RELATIONSHIP BETWEEN PHYSICAL ACTIVITY, FITNESS AND BRAIN MORPHOLOGY IN YOUTH

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ABSTRACT

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Growing evidence has displayed a relationship between physical activity, fitness and cognitive functions, yet the underlying mechanisms and changes in brain morphology explaining this connection are still quite unknown. The current study examined whether physical activity or physical fitness is related with regional brain volume of cortical thickness in youth.

The subjects were 35 Finnish adolescents (14.1 ±0.7 years, 23 females & 12 males), a subsample from Active, Fit and Smart (AFIS) – research project. Measurements included objective physical activity measurement with accelerometers, physical fitness test battery and brain imaging procedure with magnetic resonance imaging (MRI). From the larger study sample of the AFIS – research project, two groups were formed based on the physical activity measurements, active (n=18) and non-active (n=17). The active group included the most physically active subjects, measured as the average daily time involved in moderate-to-vigorous activity, and the non-active group included the most inactive subjects. The relationship between physical activity and brain morphology was examined by comparing the two groups using the analysis of covariance, controlling the effect of age, puberty status and body mass index. The relationship between physical fitness and brain morphology was examined by looking at correlations between the physical fitness tests and chosen brain variables.

It was found that physical activity had a positive relationship with the thickness of the right parahippocampal cortex [$F(1, 30)=4.44$, $p<0.05$)]. Physically more active subjects expressed a thicker right parahippocampal cortex compared to less active subjects. A relationship was also found between physical activity and the thickness of the left paracentral cortex, yet this finding lost significance after controlling the effect of age [$F(1, 30)=2.50$, $p=0.12$)]. No other brain region displayed a connection with the level of physical activity and no significant correlations were detected between physical fitness and the brain variables. These findings imply that especially the area of right parahippocampal cortex might be susceptible to physical activity induced changes in youth, and that physical activity does not necessarily have to improve physical fitness to cause changes in brain morphology.

Key words: physical activity, physical fitness, brain volume, cortical thickness

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CONTENTS

1 INTRODUCTION

Regular physical activity is widely known to improve our physical health and well-being, yet growing evidence shows that it can improve our brain function and cognitive skills as well (Hillman et al. 2008). Although animal studies have already suggested some possible mechanisms, very little is still known about the structural brain changes underlying the cognitive benefits achieved with exercise, especially in humans (Yau et al. 2014). The increasing inactivity among youth is concerning, as the number of children and adolescents fulfilling the guidelines for physical activity decreases steadily with age. While about 40% of primary school aged children are active the recommended one hour daily, only a third of 13-year-olds, and not even a fifth of 15-year-old Finnish students fulfill this recommendation. Physical activity clearly decreases during adolescence. (Kokko et al. 2016.)

Physical activity has shown to be beneficial for brain functioning, at least in adults and elderly. It seems also that regular physical activity and aerobic fitness are positively correlated with academic achievements in children. (Guiney & Machado 2012.) Also the hippocampal volume has shown to be larger and memory functioning to be better in highly fit children compared to lower fit ones (Chaddock et al. 2010). In addition to aerobic fitness, also strength and motor skill learning have been shown to have a positive relationship with certain brain areas (Anstey et al. 2007; Gryga et al. 2012; Koppelmans et al. 2015).

During childhood and adolescence, the brain is the most plastic and develops rapidly. From childhood towards maturity, the brain structure changes. For example, the white and gray matter volumes and neural connections change throughout childhood up to young adulthood. (Gogtay et al. 2004.) Since the brain is the most plastic in childhood and youth, also the external influences can have a great impact on brain development at early age. If physical activity causes beneficial changes to brain structure and function, lack of physical activity in youth might, therefore, have negative effects on cognitive functions in addition to the negative effects on physical well-being. (Herting & Nagel 2012; Voss et al. 2011.) As growing evidence shows that physical activity and fitness benefit brain health in older individuals, more research is needed to assess the similar connection in youth.

