectively and error terms ε_i are independent and identically distributed normal random variables with zero mean and same standard deviation. Body mass index (BMI) was not included as a covariate as there was no associations between BMI and any of the ROIs. All predictors were entered simultaneously into the model. Residual plots and Q−Q plots were used to check the assumptions of linearity as well as normality and homoscedasticity of the residuals. The means of the residuals in all models were close to zero. The highest correlations were between gender and eTIV r = 0.59 and between puberty and age r = 0.56 indicating that multicollinearity was not a problem. All variance inflation factors were below 2. False discovery rate (FDR) [49] was used to handle multiple comparisons (separately for MVPA and 20-m shuttle run). The relationship between either physical activity or aerobic fitness and grey matter volumes has not been previously studied in this age group. Therefore, we chose to include a more comprehensive set of brain regions in the analysis. We acknowledge that with this sample size, a strict correction for multiple comparisons may increase the number of false negative findings. To balance between false positives and false negatives we chose to use FDR threshold of 0.1. Results reported according to this criterion were considered noteworthy. FDR-adjusted p-values were calculated according to Yekutieli and Benjamini [50].

2.6. Multiple imputation

MRI volumetric measures, eTIV, age, and gender were available for all participants while missing data occurred in the pubertal stage and in both 20-m shuttle run and MVPA. The percentage of missing values per variable ranged between 10% and 22%.

Incomplete data for several variables (see Table 1 and Supplementary material) were imputed using multiple imputation under fully conditional specification (chained equations) [51]. The predominant cause of missing data entries was the subjects being absent from school during the measurement occasion because of sickness and insufficient number of valid measurement days (two weekdays and one weekend day) for physical activity. 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 puberty, shuttle-run tests (correlation with preceding 20-m shuttle run test = 0.57) and weekday measures of physical activity (correlation with total MVPA [also weekend days included] = 0.95) were available. These variables, as well as age, gender, height, BMI, results of throw and catch test, and grey matter volume in ROIs were used as predictors in the imputation model. As advised (Van Buuren, 2012 chapter 2.3.3 [52]), 50 imputed datasets were constructed and analyzed. Each data set was constructed using 50

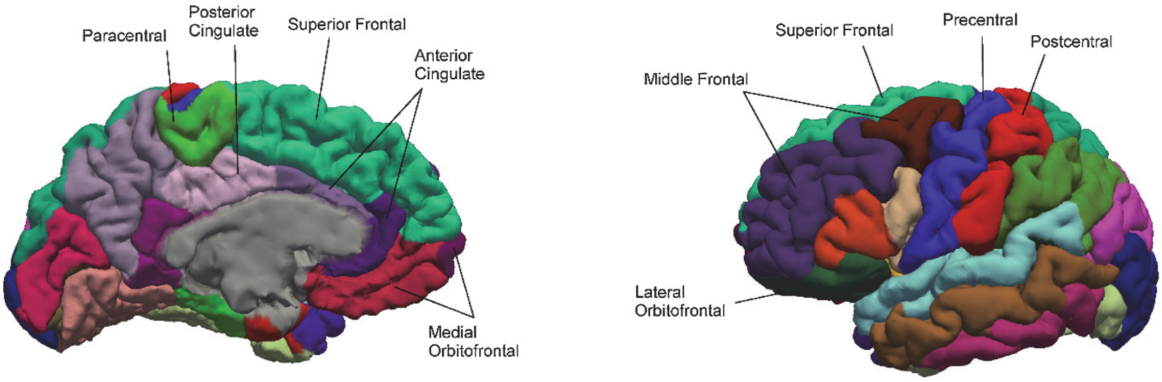

Fig. 1. Cortical ROIs. The medial (left) and lateral (right) surfaces of the human cerebral cortex parcellated with FreeSurfer.

Table 1
Missing data pattern for variables of interest. Available: number of individuals with data available; Missing: number of individuals with missing data, % missing: proportion of subjects with missing measure, Available from previous measurements: number of individuals with missing data on a variable that have data from previous occasions. Asterisk (*) indicates that seven subjects had measurement of weekday MVPA that could be utilized in imputations.

	Available	Missing	% missing	Available from previous measurements
Pubertal stage	54	6	10 %	4
Total MVPA	47	13	22 %	7*
20-m shuttle run	51	9	15 %	5

MVPA, moderate-to-vigorous intensity physical activity.

iterations of the algorithm to ensure the convergence of the iterative process. Calculations were performed in R 3.4.0 (R Core Team, 2017) using the mice 2.3 package [53]. The model parameters and their standard errors were estimated for each imputed dataset and combined using Rubin's rules [47, p. 37,38] to obtain final estimates of parameters and their standard errors. More details about multiple imputation in Supplementary material.

3. Results

Table 2 presents descriptive statistics for participant characteristics, physical activity, 20-m shuttle run, and brain volumes of the left superior frontal cortex and the left pallidum.

BMI, body mass index; MVPA, moderate-to-vigorous intensity physical activity; SFC, superior frontal cortex

Multiple linear regression analysis was carried out to investigate the relationship between aerobic fitness (Table 3) and MVPA (Table 4) with brain volumes. After correcting for multiple comparisons there was a noteworthy negative (FDR-adjusted p = 0.020) relationship between 20-m shuttle run and superior frontal cortex volume after controlling for age, puberty status, gender and eTIV (Fig. 2A). For left superior frontal cortex volume, the regression model predicted a 500 mm^3 decrease in volume for each extra minute in 20-m shuttle run test. The left superior frontal cortex volume could be predicted by the following formula: 22.3 − 0.5 (shuttle run) − 0.83 (age) + 2.35 (gender) − 0.07 (pubertal stage) + 0.013 (eTIV). Here shuttle run is measured in minutes, age in years, pubertal stage as Tanner score (values between 1–5), eTIV as cm^3, and gender is coded as 0 = female or 1 = male. The adjusted R^2 value was 0.62. There was also a positive association between left pallidum volume and 20-m shuttle run test (FDR-adjusted p = 0.069) (Fig. 2B). For left pallidum there was a 48 mm^3 expected increase in volume for each extra minute in the shuttle run test. The left pallidum volume could be predicted by the following formula: 1.87 + 0.05 (shuttle run) − 0.11 (age) − 0.03 (gender) + 0.02 (pubertal stage) + 0.001 (eTIV). There were no noteworthy relationships between MVPA and any of the ROIs. In addition, there were no associations between BMI and any of the ROIs. The correlation between 20-m shuttle run and MVPA was r = 0.45 (p = 0.001).

Table 2
Participant demographics. Data presented as mean ± SD.

	Mean	Range
Age (years)	14.3 ± 0.9	12.7–16.2
Weight (kg)	55.9 ± 9.9	35.7–94.3
Height (cm)	164.1 ± 9.6	147–194
BMI	20.7 ± 2.6	15.7–31.1
Pubertal stage	3.5 ± 0.9	1.5–5.0
20-m shuttle run (min)	5.8 ± 2.4	1.5–11.6
MVPA (min/day)	49.1 ± 20	18–105.9
Left SFC (mm^3)	28,742 ± 3359	21669–35837
Left pallidum (mm^3)	1542 ± 287	977–2177
N = 60 (female = 40)		

4. Discussion

We investigated how both physical activity and aerobic fitness associate with frontal, motor and subcortical grey matter volumes in adolescents. Our findings suggest that aerobic fitness and MVPA relate to grey matter volumes differently in the studied age range between 12.7 and 16.2 years. Aerobic fitness was negatively associated with left superior frontal cortex and positively associated with left pallidum volume. Contrary to our expectations, we did not find clear associations between MVPA and any ROI. These results demonstrate unequal contribution of physical activity and aerobic fitness on brain volume, with inherent or achieved capacity (aerobic fitness) showing clearer associations than physical activity.

The negative association between aerobic fitness and left superior frontal cortex volume supports and extends the results of Chaddock-Heyman et al. [21] who demonstrated similar association between aerobic fitness and the thickness of this area in preadolescent children. When compared with the results of Herting et al. [15] with a slightly older age group (15–18 years), our results are partially contradictory. Herting et al. [15] observed that the only cortical area associated with aerobic fitness is the right rostral middle frontal cortex, located laterally to the superior frontal cortex. Taken together, the current and earlier results suggest that better aerobic fitness is associated with lower thickness and volume of superior frontal brain areas in youth.

Adolescence is characterized by substantial changes in brain function and structure. Neuroimaging studies show that cortical grey matter decreases and white matter increases during adolescence [54–56]. Among other brain regions, also frontal cortical areas seem to undergo large changes during adolescence [57,58]. Interestingly, a recent study

Table 3
Multiple linear regression analysis of 20-m shuttle run (min) on brain volumes after adjustment for age, pubertal stage, gender and eTIV.

20-m shuttle run					
ROIs	β	95% CI	p-value	FDR-adjusted p-value	Adjusted R2
Left thalamus proper	−0.047	−0.117,0.022	0.177	0.442	0.63
Left caudate	0.009	−0.060,0.078	0.790	0.878	0.20
Left putamen	0.088	0.000,0.176	**0.050**	0.302	0.33
Left pallidum	0.048	0.016,0.081	**0.005**	**0.069**	0.30
Left hippocampus	−0.001	−0.049,0.048	0.971	0.973	0.39
Left accumbens area	0.008	−0.007,0.024	0.297	0.594	0.22
Right thalamus proper	−0.031	−0.096,0.034	0.345	0.598	0.62
Right caudate	0.025	−0.045,0.096	0.475	0.620	0.30
Right putamen	0.030	−0.047,0.106	0.439	0.598	0.28
Right pallidum	0.027	0.005,0.049	**0.018**	0.180	0.38
Right hippocampus	−0.033	−0.078,0.013	0.156	0.425	0.46
Right accumbens area	0.005	−0.007,0.017	0.432	0.598	0.30
Left anterior cingulate cortex[b]	−0.002	−0.135,0.130	0.973	0.973	0.17
Left lateral orbitofrontal	−0.094	−0.209,0.022	0.109	0.388	0.52
Left medial orbitofrontal[a]	−0.077	−0.171,0.016	0.102	0.388	0.44
Left middle frontal gyrus[c]	−0.145	−0.487,0.197	0.399	0.598	0.52
Left paracentral	−0.003	−0.084,0.078	0.942	0.973	0.31
Left postcentral	−0.046	−0.233,0.142	0.627	0.784	0.49
Left posterior cingulate	−0.049	−0.128,0.029	0.214	0.495	0.28
Left precentral	−0.035	−0.239,0.170	0.735	0.848	0.51
Left superior frontal	−0.504	−0.783,-0.226	**0.001**	**0.020**	0.62
Right anterior cingulate cortex[b]	−0.027	−0.168,0.114	0.698	0.838	0.13
Right lateral orbitofrontal	−0.086	−0.199,0.026	0.129	0.388	0.43
Right media lorbitofrontal[a]	−0.096	−0.187,-0.004	**0.042**	0.302	0.50
Right middle frontal gyrus[c]	−0.154	−0.481,0.173	0.349	0.598	0.55
Right paracentral	−0.045	−0.149,0.058	0.385	0.598	0.17
Right postcentral	−0.092	−0.259,0.074	0.270	0.579	0.39
Right posterior cingulate	−0.039	−0.127,0.048	0.369	0.598	0.17
Right precentral	−0.140	−0.317,0.038	0.120	0.388	0.52
Right superior frontal	−0.269	−0.576,0.039	0.085	0.388	0.53

β, regression coefficient; CI, confidence interval; FDR, false discovery rate; ROI, regions of interest; ROIs are measured as cm^3. Bolded values indicate p-values below 0.05 and FDR-adjusted p-values below 0.1. Adjusted R^2 denotes the adjusted proportion of the variance explained by the model.