2 BRAIN MORPHOLOGY AFFECTS COGNITIVE FUNCTIONING

The structure and organization of the brain, including the size and the arrangement of neurons, the number and type of synaptic connections and also the properties of other brain tissue, contribute to the information processing of the brain, hence has an important role in our cognitive functioning (Zatorre et al. 2012). It has been established that larger volumes in certain brain areas can contribute to better cognitive performance. For example, larger hippocampal volumes have been connected to better memory performance in both children and older adults (Chaddock et al. 2010; Erickson et al. 2011), and larger frontal brain areas have been suggested to contribute to better executive functions (Guiney & Machado 2012). In addition, greater gray matter volume in occipital-parietal areas has been shown to enhance the learning process of a complex visuo-motor task (Sampaio-Bapista et al. 2014) and memory recall abilities of people with brain injury have been shown to be directly related to regional gray matter volume in frontal and parietal cortices (Spitz et al. 2013).

However, the adolescent brain undergoes major developmental changes, including decreases in gray matter volume and cortical thickness (Konrad et al. 2013; Schnack et al. 2015). Although larger brain volumes have typically been connected with better cognitive performance, Schnack et al. (2015) found in their extensive study, that faster cortical thinning of the left cortex was in fact connected to higher intelligence in adolescents. Therefore, when studying the effect of an external factor, such as physical activity to brain morphology, it is highly important to understand the normally occurring developmental changes in brain along with the basics of brain functioning and morphology.

2.1 Neural basis of learning and memory

Memory can be defined as a lasting representation reflected in thought, experience or behavior, and learning is the acquisition of these representations (Baars & Gage 2010, 305). Learning involves a wide range of brain areas, but the main area for learning and memory is thought to be the medial temporal lobe (MTL) (Figure 1). The medial temporal lobe is a complex structure consisting of the hippocampus, entorhinal and perirhinal cortices and the parahippocampal cortex. (Lech & Suchan 2013.) These are ideally situated in the brain to combine information about the cognitive and emotional areas to bind experiences into memories (Baars & Gage 2010, 307). Convincing evidence emphasizes the importance of the MTL and hippocampus in various types of memory-related processes, such as spatial memory (Erickson et al. 2011), making novel memories permanent (Yau et al. 2014), episodic memory (Lee et al. 2014a), declarative memory and certain types of working memory as well (Lech & Suchan 2013).

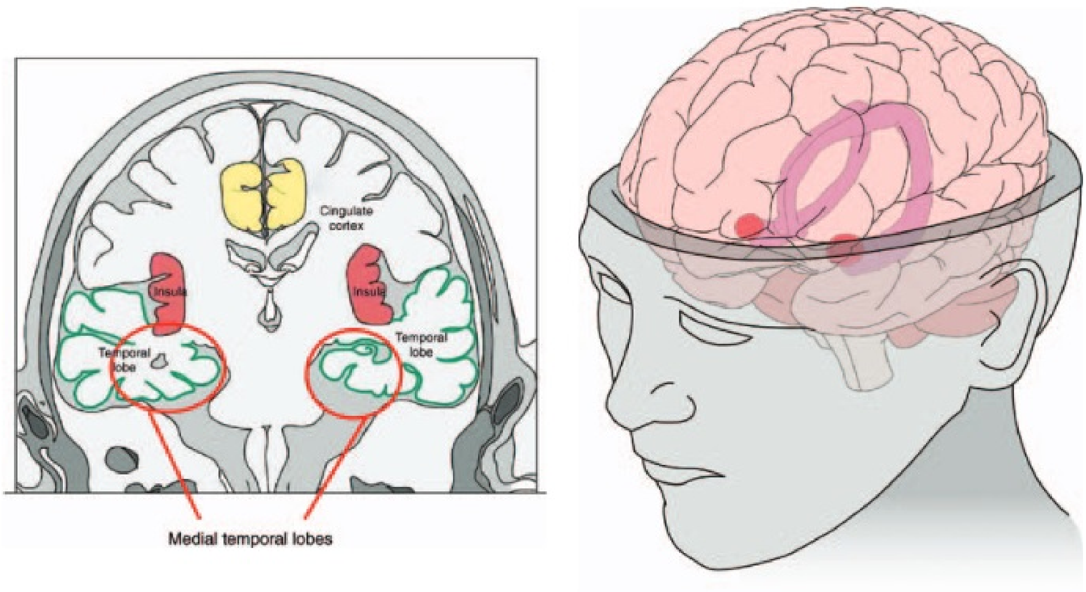

FIGURE 1. The location and anatomy of the medial temporal lobe and the hippocampus (Baars & Gage 2010, 306).