[a] = sum of medial orbitofrontal cortex and frontal pole.

[b] = sum of rostral anterior and caudal anterior division of anterior cingulate cortex.

[c] = sum of rostral and caudal divisions of middle frontal gyrus.

by Teeuw et al. [59] indicated that the largest decrease in cortical thickness during adolescence (12–17 years) takes place in the superior frontal cortex. They also demonstrated that these changes are under strong genetic control [59]. Intriguingly, aerobic fitness in adolescents seems to be related to the brain area, which presumably exhibits the largest (genetically-driven) cortical thinning between the ages of 12 and 17 years. There are several possible underlying factors for this linkage. As demonstrated by earlier studies, both aerobic fitness and changes in superior frontal cortex thickness during adolescence depend largely on genetic factors [12,59]. Our results could thus reflect, at least partly, shared genetic factors underlying both aerobic fitness and superior frontal area development.

We also found a positive association between aerobic fitness and left pallidum volume. The pallidum is a structure within the basal ganglia that is involved in regulating motor activity. Previous results suggest that aerobic fitness is related to pallidum shape and volume in normal weight preadolescent children [18,20]. Our results demonstrate that this association also exist in adolescents.

The association between objectively measured physical activity and grey matter structures, to the best of our knowledge, has not been studied in either children or adolescents. In contrast to the results concerning older adults (e.g. [1,60,61]), the current results indicate that MVPA is not related to brain volumes in frontal, motor, or subcortical regions in this age group. Herting et al. [15] used questionnaires to evaluate the physical activity of 15–18-year-old males. Although measuring physical activity with accelerometers and questionnaires differs, these methods are related to each other. Our results support the findings of Herting et al. [15], where no differences were found in terms of the size of the frontal and motor surface areas between high and low physical activity groups. However, Herting et al [15]. reported that males who were more physically active showed larger right medial pericalcarine, right cuneus, and left precuneus surface areas than males who were less active. Our results do not confirm or oppose this result, as our regions of interest did not include occipital, temporal or parietal brain areas (except for the post central gyrus).

The differential association of brain volumes with aerobic fitness vs. MVPA in adolescents may reflect the role of genetic factors. As mentioned previously, shared genetic factors could explain the association between aerobic fitness and left superior frontal cortex volume. In addition, physical activity and exercise-related factors could be contributing to the observed association, although we want to highlight that the cross-sectional nature of the current results does not allow us to determine a causal relationship. It is well-established that responsiveness to exercise or physical activity differs between individuals. Even though the level of physical activity or the intensity and duration of an exercise is same for different individuals, physiological responses may differ quite dramatically [13,62–64]. Aerobic fitness is a measure that is considered to be at least partially the outcome of long-term physical activity or exercise, and therefore, it is influenced by individual responsiveness. On the other hand, physical activity is a measurement of an individual's behaviour and does not supply information about responsiveness. It is plausible that this individual responsiveness to exercise may also apply to brain responses to physical activity or exercise. Our results also raise the possibility that only physical activity or exercise, with high enough duration, intensity and frequency to improve aerobic fitness, beneficially impacts the adolescent brain. However, intervention studies are required to determine if this is the case.

Table 4
Multiple linear regression analysis of 20-m shuttle run (min) on brain volumes after adjustment for age, pubertal stage, gender and eTIV.

MVPA					
ROIs	β	95% CI	p-value	FDR-adjusted p-value	Adjusted R2
Left thalamus proper	−0.001	−0.009,0.007	0.847	0.951	0.62
Left caudate	−0.004	−0.011,0.003	0.237	0.951	0.22
Left putamen	0.006	−0.005,0.016	0.274	0.951	0.29
Left pallidum	0.001	−0.003,0.005	0.579	0.951	0.18
Left hippocampus	−0.001	−0.006,0.005	0.706	0.951	0.39
Left accumbens area	0.000	−0.001,0.002	0.706	0.951	0.20
Right thalamus proper	−0.004	−0.011,0.003	0.259	0.951	0.62
Right caudate	−0.005	−0.012,0.003	0.197	0.951	0.31
Right putamen	0.004	−0.004,0.013	0.334	0.951	0.29
Right pallidum	0.002	−0.001,0.004	0.217	0.951	0.32
Right hippocampus	−0.002	−0.007,0.003	0.444	0.951	0.45
Right accumbens area	0.000	−0.001,0.001	0.866	0.951	0.29
Left anterior cingulate cortex[b]	−0.001	−0.016,0.015	0.919	0.951	0.17
Left lateral orbitofrontal	0.000	−0.013,0.013	0.959	0.959	0.49
Left medial orbitofrontal[a]	−0.001	−0.011,0.010	0.892	0.951	0.41
Left middle frontal gyrus[c]	−0.010	−0.049,0.029	0.596	0.951	0.51
Left paracentral	−0.002	−0.010,0.007	0.705	0.951	0.31
Left postcentral	−0.003	−0.023,0.017	0.754	0.951	0.49
Left posterior cingulate	0.005	−0.003,0.014	0.235	0.951	0.28
Left precentral	0.002	−0.020,0.025	0.828	0.951	0.50
Left superior frontal	−0.022	−0.057,0.013	0.208	0.951	0.53
Right anterior cingulate cortex[b]	−0.011	−0.026,0.005	0.168	0.951	0.16
Right lateral orbitofrontal	−0.002	−0.015,0.011	0.731	0.951	0.41
Right medial orbitofrontal[a]	0.004	−0.006,0.014	0.443	0.951	0.46
Right middle frontal gyrus[c]	−0.003	−0.040,0.034	0.873	0.951	0.55
Right paracentral	−0.003	−0.015,0.009	0.610	0.951	0.16
Right postcentral	0.005	−0.013,0.023	0.604	0.951	0.38
Right posterior cingulate	−0.003	−0.013,0.007	0.511	0.951	0.17
Right precentral	0.003	−0.017,0.023	0.768	0.951	0.50
Right superior frontal	−0.016	−0.051,0.018	0.341	0.951	0.51

MVPA, moderate-to-vigorous intensity physical activity; β, regression coefficient; CI, confidence interval; FDR, false discovery rate; ROI, regions of interest; ROIs are measured as cm^3. Adjusted R^2 denotes the adjusted proportion of the variance explained by the model.

[a] = sum of medial orbitofrontal cortex and frontal pole.

[b] = sum of rostral anterior and caudal anterior division of anterior cingulate cortex.

[c] = sum of rostral and caudal divisions of middle frontal gyrus.

Several earlier investigations suggest that physical activity is related to grey matter structures in older adults (e.g. [1,60,61,65]). Why were we not able to find this association in young subjects? One explanation for this might be that on average, older adults are much less active than adolescents [66]. There is hence a large difference in the average physical activity level between these age groups, and the proportion of less active individuals is much higher in older adults. Larger variances could lead to clearer associations, but also, factors related to capacity (aerobic fitness) may underlie the effects demonstrated in older adults. Perhaps the more active individuals in the older adults group also have proportionally higher fitness levels than those in adolescents. It remains to be shown if the association between grey matter structures and physical activity is still present if the activity levels of older adults and adolescents are matched.

Another possible reason for the differential results regarding the effect of physical activity on the brain between young and old individuals relates to cerebral blood flow, which has been demonstrated to decrease with age [67,68]. Contrary to the age-related decline in cerebral blood flow, physical activity and exercise have been shown to increase regional blood flow in older adults [69–71]. Thus, in older adults exercise may increase blood flow closer to the values observed in younger individuals. These different results might also reflect the age-dependent responses to exercise. Finally, if the associations in adolescence are just weaker than in older adults, the sample size may have been insufficient to detect the effect.

Few limitations need to be considered when interpreting the general effects reported in this study. First, the choice of the brain parcellation might have a minor influence on the results. We chose to use the Desikan-Killiany Atlas [43] to keep the regions of interest relatively small and sensitive to possible changes. However, even smaller parcellations could have been more sensitive to, but would have required more subjects for analysis. Second, hip-worn accelerometers are commonly used in research to objectively measure physical activity. However, they are not able to detect all kinds of activity, such as those featured as water sports or bike riding. Third, in the multiple imputation, the data were assumed to be missing at random. There is no way to verify this assumption empirically but the availability of good predictors for pubertal age, physical activity and shuttle run in the imputation model reduces the impact of the potential violations of this assumption.

4.1. Conclusions

Herein, we provide new information about the association between aerobic fitness and physical activity and grey matter volume in 13–16-year-old adolescents. Our results show that higher aerobic fitness is negatively associated with left superior frontal cortex volume, a brain area that exhibits large cortical thinning during adolescence, and positively associated with left pallidum volume. We also demonstrate that in this age group objectively measured physical activity does not relate with grey matter volume in frontal, motor and subcortical areas, which is in contrast to findings concerning older adults. The cortical thinning of the superior frontal cortex is proposed to be under strong genetic influence during adolescence. The current results together with previous results concerning brain development raise the possibility of the common genetic pathway between brain development and aerobic fitness in youth. Future work should determine if those common genetic pathways do exist. Finally, our results highlight the importance of

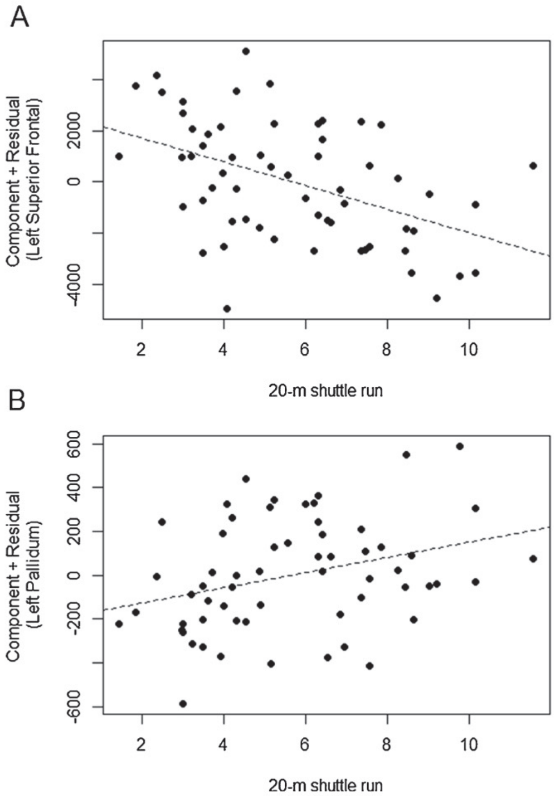

Fig. 2. Partial residual plot for the relationship between A) left superior frontal cortex volume and 20-m shuttle run and B) left pallidum volume and 20-m shuttle run.

measuring both aerobic fitness and physical activity in order to separate the effects of these distinct factors on the brain.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2018.12.041.

References

[1] 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. U. S. A. 108 (2011) 3017–3022, https://doi.org/10.1073/pnas.1015950108.

[2] A.S. Whiteman, D.E. Young, A.E. Budson, C.E. Stern, K. Schon, Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: a voxel-based morphometry study, Neuroimage 126 (2016) 229–238, https://doi.org/10.1016/J.NEUROIMAGE.2015.11.049.

[3] 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.

[4] C.J. Caspersen, K.E. Powell, G.M. Christenson, Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research, Publ. Health Rep. 100 (1985) 126–131 (accessed February 15, 2018), http://www.ncbi.nlm.nih.gov/pubmed/3920711.

[5] R.J. Shephard, Limits to the measurement of habitual physical activity by questionnaires, Br. J. Sports Med. 37 (2003) 197–206, https://doi.org/10.1136/BJSM.37.3.197 discussion 206.

[6] T.S. Church, C.P. Earnest, J.S. Skinner, S.N. Blair, Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure, JAMA 297 (2007) 2081, https://doi.org/10.1001/jama.297.19.2081.

[7] P. Oja, Dose response between total volume of physical activity and health and fitness, Med. Sci. Sports Exerc. 33 (2001) S428–S437 (Accessed 13 March 2018), https://insights.ovid.com/pubmed?pmid=11427767.

[8] G. O'Donovan, A. Owen, S.R. Bird, E.M. Kearney, A.M. Nevill, D.W. Jones, K. Woolf-May, Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate- or high-intensity exercise of equal energy cost, J. Appl. Physiol. 98 (2005) 1619–1625, https://doi.org/10.1152/japplphysiol.01310.2004.

[9] M. Dencker, O. Thorsson, M.K. Karlsson, C. Lindén, J. Svensson, P. Wollmer, L.B. Andersen, Daily physical activity and its relation to aerobic fitness in children aged 8–11 years, Eur. J. Appl. Physiol. 96 (2006) 587–592, https://doi.org/10.1007/s00421-005-0117-1.

[10] N.F. Butte, M.R. Puyau, A.L. Adolph, F.A. Vohra, I. Zakeri, Physical activity in nonoverweight and overweight hispanic children and adolescents, Med. Sci. Sports Exerc. 39 (2007) 1257–1266, https://doi.org/10.1249/mss.0b013e3180621fb6.

[11] U. Ekelund, E. Poortvliet, A. Nilsson, A. Yngve, A. Holmberg, M. Sjöström, Physical activity in relation to aerobic fitness and body fat in 14- to 15-year-old boys and girls, Eur. J. Appl. Physiol. 85 (2001) 195–201, https://doi.org/10.1007/s004210100460.

[12] N.M. Schutte, I. Nederend, J.J. Hudziak, M. Bartels, E.J.C. de Geus, Twin-sibling study and meta-analysis on the heritability of maximal oxygen consumption, Physiol. Genom. 48 (2016) 210–219, https://doi.org/10.1152/physiolgenomics.00117.2015.

[13] C. Bouchard, P. An, T. Rice, J.S. Skinner, J.H. Wilmore, J. Gagnon, L. Pérusse, A.S. Leon, D.C. Rao, Familial aggregation of VO2max response to exercise training: results from the HERITAGE Family Study, J. Appl. Physiol. 87 (1999) 1003–1008, https://doi.org/10.1055/s-2000-12983.

[14] 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.

[15] M.M. Herting, M.F. Keenan, B.J. Nagel, Aerobic fitness linked to cortical brain development in adolescent males: preliminary findings suggest a possible role of BDNF genotype, Front. Hum. Neurosci. 10 (2016) 327, https://doi.org/10.3389/fnhum.2016.00327.

[16] L. Chaddock, K.I. Erickson, R.S. Prakash, M. VanPatter, M.W. Voss, M.B. Pontifex, L.B. Raine, C.H. Hillman, A.F. Kramer, Basal ganglia volume is associated with aerobic fitness in preadolescent children, Dev. Neurosci. 32 (2010) 249–256, https://doi.org/10.1159/000316648.

[17] L. Chaddock, K.I. Erickson, R.S. Prakash, J.S. Kim, M.W. Voss, M. VanPatter, M.B. Pontifex, L.B. Raine, A. Konkel, C.H. Hillman, N.J. Cohen, A.F. Kramer, A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children, Brain Res. 1358 (2010) 172–183, https://doi.org/10.1016/J.BRAINRES.2010.08.049.

[18] F.B. Ortega, D. Campos, C. Cadenas-Sanchez, S. Altmäe, C. Martínez-Zaldívar, M. Martín-Matillas, A. Catena, C. Campoy, Physical fitness and shapes of subcortical brain structures in children, Br. J. Nutr. (2017) 1–10, https://doi.org/10.1017/S0007114516001239.

[19] I. Esteban-Cornejo, C. Cadenas-Sanchez, O. Contreras-Rodriguez, J. Verdejo-Roman, J. Mora-Gonzalez, J.H. Migueles, P. Henriksson, C.L. Davis, A. Verdejo-Garcia, A. Catena, F.B. Ortega, A whole brain volumetric approach in overweight/obese children: examining the association with different physical fitness components and academic performance. The Active Brains project, Neuroimage 159 (2017) 346–354, https://doi.org/10.1016/J.NEUROIMAGE.2017.08.011.

[20] L. Chaddock, C.H. Hillman, M.B. Pontifex, C.R. Johnson, L.B. Raine, A.F. Kramer, Childhood aerobic fitness predicts cognitive performance one year later, J. Sports Sci. 30 (2012) 421–430, https://doi.org/10.1080/02640414.2011.647706.

[21] L. Chaddock-Heyman, K.I. Erickson, C. Kienzler, M. King, M.B. Pontifex, L.B. Raine, C.H. Hillman, A.F. Kramer, The role of aerobic fitness in cortical thickness and mathematics achievement in preadolescent children, PLoS One 10 (2015) e0134115, https://doi.org/10.1371/journal.pone.0134115.

[22] M.S. Nokia, S. Lensu, J.P. Ahtiainen, P.P. Johansson, L.G. Koch, S.L. Britton, H. Kainulainen, Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained, J. Physiol. 594 (2016) 1855–1873, https://doi.org/10.1113/JP271552.

[23] S. Lensu, M. Nokia, E. Mäkinen, L.G. Koch, S. Britton, J. Wikgren, H. Kainulainen, Vaikuttaako aikuisiässä aloitettu vapaaehtoinen liikuntaharjoittelu oppimiseen, suorituskykyyn tai aivojen hermosolujen uudistuotantoon? [Does voluntary physical exercise started during adulthood affect learning, performance or neurogenesis in the brain], Liik. T. 5 (2017), p. 98.

[24] O. Marton, E. Koltai, M. Takeda, T. Mimura, M. Pajk, D. Abraham, L.G. Koch, S.L. Britton, M. Higuchi, I. Boldogh, Z. Radak, The rate of training response to aerobic exercise affects brain function of rats, Neurochem. Int. 99 (2016) 16–23, https://doi.org/10.1016/J.NEUINT.2016.05.012.

[25] T.C. Nordin, A.J. Done, T. Traustadóttir, Acute exercise increases resistance to

oxidative stress in young but not older adults, Age (Omaha) 36 (2014) 9727, https://doi.org/10.1007/s11357-014-9727-z.

[26] M. Nussbaumer, L. Donath, M. Fischer, J. Schäfer, O. Faude, L. Zahner, A. Schmidt-Trucksäss, H. Hanssen, Effects of acute bouts of endurance exercise on retinal vessel diameters are age and intensity dependent, Age (Omaha) 36 (2014) 9650, https://doi.org/10.1007/s11357-014-9650-3.

[27] E. Wang, M.S. Næss, J. Hoff, T.L. Albert, Q. Pham, R.S. Richardson, J. Helgerud, Exercise-training-induced changes in metabolic capacity with age: the role of central cardiovascular plasticity, Age (Omaha) 36 (2014) 665–676, https://doi.org/10.1007/s11357-013-9596-x.

[28] C.-H. Chu, A.F. Kramer, T.-F. Song, C.-H. Wu, T.-M. Hung, Y.-K. Chang, Acute exercise and neurocognitive development in preadolescents and young adults: an ERP study, Neural Plast. 2017 (2017) 1–13, https://doi.org/10.1155/2017/2631909.

[29] N.A. Asl, F. Sheikhzade, M. Torchi, L. Roshangar, S. Khamnei, Long-term regular exercise promotes memory and learning in young but not in older rats, Pathophysiology 15 (2008) 9–12, https://doi.org/10.1016/J.PATHOPHYS.2007.10.002.

[30] M.E. Hopkins, R. Nitecki, D.J. Bucci, Physical exercise during adolescence versus adulthood: differential effects on object recognition memory and brain-derived neurotrophic factor levels, Neuroscience 194 (2011) 84–94, https://doi.org/10.1016/J.NEUROSCIENCE.2011.07.071.

[31] J.M. Muller-Delp, K. Hotta, B. Chen, B.J. Behnke, J.J. Maraj, M.D. Delp, T.R. Lucero, J.A. Bramy, D.B. Alarcon, H.E. Morgan, M.R. Cowan, A.D. Haynes, Effects of age and exercise training on coronary microvascular smooth muscle phenotype and function, J. Appl. Physiol. 124 (2018) 140–149, https://doi.org/10.1152/japplphysiol.00459.2017.

[32] L. Joensuu, H. Syväoja, J. Kallio, J. Kulmala, U.M. Kujala, T.H. Tammelin, Objectively measured physical activity, body composition and physical fitness: cross-sectional associations in 9- to 15-year-old children, Eur. J. Sport Sci. 18 (2018) 1–11, https://doi.org/10.1080/17461391.2018.1457081.

[33] W.A. Marshall, J.M. Tanner, Variations in pattern of pubertal changes in girls, Arch. Dis. Child. 44 (1969) 291–303 (Accessed 15 February 2018), http://www.ncbi.nlm.nih.gov/pubmed/5785179.