Without the hippocampus and the MTL, it is not possible to create any new memories. This finding has initially been discovered with brain lesions, where hippocampus and the MTL have been removed. Old memories and the working memory remain intact, but the ability to create any novel long-term memories vanishes. Brain simply cannot consolidate any more permanent memories in the absence of hippocampus. (Eichenbaum 2013.) Besides creating new memories, hippocampus makes it possible to retrieve specific episodic memories consciously (Reber 2013). Also spatial memory seems to be highly dependent of the hippocampus and larger hippocampal volumes have shown to mediate better spatial memory (Erickson et al. 2011). Besides the mere existence of hippocampus and MTL, evidence has shown also hippocampal neurogenesis to play an important role in certain memory processes. Neurogenesis refers to the formation of new neurons, and it has been noticed to occur in the dentate gyrus of the hippocampus, even in adults and elderly. Studies have shown that the forming of new neurons in adult hippocampus might play a functional role in learning and memory, and that neurogenesis in dentate gyrus is an important factor in hippocampal-dependent learning and memory. (Yau et al. 2014.)

2.2 Brain development in youth

The brain changes drastically both anatomically and functionally during childhood and adolescence. Some parts of the brain can reach maturity already in early childhood, but some regions develop even up to early adulthood. For example, the sensory regions have been noticed to achieve maturity already by the age of seven, while the prefrontal cortex keeps developing throughout the entire childhood, explaining also the late development of executive functioning in children. (Khan & Hillman 2014.)

After birth, most neurons in the brain have reached their final locations, but the most obvious change in neural development postnatal is the increase in size and complexity of the dendritic trees of the neurons; the increase of the inputs and outputs of the cell. (Baars & Gage 2010, 477.) Although the level of neurogenesis is at its highest before and after birth, the formation of new neurons is still at a quite high level in adolescence, and it does not face a drastic decline until the transition into adulthood (Leuner & Gould 2010). The forming and migration of glial cells continues also throughout childhood and adulthood. These cells are thought to be important in the organization of neural circuits, and in increasing the conduction speed in the brain. When neurons are covered with a fatty sheath, a process called myelination, the efficiency in the transmission of information in the brain is enhanced. Myelination increases the brain's white matter volume, which has been noticed to increase linearly up to young adulthood. (Houston et al. 2014.)

In addition to the increase of connections and white matter during brain development, the unused connections are also being eliminated, increasing the capacity of the brain and information processing speed. This synaptical pruning continues in different parts of the brain at different velocities, leading to some brain areas mature earlier than others. Together with white matter increase, synaptical pruning is an important process in neurocognitive development, making information processing more efficient and improving cognition. (Khan & Hillman 2014.) For example, the hippocampal volume has been noticed to increase up to early adolescence, yet some hippocampal subfields have also been noticed to decrease in volume, and most of the shrinkage seems to appear at mid-adolescence (Tamnes et al. 2014). Total brain volume has been noticed to increase steadily up to the age of 13 years, from where it starts to gradually decrease (Hedman et al. 2012). In addition, the greatest changes regarding cortical thinning seem to occur during adolescence (Tamnes et al. 2010). Besides age, also pubertal development has been noticed to relate with brain structure changes, and it has been suggested that the hormonal changes occurring in puberty are also influencing structural brain growth (Goddings et al. 2014).

Brains are highly individual in their size, shape and structure. Although previous studies have suggested that, for example, total cerebral volume and both gray and white matter volumes are mainly determined by genes, some brain areas and their development have shown to be almost entirely mediated by environmental factors. It has been suggested, that the earliest stages of brain development are mostly mediated by genetic effects, whereas later stages of brain development involve a much more complex interaction from both genetic and environmental influences. (Baare et al. 2001; Yoon et al. 2010.) For example, the frontal and temporal gray matter structures seem to be less mediated by genetic, yet increasingly mediated by environmental factors with age (Wallace et al. 2006). Since the brain undergoes such great changes during childhood and adolescence, and is highly sensitive to environmental influences at that time, a physically active lifestyle during that period might influence the brain development positively and, therefore, improve cognitive capacity as well (Herting & Nagel 2012).

2.3 Plasticity of the brain

Neuroplasticity refers to the ability of the brain and its neural circuits to adapt to new challenges and environments. For example, learning can induce changes in the neurotransmitters and their release, which might eventually lead into structural brain changes as well. In addition to learning, also behavioral and environmental factors can either facilitate or hinder neuroplasticity. (Hötting & Röder 2013.) For example, aging, stress and drug use have been noticed to deteriorate neural plasticity (Khan & Hillman 2014; Konrad et al. 2013). On the other hand, factors noticed to improve neuroplasticity include special types of dietary habits, medical treatments, enriched environments, cognitive stimulation and physical exercise (Hötting & Röder 2013). Along with the brain structure, also the plasticity of the brain seems to have a significant role considering intelligence (Schnack et al. 2015).

The brain can express changes in both gray and white matter volumes and structures. Possible mechanisms explaining these changes include neurogenesis, changes in neuronal morphology, vascular changes, changes in glia cell number and size, myelination or axonal changes. Neurogenesis refers to the formation of new neurons, yet it is an unlikely explanation for brain structure changes outside the hippocampus, one of the only brain areas new neurons have been noticed to originate. However, other plausible neuronal morphology changes include, for example, synaptogenesis, the formation of new synapses between neurons and dendritic spine formation. The vasculature of the brain can also express plasticity, and it has been discovered in both animals and humans that exercise can increase the blood volume in the dentate gyrus of the hippocampus. (Zatorre et al. 2012.) Aerobic fitness has also been linked to higher blood flow velocity of the middle cerebral artery, indicating global cerebral blood perfusion, thus suggesting superior cerebrovascular functioning in higher-fit individuals (Guiney & Machado 2013). Animal studies have also discovered exercise-induced increases in angiogenesis, the creation of new blood vessels in the brain. Angiogenesis has been noticed to take place in the hippocampus and in areas involved in executing voluntary movements, like the cerebellum and the primary motor cortex. Interestingly, these findings are limited to young animals only, whereas no changes in angiogenesis have been found in aged animals. (Voss et al. 2011.)

Changes in white matter can be explained with either myelination or axonal modifications. Myelination continues linearly up to young adulthood (Houston et al. 2014), yet behavioral factors have also been noticed to influence the process (Zatorre et al. 2012). White matter changes can also be due to modifications in axon diameter or permeability (Zatorre et al. 2012). In addition to changes in gray or white matter, external factors can induce changes also in the levels of growth factors or neurotransmitters. For example, physical activity has been noticed to increase the release of brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1), and also to elevate the levels of serotonin, noradrenaline and acetylcholine. These have also been noticed to play an important role in neuroplasticity. (Hötting & Röder 2013.)

3 PHYSICAL ACTIVITY AND BRAIN MORPHOLOGY

The relationship between physical activity and brain morphology has mainly been studied in the elderly or in animal studies. At least animal studies have shown clearly that physical activity can modify the brain structure and functioning, especially in the areas of hippocampus (Yau et al. 2014), and similar findings have been established among older adults as well (Erickson et al. 2014). Some studies have also found a positive correlation between physical activity and brain volume in younger subjects (Chaddock et al. 2010; Chaddock-Heyman et al. 2014; Gondoh et al. 2009), yet studies on children and adolescents on this subject remain still quite limited.