[34] W.A. Marshall, J.M. Tanner, Variations in the pattern of pubertal changes in boys, Arch. Dis. Child. 45 (1970) 13–23 (Accessed 15 February 2018), http://www.ncbi.nlm.nih.gov/pubmed/5440182.

[35] S.G. Trost, P.D. Loprinzi, R. Moore, K.A. Pfeiffer, A. Trost, P.D. Loprinzi, R. Moore, K.A. Pfeiffer, Comparison of accelerometer cut points for predicting activity intensity in youth, Med. Sci. Sports Exerc. 43 (2011) 1360–1368, https://doi.org/10.1249/MSS.0b013e318206476e.

[36] K.R. Evenson, D.J. Catellier, K. Gill, K.S. Ondrak, R.G. McMurray, Calibration of two objective measures of physical activity for children, J. Sports Sci. 26 (2008) 1557–1565, https://doi.org/10.1080/02640410802334196.

[37] H. Nupponen, H. Soini, R. Telama, Koululaisten kunnon ja liikehallinnan mittaaminen [Test manual of motor fitness and abilities for schools], 2nd ed., (1999) Likes.

[38] A.J.W. van der Kouwe, T. Benner, B. Fischl, F. Schmitt, D.H. Salat, M. Harder, A.G. Sorensen, A.M. Dale, On-line automatic slice positioning for brain MR imaging, Neuroimage 27 (2005) 222–230, https://doi.org/10.1016/J.NEUROIMAGE.2005.03.035.

[39] A.M. Dale, B. Fischl, M.I. Sereno, Cortical surface-based analysis, Neuroimage 9 (1999) 179–194, https://doi.org/10.1006/nimg.1998.0395.

[40] B. Fischl, D.H. Salat, E. Busa, M. Albert, M. Dieterich, C. Haselgrove, A. van der Kouwe, R. Killiany, D. Kennedy, S. Klaveness, A. Montillo, N. Makris, B. Rosen, A.M. Dale, Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain, Neuron 33 (2002) 341–355, https://doi.org/10.1016/S0896-6273(02)00569-X.

[41] B. Fischl, D.H. Salat, A.J.W. van der Kouwe, N. Makris, F. Ségonne, B.T. Quinn, A.M. Dale, Sequence-independent segmentation of magnetic resonance images, Neuroimage 23 (2004) S69–S84, https://doi.org/10.1016/J.NEUROIMAGE.2004.07.016.

[42] R.L. Buckner, D. Head, J. Parker, A.F. Fotenos, D. Marcus, J.C. Morris, A.Z. Snyder, A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume, Neuroimage 23 (2004) 724–738, https://doi.org/10.1016/J.NEUROIMAGE.2004.06.018.

[43] R.S. Desikan, F. Ségonne, B. Fischl, B.T. Quinn, B.C. Dickerson, D. Blacker, R.L. Buckner, A.M. Dale, R.P. Maguire, B.T. Hyman, M.S. Albert, R.J. Killiany, An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Neuroimage 31 (2006) 968–980, https://doi.org/10.1016/J.NEUROIMAGE.2006.01.021.

[44] M.S. Nokia, S. Lensu, J.P. Ahtiainen, P.P. Johansson, L.G. Koch, S.L. Britton, H. Kainulainen, Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained, J. Physiol. 594 (2016) 1855–1873, https://doi.org/10.1113/JP271552.

[45] M.R. Scudder, E.S. Drollette, A.N. Szabo-Reed, K. Lambourne, C.I. Fenton, J.E. Donnelly, C.H. Hillman, Tracking the relationship between children's aerobic fitness and cognitive control, Health Psychol. 35 (2016) 967–978, https://doi.org/10.1037/hea0000343.

[46] J. Vanhelst, L. Béghin, A. Duhamel, Y. Manios, D. Molnar, S. De Henauw, L.A. Moreno, F.B. Ortega, M. Sjöström, K. Widhalm, F. Gottrand, L.A. Moreno, L.A. Moreno, F. Gottrand, S. De Henauw, M. González-Gross, C. Gilbert, A. Kafatos, L.A. Moreno, C. Libersa, S. De Henauw, J. Sánchez, F. Gottrand, M. Kersting, M. Sjöstrom, D. Molnár, M. González-Gross, J. Dallongeville, C. Gilbert, G. Hall, L. Maes, L. Scalfi, P. Meléndez, L.A. Moreno, J. Fleta, J.A. Casajús, G. Rodríguez, C. Tomás, M.I. Mesana, G. Vicente-Rodríguez, A. Villarroya, C.M. Gil, I. Ara, J. Revenga, C. Lachen, J.F. Alvira, G. Bueno, A. Lázaro, O. Bueno, J.F. León, J.M. Garagorri, M. Bueno, J.P. Rey López, I. Iglesia, P. Velasco, S. Bel, A. Marcos, J. Wärnberg, E. Nova, S. Gómez, E.L. Díaz, J. Romeo, A. Veses, M.A. Puertollano, B. Zapatera, T. Pozo, D. Martínez, L. Beghin, C. Libersa, F. Gottrand, C. Iliescu, J. Von Berlepsch, M. Kersting, W. Sichert-Hellert, E. Koeppen, D. Molnar, E. Erhardt, K. Csernus, K. Török, S. Bokor, M. Angster, E. Nagy, O. Kovács, J. Repásy, A. Kafatos, C. Codrington, M. Plada, A. Papadaki, K. Sarri, A. Viskadourou, C. Hatzis, M. Kiriakakis, G. Tsibinos, C. Vardavas, M. Sbokos, E. Protoyeraki, M. Fasoulaki, P. Stehle, K. Pietrzik, M. González-Gross, C. Breidenassel, A. Spinneker, J. Al-Tahan, M. Segoviano, A. Berchtold, C. Bierschbach, E. Blatzheim, A. Schuch, P. Pickert, M.J. Castillo, Á. Gutiérrez, F.B. Ortega, J.R. Ruiz, E.G. Artero, V. España-Romero, D. Jiménez-Pavón, P. Chillón, M. Cuenca-García, D. Arcella, E. Azzini, E. Barrison, N. Bevilacqua, P. Buonocore, G. Catasta, L. Censi, D. Ciarapica, P. D'Acapito, M. Ferrari, M. Galfo, C. Le Donne, C. Leclercq, G. Maiani, B. Mauro, L. Mistura, A. Pasquali, R. Piccinelli, A. Polito, R. Spada, S. Sette, M. Zaccaria, L. Scalfi, P. Vitaglione, C. Montagnese, I. De Bourdeaudhuij, S. De Henauw, T. De Vriendt, L. Maes, C. Matthys, C. Vereecken, M. de Maeyer, C. Ottevaere, I. Huybrechts, K. Widhalm, K. Phillipp, S. Dietrich, B. Kubelka, M. Boriss-Riedl, Y. Manios, E. Grammatikaki, Z. Bouloubasi, T.L. Cook, S. Eleutheriou, O. Consta, G. Moschonis, I. Katsaroli, G. Kraniou, S. Papoutsou, D. Keke, I. Petraki, E. Bellou, S. Tanagra, K. Kallianoti, D. Argyropoulou, K. Kondaki, S. Tsikrika, C. Karaiskos, J. Dallongeville, A. Meirhaeghe, M. Sjöstrom, P. Bergman, M. Hagströmer, L. Hallström, M. Hallberg, E. Poortvliet, J. Wärnberg, N. Rizzo, L. Beckman, A.H. Wennlöf, E. Patterson, L. Kwak, L. Cernerud, P. Tillgren, S. Sörensen, J. Sánchez-Molero, E. Picó, M. Navarro, B. Viadel, J.E. Carreres, G. Merino, R. Sanjuán, M. Lorente, M.J. Sánchez, S. Castelló, C. Gilbert, S. Thomas, E. Allchurch, P. Burguess, G. Hall, A. Astrom, A. Sverkén, A. Broberg, A. Masson, C. Lehoux, P. Brabant, P. Pate, L. Fontaine, A. Sebok, T. Kuti, A. Hegyi, C. Maldonado, A. Llorente, E. García, H. von Fircks, M.L. Hallberg, M. Messerer, M. Larsson, H. Fredriksson, V. Adamsson, I. Börjesson, L. Fernández, L. Smillie, J. Wills, M. González-Gross, A. Meléndez, P.J. Benito, J. Calderón, D. Jiménez-Pavón, J. Valtueña, P. Navarro, A. Urzanqui, U. Albers, R. Pedrero, J.J. Gómez Lorente, Physical activity is associated with attention capacity in adolescents, J. Pediatr. 168 (2016) 126–131, https://doi.org/10.1016/J.JPEDS.2015.09.029 e2.

[47] J.E. Donnelly, C.H. Hillman, D. Castelli, J.L. Etnier, S. Lee, P. Tomporowski, K. Lambourne, A.N. Szabo-Reed, Physical activity, fitness, cognitive function, and academic achievement in children, Med. Sci. Sports Exerc. 48 (2016) 1197–1222, https://doi.org/10.1249/MSS.0000000000000901.

[48] A.M. Owen, R.G. Morris, B.J. Sahakian, C.E. Polkey, T.W. Robbins, Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man, Brain 119 (Pt 5) (1996) 1597–1615 (Accessed 16 November 2018), http://www.ncbi.nlm.nih.gov/pubmed/8931583.

[49] Y. Benjamini, Y. Hochberg, Controlling the false discovery rate: a practical and powerful approach to multiple testing, J. R. Stat. Soc. Ser. B 57 (1995) 289–300, https://doi.org/10.2307/2346101.

[50] D. Yekutieli, Y. Benjamini, Resampling-based false discovery rate controlling multiple test procedures for correlated test statistics, J. Stat. Plan. Inference 82 (1999) 171–196, https://doi.org/10.1016/S0378-3758(99)00041-5.

[51] S. Van Buuren, J.P.L. Brand, C.G.M. Groothuis-Oudshoorn, D.B. Rubin, Fully conditional specification in multivariate imputation, J. Stat. Comput. Simul. 76 (2006) 1049–1064, https://doi.org/10.1080/10629360600810434.

[52] S. Van Buuren, Flexible Imputation of Missing Data, CRC Press, 2012.

[53] S. Van Buuren, K. Groothuis-Oudshoorn, Mice: multivariate imputation by chained equations in R, J. Stat. Softw. 45 (2011) 1–67, https://doi.org/10.18637/jss.v045.i03.

[54] K.L. Mills, A.-L. Goddings, M.M. Herting, R. Meuwese, S.-J. Blakemore, E.A. Crone, R.E. Dahl, B. Güroğlu, A. Raznahan, E.R. Sowell, C.K. Tamnes, Structural brain development between childhood and adulthood: convergence across four longitudinal samples, Neuroimage 141 (2016) 273–281, https://doi.org/10.1016/J.NEUROIMAGE.2016.07.044.