3.1 Definition and recommendations of physical activity and current trends in youth

Physical activity can be defined as bodily activity that increases energy expenditure above resting levels (Thomas et al. 2012). The generally accepted recommendation of physical activity for school-aged children is at least 60 minutes of moderate-to-vigorous physical activity a day (Armstrong 2013). Physical activity should be variable and suitable for each age group. Additionally, sitting periods should not last over two hours, and screen time should be limited to two hours per day. These basic recommendations are targeted for all 7–18 -year old children, despite of special needs. (Nuori Suomi 2008.)

The current recommendations are, however, met by only a minority of children and adolescents. Half of Finnish primary school students were active at least one hour per day, and only 17% of secondary school students fulfilled the minimum requirement of physical activity (Figure 2). In addition, screen time limitations were exceeded by a considerable amount. (Tammelin et al. 2013.) The situation is similar in other countries as well. For example, in the USA, only 19–38% of 12–17 year-olds and in England, just 15–33% of 9–15 year-olds were physically active at least 60 minutes a day. (Booth et al. 2015.)

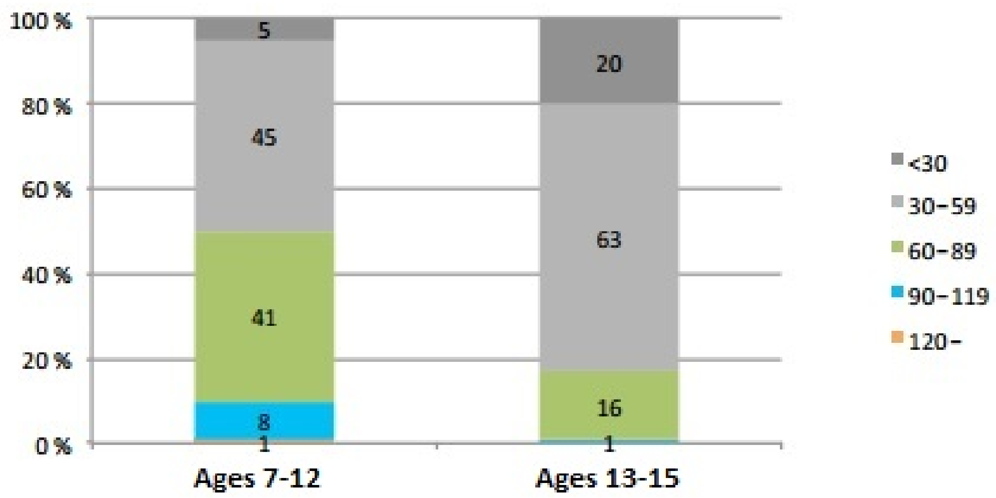

FIGURE 2. The relational number of those students (%) being physically active < 30, 30–59, 60–89, 90–119 or at least 120 minutes per day (Modified from Tammelin et al. 2013).

Physical activity seems to gradually drop when moving from childhood into adolescence and young adulthood. Whereas about 40% of Finnish 9– and 11–year-olds seem to fulfill the recommendations, only fourth of 13-year-olds and merely a fifth of 15-year-olds met the guidelines. The gradual drop in physical activity is visible in both boys and girls. In addition, about 20% of 15-year-olds displayed sedentary behavior, participating in physical activity only for 0–2 days per week. (Kokko et al. 2016.) Therefore, the period of adolescence (10–19 years) has shown to be critical period in life in terms of physical activity change. The amount of physical activity has shown to decline about 7% each year, leading to an overall decline of 60–70% throughout adolescence. These findings address the importance of promoting physical activity to children and adolescents. (Dumith et al. 2011.)

3.2 Brain areas and cognitive functions susceptible to physical activity

Physical activity does not seem to influence all brain regions similarly. It has been noticed that while some brain areas are more susceptible to exercise, other brain regions show minimal or no change followed by physical training. (Erickson et al. 2011.) By influencing in only specific brain areas, physical activity seems to cause selective improvement in cognitive functions. Although some studies suggest also comprehensive cognitive benefits due to physical activity, several previous studies have found physical activity to improve primarily executive functions and hippocampal dependent memory functioning. (Erickson et al. 2011; Erickson et al. 2014; Flöel et al. 2010; Hillmann et al. 2005; Voss et al. 2011.)