[55] R.K. Lenroot, J.N. Giedd, Brain development in children and adolescents: insights from anatomical magnetic resonance imaging, Neurosci. Biobehav. Rev. 30 (2006) 718–729, https://doi.org/10.1016/J.NEUBIOREV.2006.06.001.

[56] J.M. Juraska, J. Willing, Pubertal onset as a critical transition for neural development and cognition, Brain Res. 1654 (2017) 87–94, https://doi.org/10.1016/J.BRAINRES.2016.04.012.

[57] C.K. Tamnes, M.M. Herting, A.-L. Goddings, R. Meuwese, S.-J. Blakemore, R.E. Dahl, B. Güroğlu, A. Raznahan, E.R. Sowell, E.A. Crone, K.L. Mills, Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness, J. Neurosci. 37 (2017) 3402–3412, https://doi.org/10.1523/JNEUROSCI.3302-16.2017.

[58] E.R. Sowell, P.M. Thompson, C.J. Holmes, R. Batth, T.L. Jernigan, A.W. Toga, Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping, Neuroimage 9 (1999) 587–597, https://doi.org/10.1006/NIMG.1999.0436.

[59] J. Teeuw, R.M. Brouwer, M.M.G. Koenis, S.C. Swagerman, D.I. Boomsma, H.E. Hulshoff Pol, Genetic influences on the development of cerebral cortical thickness during childhood and adolescence in a dutch longitudinal twin sample: the brainscale study, Cereb. Cortex (2018), https://doi.org/10.1093/cercor/bhy005.

[60] 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.

[61] A. Flöel, R. Ruscheweyh, K. Krüger, C. Willemer, B. Winter, K. Völker, H. Lohmann, M. Zitzmann, F. Mooren, C. Breitenstein, S. Knecht, Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? Neuroimage 49 (2010) 2756–2763, https://doi.org/10.1016/J.NEUROIMAGE.2009.10.043.

[62] C. Bouchard, T. Rankinen, Individual differences in response to regular physical activity, Med. Sci. Sports Exerc. 33 (2001) S446-51–3. http://www.ncbi.nlm.nih.gov/pubmed/11427769 (Accessed 18 April 2018).

[63] J.T. Bonafiglia, M.P. Rotundo, J.P. Whittall, T.D. Scribbans, R.B. Graham, B.J. Gurd, Inter-individual variability in the adaptive responses to endurance and sprint interval training: a randomized crossover study, PLoS One 11 (2016) e0167790, https://doi.org/10.1371/journal.pone.0167790.

[64] D. Montero, C. Lundby, Refuting the myth of non-response to exercise training: “non-responders” do respond to higher dose of training, J. Physiol. 595 (2017) 3377–3387, https://doi.org/10.1113/JP273480.

[65] V.R. Varma, X. Tang, M.C. Carlson, Hippocampal sub-regional shape and physical activity in older adults, Hippocampus 26 (2016) 1051–1060, https://doi.org/10.1002/hipo.22586.

[66] J.F. Sallis, Age-related decline in physical activity: a synthesis of human and animal studies, Med. Sci. Sports Exerc. 32 (2000) 1598–1600 (Accessed 20 April 2018), http://www.ncbi.nlm.nih.gov/pubmed/10994911.

[67] J.B. De Vis, J. Hendrikse, A. Bhogal, A. Adams, L.J. Kappelle, E.T. Petersen, Age-related changes in brain hemodynamics; a calibrated MRI study, Hum. Brain Mapp. 36 (2015) 3973–3987, https://doi.org/10.1002/hbm.22891.

[68] J.J. Chen, H.D. Rosas, D.H. Salat, Age-associated reductions in cerebral blood flow are independent from regional atrophy, Neuroimage 55 (2011) 468–478, https://doi.org/10.1016/j.neuroimage.2010.12.032.

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

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

[71] B. Zimmerman, B.P. Sutton, K.A. Low, M.A. Fletcher, C.H. Tan, N. Schneider-Garces, Y. Li, C. Ouyang, E.L. Maclin, G. Gratton, M. Fabiani, Cardiorespiratory fitness mediates the effects of aging on cerebral blood flow, Front. Aging Neurosci. 6 (2014) 59, https://doi.org/10.3389/fnagi.2014.00059.

II

PHYSICAL ACTIVITY, AEROBIC FITNESS, AND BRAIN WHITE MATTER: THEIR ROLE FOR EXECUTIVE FUNCTIONS IN ADOLESCENCE

by

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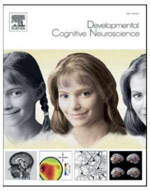

Physical activity, aerobic fitness, and brain white matter: Their role for executive functions in adolescence

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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

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Abbreviations: AD, axial diffusivity; CANTAB, Cambridge Neuropsychological Automated Test Battery; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MD, mean diffusivity; MRI, magnetic resonance imaging; MVPA, moderate-to-vigorous intensity physical activity; RD, radial diffusivity; RVP, rapid visual information processing; SWM, patial working memory; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement.

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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 $\beta = -5.56$, $t = -2.64$, $p = 0.012$, 95 % confidence interval (CI) = −9.82, −1.30. For the FA of the right superior corona radiata*20-m shuttle run, this was $\beta = -5.25$, $t = -2.14$, $p = 0.038$, 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 $\beta = -0.81$, $t = -2.52$, $p = 0.016$, 95 % CI = −1.47, −0.16. For the FA of the genu of corpus callosum, this was *MVPA $\beta = -0.65$, $t = -2.30$, $p = 0.026$, 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 ($\beta = -0.21$, $t = -2.19$, $p = 0.034$, 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: $\beta = 0.03$, $t = 2.38$, $p = 0.023$, 95 % CI = 0.01, 0.06 and low FA in the genu of corpus callosum: $\beta = 0.02$, $t = 2.20$, $p = 0.034$, 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

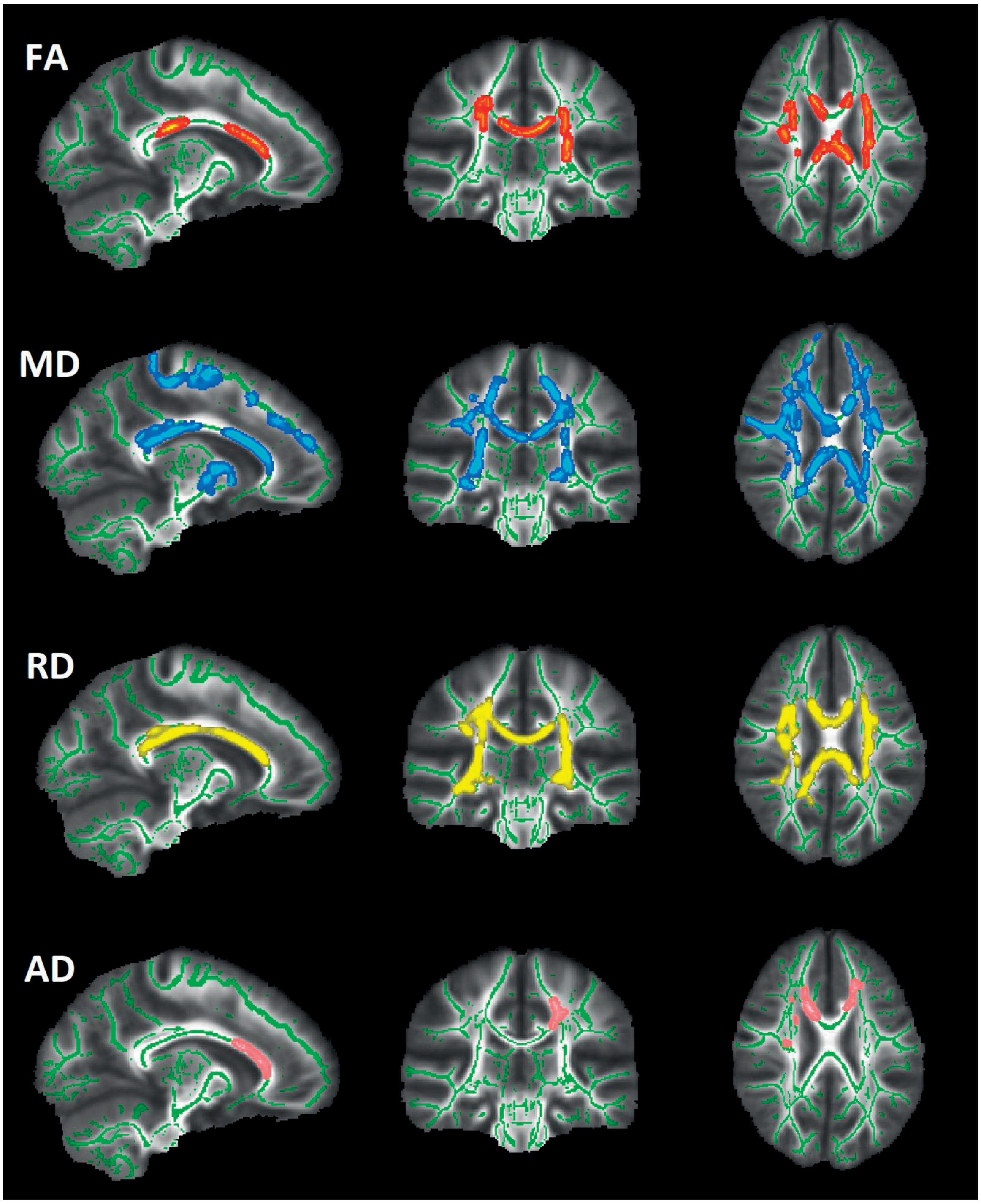

Fig. 1. Associations ($p < 0.05$, corrected for family-wise error) between aerobic fitness and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). The results are overlaid on an MNI152 1-mm template (MNI coordinates of all slices are −12, −24 and 25). 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

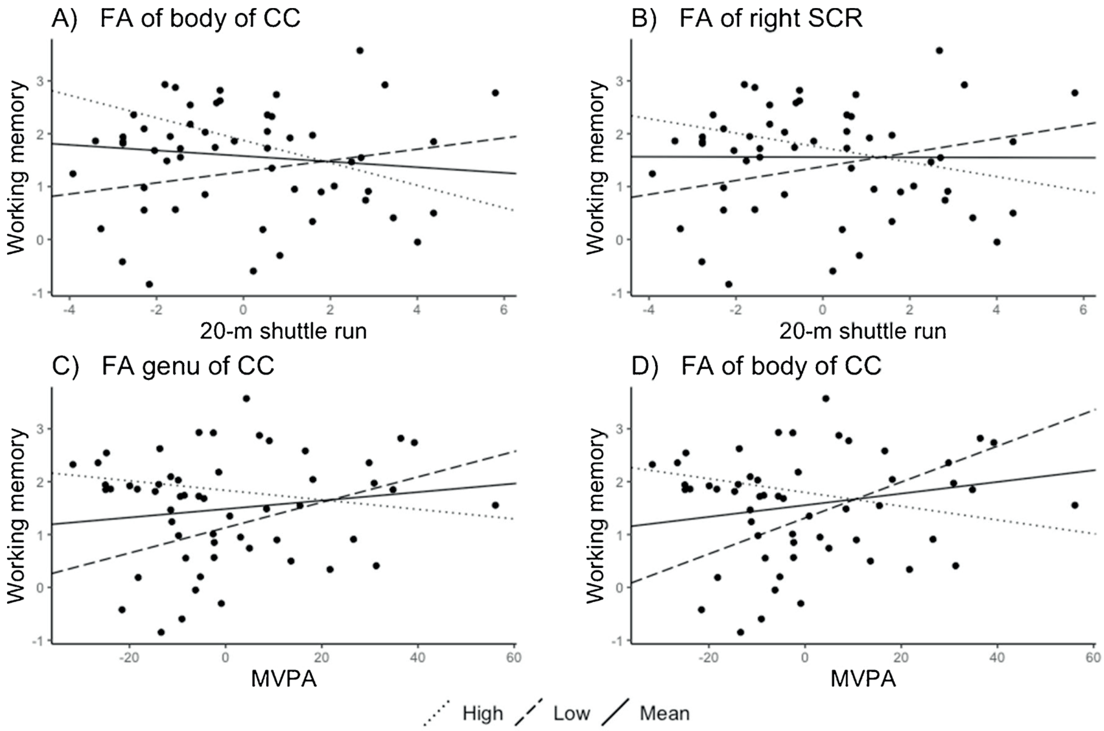

Fig. 2. The moderating effect of FA of (High: + 1 SD, Low: −1 SD) (A) the body of corpus callosum (CC), and (B) the right superior corona radiata (SCR) regarding the relationship between working memory and the 20-m shuttle run performance. The moderating effect of FA of (C) the genu and (D) the body 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.

References

Allan, J.L., McMinn, D., Daly, M., 2016. A Bidirectional Relationship between Executive Function and Health Behavior: Evidence, Implications, and Future Directions. Front. Neurosci. 10, 386. https://doi.org/10.3389/fnins.2016.00386.

Alosco, M.L., Stanek, K.M., Galioto, R., Korgaonkar, M.S., Grieve, S.M., Brickman, A.M., Spitznagel, M.B., Gunstad, J., 2014. Body mass index and brain structure in healthy children and adolescents. Int. J. Neurosci. 124, 49–55. https://doi.org/10.3109/00207454.2013.817408.

Álvarez-Bueno, C., Pesce, C., Cavero-Redondo, I., Sánchez-López, M., Martínez-Hortelano, J.A., Martínez-Vizcaíno, V., 2017. The Effect of Physical Activity Interventions on Children's Cognition and Metacognition: A Systematic Review and Meta-Analysis. J. Am. Acad. Child Adolesc. Psychiatry 56, 729–738. https://doi.org/10.1016/J.JAAC.2017.06.012.

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 125, 1063–1078. https://doi.org/10.1016/J.NEUROIMAGE.2015.10.019.

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage 20, 870–888. https://doi.org/10.1016/S1053-8119(03)00336-7.

Andersson, J.L.R., Graham, M.S., Zsoldos, E., Sotiropoulos, S.N., 2016. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage 141, 556–572. https://doi.org/10.1016/j.neuroimage.2016.06.058.

Andersson, J.L.R., Graham, M.S., Drobnjak, I., Zhang, H., Filippini, N., Bastiani, M., 2017. Towards a comprehensive framework for movement and distortion correction of diffusion MR images: Within volume movement. Neuroimage 152, 450–466. https://doi.org/10.1016/J.NEUROIMAGE.2017.02.085.

Barha, C.K., Galea, L.A., Nagamatsu, L.S., Erickson, K.I., Liu-Ambrose, T., 2017. Personalising exercise recommendations for brain health: considerations and future directions. Br. J. Sports Med. 51, 636–639. https://doi.org/10.1136/bjsports-2016-096710.

Baum, G.L., Ciric, R., Roalf, D.R., Betzel, R.F., Moore, T.M., Shinohara, R.T., Kahn, A.E., Vandekar, S.N., Rupert, P.E., Quarmley, M., Cook, P.A., Elliott, M.A., Ruparel, K., Gur, R.E., Gur, R.C., Bassett, D.S., Satterthwaite, T.D., 2017. Modular Segregation of Structural Brain Networks Supports the Development of Executive Function in Youth. Curr. Biol. 27, 1561–1572. https://doi.org/10.1016/J.CUB.2017.04.051 e8.

Bells, S., Lefebvre, J., Prescott, S.A., Dockstader, C., Bouffet, E., Skocic, J., Laughlin, S., Mabbott, D.J., 2017. Changes in White Matter Microstructure Impact Cognition by Disrupting the Ability of Neural Assemblies to Synchronize. J. Neurosci. 37, 8227–8238. https://doi.org/10.1523/JNEUROSCI.0560-17.2017.

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. R. Stat. Soc. Ser. B. https://doi.org/10.2307/2346101.

Best, J.R., Miller, P.H., Naglieri, J.A., 2011. Relations between executive function and academic achievement from ages 5 to 17 in a large, representative national sample. Learn. Individ. Differ. 21, 327–336. https://doi.org/10.1016/J.LINDIF.2011.01.007.

Bouchard, C., Sarzynski, M.A., Rice, T.K., Kraus, W.E., Church, T.S., Sung, Y.J., Rao, D.C., Rankinen, T., 2011. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. J. Appl. Physiol. 110, 1160–1170. https://doi.org/10.1152/japplphysiol.00973.2010.

Breusch, T., Pagan, A.R., 1979. A Simple Test for Heteroscedasticity and Random Coefficient Variation. Econometrica 47, 1287–1294. https://doi.org/10.2307/1911963.

Carbine, K.A., Duraccio, K.M., Hedges-Muncy, A., Barnett, K.A., Kirwan, C.B., Jensen, C. D., 2019. White matter integrity disparities between normal-weight and overweight/obese adolescents: an automated fiber quantification tractography study. Brain Imaging Behav. https://doi.org/10.1007/s11682-019-00036-4.

Chaddock, L., Erickson, K.I., Prakash, R.S., Kim, J.S., Voss, M.W., VanPatter, M., Pontifex, M.B., Raine, L.B., Konkel, A., Hillman, C.H., Cohen, N.J., Kramer, A.F., 2010a. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res. 1358, 172–183. https://doi.org/10.1016/J.BRAINRES.2010.08.049.

Chaddock, L., Erickson, K.I., Prakash, R.S., VanPatter, M., Voss, M.W., Pontifex, M.B., Raine, L.B., Hillman, C.H., Kramer, A.F., 2010b. Basal ganglia volume is associated with aerobic fitness in preadolescent children. Dev. Neurosci. 32, 249–256. https://doi.org/10.1159/000316648.

Chaddock-Heyman, L., Erickson, K.I., Voss, M.W., Powers, J.P., Knecht, A.M., Pontifex, M.B., Drollette, E.S., Moore, R.D., Raine, L.B., Scudder, M.R., Hillman, C. H., Kramer, A.F., 2013. White matter microstructure is associated with cognitive control in children. Biol. Psychol. 94, 109–115. https://doi.org/10.1016/J.BIOPSYCHO.2013.05.008.

Chaddock-Heyman, L., Erickson, K.I., Holtrop, J.L., Voss, M.W., Pontifex, M.B., Raine, L. B., Hillman, C.H., Kramer, A.F., 2014. Aerobic fitness is associated with greater white matter integrity in children. Front. Hum. Neurosci. 8, 584. https://doi.org/10.3389/fnhum.2014.00584.

Chaddock-Heyman, L., Erickson, K.I., Kienzler, C., Drollette, E.S., Raine, L.B., Kao, S.-C., Bensken, J., Weisshappel, R., Castelli, D.M., Hillman, C.H., Kramer, A.F., 2018. Physical Activity Increases White Matter Microstructure in Children. Front. Neurosci. 12, 950. https://doi.org/10.3389/fnins.2018.00950.

Chang, E.H., Argyelan, M., Aggarwal, M., Chandon, T.-S.S., Karlsgodt, K.H., Mori, S., Malhotra, A.K., 2017. The role of myelination in measures of white matter integrity: Combination of diffusion tensor imaging and two-photon microscopy of CLARITY intact brains. Neuroimage 147, 253–261. https://doi.org/10.1016/j.neuroimage.2016.11.068.

Chiang, M.-C., McMahon, K.L., de Zubicaray, G.I., Martin, N.G., Hickie, I., Toga, A.W., Wright, M.J., Thompson, P.M., 2011. Genetics of white matter development: A DTI study of 705 twins and their siblings aged 12 to 29. Neuroimage 54, 2308–2317. https://doi.org/10.1016/j.neuroimage.2010.10.015.

Core Team, R., 2018. R: A Language and Environment for Statistical Computing.

Davis, C.L., Tomporowski, P.D., McDowell, J.E., Austin, B.P., Miller, P.H., Yanasak, N.E., Allison, J.D., Naglieri, J.A., 2011. Exercise improves executive function and achievement and alters brain activation in overweight children: A randomized, controlled trial. Heal. Psychol. 30, 91–98. https://doi.org/10.1037/a0021766.

de Greeff, J.W., Hartman, E., Mullender-Wijnsma, M.J., Bosker, R.J., Doolaard, S., Visscher, C., 2016. Long-term effects of physically active academic lessons on physical fitness and executive functions in primary school children. Health Educ. Res. 31, 185–194. https://doi.org/10.1093/her/cyv102.

de Lange, A.-M.G., Bråthen, A.C.S., Grydeland, H., Sexton, C., Johansen-Berg, H., Andersson, J.L.R., Rohani, D.A., Nyberg, L., Fjell, A.M., Walhovd, K.B., 2016. White matter integrity as a marker for cognitive plasticity in aging. Neurobiol. Aging 47, 74–82. https://doi.org/10.1016/J.NEUROBIOLAGING.2016.07.007.

de Lange, A.-M.G., Bråthen, A.C.S., Rohani, D.A., Grydeland, H., Fjell, A.M., Walhovd, K. B., 2017d. The effects of memory training on behavioral and microstructural plasticity in young and older adults. Hum. Brain Mapp. 38, 5666–5680. https://doi.org/10.1002/hbm.23756.

Denson, T.F., Pedersen, W.C., Friese, M., Hahm, A., Roberts, L., 2011. Understanding impulsive aggression: angry rumination and reduced self-control capacity are mechanisms underlying the provocation-aggression relationship. Personal. Soc. Psychol. Bull. 37, 850–862. https://doi.org/10.1177/0146167211401420.