The frontal cortex. It has been hypothesized that physical activity affects cognitive functions and brain areas mostly during the time, when they undergo developmental changes, thus age might be a moderating factor in the relationship between physical activity and brain health. Frontal brain regions mature late in adolescence, which might make them more sensitive to own activity dependent external factors, like physical activity, compared to mature structures. (Hötting & Röder 2013.) Late maturation of the frontal regions also explains the relatively late development of executive functions, which are thought to be subserved by the frontal lobes. These functions refer to higher level cognitive processes, such as planning, self-regulation, initiation, inhibition and cognitive flexibility. (Verburgh et al. 2014.) In addition, frontal brain regions are especially prone to age-related deterioration, explaining the benefits of physical activity to those areas also in older population (Hötting & Röder 2013).

The medial temporal lobe and the hippocampus. Along with the frontal lobes and executive functions, also the hippocampus and several memory functions seem to express beneficial changes due to physical activity. Studies in both animals and humans have discovered positive changes in the hippocampal area as a result of aerobic exercise. (Erickson et al. 2011; Erickson et al. 2014; Nokia et al. 2016.) In older adults, the hippocampal volume has been noticed to shrink approximately 1–2% a year, showing significant age-related deterioration similar to the frontal brain regions. However, physical activity has shown to be an effective way to decelerate the degradation, or even increase hippocampal volume. (Erickson et al. 2011.) Aerobic exercise has shown to increase the hippocampal volume also in adolescents, coinciding with better learning (Herting & Nagel 2012). Moreover, a review by Khan and Hillman (2014) concludes that positive associations between fitness and memory performance was found only for the hippocampal-related memory tasks, consistent with the results from animal studies, indicating that physical activity has a positive influence especially on hippocampus. Taken these data together, the hippocampus seems to be one of the brain areas in which physical activity can bring positive changes throughout lifetime. (Erickson et al. 2014; Herting & Nagel 2012; Killgore et al. 2013.)

Even self-reported physical activity measures have shown to correlate with the gray matter volume of the brain. In addition, it has been suggested, that even moderate levels of physical activity can be beneficial for the brain. However, not all studies have shown a relationship between physical activity and brain volume, and some studies have also noticed the significant relationship disappear, when a moderating factor, such as age, stress or body mass index (BMI) is taken into account. (Erickson et al. 2014.) Nonetheless, a clear majority of the studies reported in the comprehensive review by Erickson et al. (2014), looking at the relationship between physical activity and brain volume, reported physical activity or fitness to have an effect on the prefrontal and/or hippocampal volumes. Although the consistency of the results varies and the mechanism of how physical activity and fitness can increase the brain volume is not clear, the evidence is still promising.

3.3 Exercise induced neurogenesis

A possible mechanism explaining the connection between physical activity and cognitive functions is the proliferation of new neurons, process called neurogenesis (Yau et al. 2014). Although it was long believed, that once matured, the brain does not generate new neurons, it is now commonly known that even the adult brain does show neurogenesis. However, the brain regions establishing neurogenesis are very limited, and it is thought to appear only in the dentate gyrus of hippocampus and in the subventricular zone of the lateral ventricle. (Khan & Hillman 2014.) Neurogenesis appears naturally, but the rate of it declines with age. There are, however, factors that can speed up neurogenesis or at least slow down the age-related degradation and one such influencing factor is exercise. (Erickson et al. 2011.) Exercise has shown to upregulate the hippocampal neurogenesis, leading to improved hippocampal-dependent cognitive performance (Thomas et al. 2012).