Diamond, A., 2013. Executive functions. Annu. Rev. Psychol. 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750.

Diamond, A., Ling, D.S., 2016. Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. Dev. Cogn. Neurosci. 18, 34–48. https://doi.org/10.1016/J.DCN.2015.11.005.

Diamond, A., Ling, D.S., 2019. Aerobic-Exercise and resistance-training interventions have been among the least effective ways to improve executive functions of any method tried thus far. Dev. Cogn. Neurosci. 37, 100572 https://doi.org/10.1016/J.DCN.2018.05.001.

Ellis, M.U., DeBoard Marion, S., McArthur, D.L., Babikian, T., Giza, C., Kernan, C.L., Newman, N., Moran, L., Akarakian, R., Houshiarnejad, A., Mink, R., Johnson, J., Babbitt, C.J., Olsen, A., Asarnow, R.F., 2016. The UCLA study of children with moderate-to-Severe traumatic brain injury: event-related potential measure of interhemispheric transfer time. J. Neurotrauma 33, 990–996. https://doi.org/10.1089/neu.2015.4023.

Engel, A., Konig, P., Kreiter, A., Singer, W., 1991. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. Science 252 (80-), 1177–1179. https://doi.org/10.1126/science.252.5009.1177.

Engvig, A., Fjell, A.M., Westlye, L.T., Moberget, T., Sundseth, Ø., Larsen, V.A., Walhovd, K.B., 2012. Memory training impacts short-term changes in aging white matter: a longitudinal diffusion tensor imaging study. Hum. Brain Mapp. 33, 2390–2406. https://doi.org/10.1002/hbm.21370.

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

Eriksen, B.A., Eriksen, C.W., 1974. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept. Psychophys. 16, 143–149. https://doi.org/10.3758/BF03203267.

Evenson, K.R., Catellier, D.J., Gill, K., Ondrak, K.S., McMurray, R.G., 2008. Calibration of two objective measures of physical activity for children. J. Sports Sci. 26, 1557–1565. https://doi.org/10.1080/02640410802334196.

Fabri, M., Pierpaoli, C., Barbaresi, P., Polonara, G., 2014. Functional topography of the corpus callosum investigated by DTI and fMRI. World J. Radiol. 6, 895–906. https://doi.org/10.4329/wjr.v6.i12.895.

Gold, B.T., Powell, D.K., Xuan, L., Jicha, G.A., Smith, C.D., 2010. Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. Neurobiol. Aging 31, 512–522. https://doi.org/10.1016/j.neurobiolaging.2008.04.005.

Golestani, A.M., Miles, L., Babb, J., Castellanos, F.X., Malaspina, D., Lazar, M., 2014. Constrained by our connections: white matter's key role in interindividual variability in visual working memory capacity. J. Neurosci. 34, 14913–14918. https://doi.org/10.1523/JNEUROSCI.2317-14.2014.

Gorgolewski, K.J., Varoquaux, G., Rivera, G., Schwarz, Y., Ghosh, S.S., Maumet, C., Sochat, V.V., Nichols, T.E., Poldrack, R.A., Poline, J.-B., Yarkoni, T., Margulies, D.S., 2015. NeuroVault.org: a web-based repository for collecting and sharing unthresholded statistical maps of the human brain. Front. Neuroinform. 9, 8. https://doi.org/10.3389/fninf.2015.00008.

Grund, S., Robitzsch, A., Luedtke, O., 2019. mitml: Tools for Multiple Imputation in Multilevel Modeling.

Hallal, P.C., Andersen, L.B., Bull, F.C., Guthold, R., Haskell, W., Ekelund, U., 2012. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 380, 247–257. https://doi.org/10.1016/S0140-6736(12)60646-1.

Herting, M.M., Colby, J.B., Sowell, E.R., Nagel, B.J., 2014. White matter connectivity and aerobic fitness in male adolescents. Dev. Cogn. Neurosci. 7, 65–75. https://doi.org/10.1016/J.DCN.2013.11.003.

Hillman, C.H., Pontifex, M.B., Castelli, D.M., Khan, N.A., Raine, L.B., Scudder, M.R., Drollette, E.S., Moore, R.D., Wu, C.-T., Kamijo, K., 2014. Effects of the FITKids randomized controlled trial on executive control and brain function. Pediatrics 134, e1063–e1071. https://doi.org/10.1542/peds.2013-3219.

Hillman, C.H., McAuley, E., Erickson, K.I., Liu-Ambrose, T., Kramer, A.F., 2018. On mindful and mindless physical activity and executive function: a response to Diamond and Ling (2016). Dev. Cogn. Neurosci. 100529. https://doi.org/10.1016/J.DCN.2018.01.006.

Huang, T., Tarp, J., Domazet, S.L., Thorsen, A.K., Froberg, K., Andersen, L.B., Bugge, A., 2015. Associations of adiposity and aerobic fitness with executive function and math performance in danish adolescents. J. Pediatr. 167, 810–815. https://doi.org/10.1016/j.jpeds.2015.07.009.

Jacobus, J., Thayer, R.E., Trim, R.S., Bava, S., Frank, L.R., Tapert, S.F., 2013. White matter integrity, substance use, and risk taking in adolescence. Psychol. Addict. Behav. 27, 431–442. https://doi.org/10.1037/a0028235.

Joensuu, L., Syväoja, H., Kallio, J., Kulmala, J., Kujala, U.M., Tammelin, T.H., 2018. Objectively measured physical activity, body composition and physical fitness: cross-sectional associations in 9- to 15-year-old children. Eur. J. Sport Sci. 1–11. https://doi.org/10.1080/17461391.2018.1457081.

Kamijo, K., Masaki, H., 2016. Fitness and ERP indices of cognitive control mode during task preparation in preadolescent children. Front. Hum. Neurosci. 10, 441. https://doi.org/10.3389/fnhum.2016.00441.

Kim, J.S., Pope, A., 2005. Somatotopically located motor fibers in corona radiata: evidence from subcortical small infarcts. Neurology 64, 1438–1440. https://doi.org/10.1212/01.WNL.0000158656.09335.E7.

Krafft, Cynthia E., Schaeffer, D.J., Schwarz, N.F., Chi, L., Weinberger, A.L., Pierce, J.E., Rodrigue, A.L., Allison, J.D., Yanasak, N.E., Liu, T., Davis, C.L., McDowell, J.E., 2014a. Improved frontoparietal white matter integrity in overweight children is associated with attendance at an after-school exercise program. Dev. Neurosci. 36, 1–9. https://doi.org/10.1159/000356219.

Krafft, C.E., Schwarz, N.F., Chi, L., Weinberger, A.L., Schaeffer, D.J., Pierce, J.E., Rodrigue, A.L., Yanasak, N.E., Miller, P.H., Tomporowski, P.D., Davis, C.L., McDowell, J.E., 2014b. An 8-month randomized controlled exercise trial alters brain activation during cognitive tasks in overweight children. Obesity Silver Spring (Silver Spring) 22, 232–242. https://doi.org/10.1002/oby.20518.

Lebel, C., Walker, L., Leemans, A., Phillips, L., Beaulieu, C., 2008. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage 40, 1044–1055. https://doi.org/10.1016/J.NEUROIMAGE.2007.12.053.

Mabbott, D.J., Noseworthy, M., Bouffet, E., Laughlin, S., Rockel, C., 2006. White matter growth as a mechanism of cognitive development in children. Neuroimage 33, 936–946. https://doi.org/10.1016/J.NEUROIMAGE.2006.07.024.

Mackey, A.P., Whitaker, K.J., Bunge, S.A., 2012. Experience-dependent plasticity in white matter microstructure: reasoning training alters structural connectivity. Front. Neuroanat. 6, 32. https://doi.org/10.3389/fnana.2012.00032.

Mahar, M.T., Welk, G.J., Rowe, D.A., 2018. Estimation of aerobic fitness from PACER performance with and without body mass index. Meas. Phys. Educ. Exerc. Sci. 22, 239–249. https://doi.org/10.1080/1091367X.2018.1427590.

Marshall, W.A., Tanner, J.M., 1969. Variations in pattern of pubertal changes in girls. Arch. Dis. Child. 44, 291–303.

Marshall, W.A., Tanner, J.M., 1970. Variations in the pattern of pubertal changes in boys. Arch. Dis. Child. 45, 13–23.

McGee, A.W., Yang, Y., Fischer, Q.S., Daw, N.W., Strittmatter, S.M., 2005. Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. Science 309, 2222–2226. https://doi.org/10.1126/science.1114362.

Miller, E.K., Lundqvist, M., Bastos, A.M., 2018. Working memory 2.0. Neuron 100, 463–475. https://doi.org/10.1016/j.neuron.2018.09.023.

Mora-Gonzalez, J., Esteban-Cornejo, I., Cadenas-Sanchez, C., Migueles, J.H., Molina-Garcia, P., Rodriguez-Ayllon, M., Henriksson, P., Pontifex, M.B., Catena, A., Ortega, F.B., 2019. Physical fitness, physical activity, and the executive function in children with overweight and obesity. J. Pediatr. 208, 50–56. https://doi.org/10.1016/J.JPEDS.2018.12.028 e1.

Mora-Gonzalez, J., Esteban-Cornejo, I., Cadenas-Sanchez, C., Migueles, J.H., Rodriguez-Ayllon, M., Molina-García, P., Hillman, C.H., Catena, A., Pontifex, M.B., Ortega, F.B., 2019. Fitness, physical activity, working memory, and neuroelectric activity in children with overweight/obesity. Scand. J. Med. Sci. Sports 29, 1352–1363. https://doi.org/10.1111/sms.13456.

Nagy, Z., Westerberg, H., Klingberg, T., 2004. Maturation of white matter is associated with the development of cognitive functions during childhood. J. Cogn. Neurosci. 16, 1227–1233. https://doi.org/10.1162/0898929041920441.

Nupponen, H., Soini, H., Telama, R., 1999. Likes. Koululaisten Kunnon Ja Liikehallinnan Mittaaminen [Test Manual of Motor Fitness and Abilities for Schools], 2nd ed.

Oberlin, L.E., Verstynen, T.D., Burzynska, A.Z., Voss, M.W., Prakash, R.S., Chaddock-Heyman, L., Wong, C., Fanning, J., Awick, E., Gothe, N., Phillips, S.M., Mailey, E., Ehlers, D., Olson, E., Wojcicki, T., McAuley, E., Kramer, A.F., Erickson, K.I., 2016. White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. Neuroimage 131, 91–101. https://doi.org/10.1016/J.NEUROIMAGE.2015.09.053.

Pajevic, S., Basser, P.J., Fields, R.D., 2014. Role of myelin plasticity in oscillations and synchrony of neuronal activity. Neuroscience 276, 135–147. https://doi.org/10.1016/J.NEUROSCIENCE.2013.11.007.

Piekarski, D.J., Johnson, C.M., Boivin, J.R., Thomas, A.W., Lin, W.C., Delevich, K., M Galarce, E., Wilbrecht, L., 2017. Does puberty mark a transition in sensitive periods for plasticity in the associative neocortex? Brain Res. 1654, 123–144. https://doi.org/10.1016/j.brainres.2016.08.042.

Ross, R., Goodpaster, B.H., Koch, L.G., Sarzynski, M.A., Kohrt, W.M., Johannsen, N.M., Skinner, J.S., Castro, A., Irving, B.A., Noland, R.C., Sparks, L.M., Spielmann, G., Day, A.G., Pitsch, W., Hopkins, W.G., Bouchard, C., 2019. Precision exercise medicine: understanding exercise response variability. Br. J. Sports Med. 53, 1141–1153. https://doi.org/10.1136/bjsports-2018-100328.

Rovio, S.P., Pahkala, K., Nevalainen, J., Juonala, M., Salo, P., Kähönen, M., Hutri-Kähönen, N., Lehtimäki, T., Jokinen, E., Laitinen, T., Taittonen, L., Tossavainen, P., Viikari, J., Rinne, J.O., Raitakari, O.T., 2016. Cognitive performance in young adulthood and midlife: relations with age, sex, and education—the Cardiovascular Risk in Young Finns Study. Neuropsychology 30, 532–542. https://doi.org/10.1037/neu0000239.

Ruotsalainen, I., Renvall, V., Gorbach, T., Syväoja, H.J., Tammelin, T.H., Karvanen, J., Parviainen, T., 2019. Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents. Behav. Brain Res. 362, 122–130. https://doi.org/10.1016/J.BBR.2018.12.041.

Schaeffer, D.J., Krafft, C.E., Schwarz, N.F., Chi, L., Rodrigue, A.L., Pierce, J.E., Allison, J. D., Yanasak, N.E., Liu, T., Davis, C.L., McDowell, J.E., 2014. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology 51, 728–733. https://doi.org/10.1111/psyp.12227.

Seghete, K.L.M., Herting, M.M., Nagel, B.J., 2013. White matter microstructure correlates of inhibition and task-switching in adolescents. Brain Res. 1527, 15–28. https://doi.org/10.1016/J.BRAINRES.2013.06.003.

Simmonds, D.J., Hallquist, M.N., Asato, M., Luna, B., 2014. Developmental stages and sex differences of white matter and behavioral development through adolescence: a longitudinal diffusion tensor imaging (DTI) study. Neuroimage 92, 356–368. https://doi.org/10.1016/j.neuroimage.2013.12.044.

Singh, A.S., Saliasi, E., van den Berg, V., Uijtdewilligen, L., de Groot, R.H.M., Jolles, J., Andersen, L.B., Bailey, R., Chang, Y.-K., Diamond, A., Ericsson, I., Etnier, J.L., Fedewa, A.L., Hillman, C.H., McMorris, T., Pesce, C., Pühse, U., Tomporowski, P.D., Chinapaw, M.J.M., 2018. Effects of physical activity interventions on cognitive and academic performance in children and adolescents: a novel combination of a systematic review and recommendations from an expert panel. Br. J. Sports Med. bjsports-2017-098136. https://doi.org/10.1136/bjsports-2017-098136.

Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E.J., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505. https://doi.org/10.1016/J.NEUROIMAGE.2006.02.024.

Spear, L.P., 2013. Adolescent neurodevelopment. J. Adolesc. Health 52, S7–13. https://doi.org/10.1016/j.jadohealth.2012.05.006.

Strömmer, J.M., Davis, S.W., Henson, R.N., Tyler, L.K., Tyler, L.K., Brayne, C., Bullmore, E.T., Calder, A.C., Cusack, R., Dalgleish, T., Duncan, J., Henson, R.N., Matthews, F.E., Marslen-Wilson, W.D., Rowe, J.B., Shafto, M.A., Campbell, K., Cheung, T., Davis, S., Geerligs, L., Kievit, R., McCarrey, A., Mustafa, A., Price, D., Samu, D., Taylor, J.R., Treder, M., Tsvetanov, K., van Belle, J., Williams, N., Bates, L., Emery, T., Erzinçlioglu, S., Gadie, A., Gerbase, S., Georgieva, S., Hanley, C., Parkin, B., Troy, D., Auer, T., Correia, M., Gao, L., Green, E., Henriques, R., Allen, J., Amery, G., Amunts, L., Barcroft, A., Castle, A., Dias, C., Dowrick, J., Fair, M., Fisher, H., Goulding, A., Grewal, A., Hale, G., Hilton, A., Johnson, F., Johnston, P., Kavanagh-Williamson, T., Kwasniewska, M., McMinn, A., Norman, K., Penrose, J., Roby, F., Rowland, D., Sargeant, J., Squire, M., Stevens, B., Stoddart, A., Stone, C., Thompson, T., Yazlik, O., Barnes, D., Dixon, M., Hillman, J., Mitchell, J., Villis, L., Davis, S.W., Strömmer, J.M., Campbell, K., Campbell, K.L., 2018. Physical activity predicts population-level age-related differences in frontal white matter. Journals Gerontol. Ser. A. https://doi.org/10.1093/gerona/gly220.

Stroth, S., Kubesch, S., Dieterle, K., Ruchsow, M., Heim, R., Kiefer, M., 2009. Physical fitness, but not acute exercise modulates event-related potential indices for executive control in healthy adolescents. Brain Res. 1269, 114–124. https://doi.org/10.1016/J.BRAINRES.2009.02.073.

Subramanian, S.K., Sharma, V.K., Arunachalam, V., Radhakrishnan, K., Ramamurthy, S., 2015. Effect of structured and unstructured physical activity training on cognitive functions in adolescents - a randomized control trial. J. Clin. Diagn. Res. 9, CC04–CC09. https://doi.org/10.7860/JCDR/2015/14881.6818.

Tarp, J., Domazet, S.L., Froberg, K., Hillman, C.H., Andersen, L.B., Bugge, A., 2016. Effectiveness of a school-based physical activity intervention on cognitive performance in danish adolescents: LCoMotion—learning, cognition and motion – a cluster randomized controlled trial. PLoS One 11, e0158087. https://doi.org/10.1371/journal.pone.0158087.

Tian, Q., Glynn, N.W., Erickson, K.I., Aizenstein, H.J., Simonsick, E.M., Yaffe, K., Harris, T.B., Kritchevsky, S.B., Boudreau, R.M., Newman, A.B., Lopez, O.L., Saxton, J., Rosano, C., Health ABC Study, 2015. Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. Behav. Brain Res. 284, 51–57. https://doi.org/10.1016/j.bbr.2015.01.045.

Treit, S., Chen, Z., Rasmussen, C., Beaulieu, C., 2014. White matter correlates of cognitive inhibition during development: a diffusion tensor imaging study. Neuroscience 276, 87–97. https://doi.org/10.1016/j.neuroscience.2013.12.019.

Trost, S.G., Loprinzi, P.D., Moore, R., Pfeiffer, K.A., Trost, A., Loprinzi, P.D., Moore, R., Pfeiffer, K.A., 2011. Comparison of accelerometer cut points for predicting activity intensity in youth. Med. Sci. Sport. Exerc 43, 1360–1368. https://doi.org/10.1249/MSS.0b013e318206476e.

Van Buuren, S., 2012. Flexible Imputation of Missing Data. CRC Press.

Van Buuren, S., Groothuis-Oudshoorn, K., 2011. Mice : multivariate imputation by chained equations in R. J. Bull. South Ural. State Univ. Ser. "computational Math. Softw. Eng. 45, 1–67. https://doi.org/10.18637/jss.v045.i03.

Van Buuren, S., Brand, J.P.L., Groothuis-Oudshoorn, C.G.M., Rubin, D.B., 2006. Fully conditional specification in multivariate imputation. J. Stat. Comput. Simul. 76, 1049–1064. https://doi.org/10.1080/10629360600810434.

van der Kouwe, A.J.W., Benner, T., Fischl, B., Schmitt, F., Salat, D.H., Harder, M., Sorensen, A.G., Dale, A.M., 2005. On-line automatic slice positioning for brain MR imaging. Neuroimage 27, 222–230. https://doi.org/10.1016/J.NEUROIMAGE.2005.03.035.

Van Hecke, L., Loyen, A., Verloigne, M., van der Ploeg, H.P., Lakerveld, J., Brug, J., De Bourdeaudhuij, I., Ekelund, U., Donnelly, A., Hendriksen, I., Deforche, B., 2016. Variation in population levels of physical activity in European children and adolescents according to cross-European studies: a systematic literature review within DEDIPAC. Int. J. Behav. Nutr. Phys. Act. 13, 70. https://doi.org/10.1186/s12966-016-0396-4.

Wahl, M., Lauterbach-Soon, B., Hattingen, E., Jung, P., Singer, O., Volz, S., Klein, J.C., Steinmetz, H., Ziemann, U., 2007. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J. Neurosci. 27, 12132–12138. https://doi.org/10.1523/JNEUROSCI.2320-07.2007.

Westfall, D.R., Gejl, A.K., Tarp, J., Wedderkopp, N., Kramer, A.F., Hillman, C.H., Bugge, A., 2018. Associations between aerobic fitness and cognitive control in adolescents. Front. Psychol. 9, 1298. https://doi.org/10.3389/fpsyg.2018.01298.

Whiteman, A.S., Young, D.E., Budson, A.E., Stern, C.E., Schon, K., 2016. Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: a voxel-based morphometry study. Neuroimage 126, 229–238. https://doi.org/10.1016/J.NEUROIMAGE.2015.11.049.

Wijndaele, K., Westgate, K., Stephens, S.K., Blair, S.N., Bull, F.C., Chastin, S.F.M., Dunstan, D.W., Ekelund, U., Esliger, D.W., Freedson, P.S., Granat, M.H., Matthews, C.E., Owen, N., Rowlands, A.V., Sherar, L.B., Tremblay, M.S., Troiano, R. P., Brage, S., Healy, G.N., 2015. Utilization and harmonization of adult accelerometry data: review and expert consensus. Med. Sci. Sports Exerc. https://doi.org/10.1249/MSS.0000000000000661.

Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. Neuroimage 92, 381–397. https://doi.org/10.1016/J.NEUROIMAGE.2014.01.060.

Zeileis, A., Hothorn, T., 2002. Diagnostic checking in regression relationships. R News 2, 7–10.

III

PHYSICAL ACTIVITY IS POSITIVELY ASSOCIATED WITH LOCAL FUNCTIONAL CONNECTIVITY IN ADOLESCENTS' BRAINS

by

Ilona Ruotsalainen, Enrico Glerean, Juha Karvanen, Tetiana Gorbach,
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