The exact mechanism of how physical exercise upregulates hippocampal neurogenesis is still unclear, but factors such as increased cerebral blood flow and certain neurotrophins have been suggested to work as moderators of the process (Yau et al. 2014). Increasing evidence suggests the connection between exercise and improved cognition is most likely to be explained by the increase of brain-derived neurotrophic factor (BDNF) (Erickson et al. 2011; Griffin et al. 2011;

Huang et al. 2014). BDNF is a part of the neurotrophin family, and it is expressed in both developing and adult brain, as well as in peripheral tissues, including the muscle and adipose tissue. BDNF has been linked to the plasticity of the brain in a variety of ways, including neurogenesis, the survival of new neurons and synaptical plasticity. (Huang et al. 2014.) Higher levels of BDNF have also been connected to better spatial, episodic and verbal memory, as well as improved hippocampal functioning (Szuhany et al. 2015). In addition to changes in neurotrophin levels, exercise has been noticed to increase cerebral blood flow, the permeability of the blood brain barrier and to induce angiogenesis, the generation of new blood vessels. The relationship between physical exercise and cognitive performance might therefore be moderated to some extent by hippocampal angio- and neurogenesis as well. (Yau et al. 2014.)

Aerobic training has been the most studied training modality in the field and has the most convincing evidence to enhance neurogenesis, whereas evidence regarding the effects of resistance training lack both consistency and volume. (Szuhany et al. 2015.) In addition, evidence suggests that aerobic exercise must be intensive enough to elevate BDNF levels (Huang et al. 2014). This finding has been established when studying humans, but interestingly contrary results have been discovered in animal studies (Huang et al. 2014; Nokia et al. 2016). For example, Nokia et al. (2016) found in their study that high-intensity interval training (HIT) had in fact minor effects on neurogenesis when compared to longer duration and less intensive aerobic training.

In addition to BDNF, also vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) have been noticed to be possibly involved in the connection between exercise and hippocampal-dependent learning. Previous studies have established IGF-1 and VEGF to be involved in activating both hippocampal neurogenesis and angiogenesis. In addition, neurogenesis is suppressed when peripheral IGF-1 and VEGF are blocked. (Lee et al. 2014b; Thomas et al. 2012.) Different types of exercise seem to operate via different mechanisms, for example aerobic exercise has strongly been linked to the levels of BDNF, whereas resistance training seems to be involved especially in the IGF-1 levels. Combining both aerobic and resistance training might therefore be especially beneficial for cognitive functioning. (Hötting & Röder 2013.)

4 EFFECTS OF AEROBIC, RESISTANCE AND MOTOR SKILL TRAINING ON BRAIN MORPHOLOGY AND COGNITIVE FUNCTIONING

Besides physical activity, also exercise and physical fitness have shown to influence brain anatomy and functioning (Voss et al. 2011). Although closely related, the terms physical activity and physical exercise must be considered as independent variables. Whereas physical activity can be defined as bodily activity that increases energy expenditure above resting levels, physical exercise refers to more organized training with the intension of improving physical fitness (Thomas et al. 2012). In the current study, the focus is on three different components of physical fitness and their effects on brain health: aerobic training and cardiovascular fitness, resistance training and strength, and motor skills and skill training.

4.1 Aerobic training and cardiovascular fitness

Aerobic or cardiovascular fitness, is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity and to eliminate fatiguing products (Gahche et al. 2014). Aerobic fitness can be improved with aerobic training, which results in various physiological adaptations. Aerobic training increases blood volume, capillar density, mitochondrial size and density, and improves fat mobilization, collectively leading to improved aerobic fitness. (Thomas et al. 2012.) The *'golden standard'* for measuring aerobic fitness is to measure maximal oxygen consumption (VO_{2max}), which represents the maximum capacity of oxygen transport and usage during physical activity (Gahche et al. 2014). There have been controversial results, whether the effects of physical activity on brain volume and function are independent or moderated by some physiological factor, such as cardiovascular fitness. (Colcombe et al. 2004; Flöel et al. 2010.) However, whether studying either the effect of physical activity or cardiorespiratory fitness on brain structure and function, they both seem to have similar outcomes and have specific effects on the same brain areas (Erickson et al. 2014).

Aerobic exercise has shown to have an effect predominantly in executive functions, which are thought to be subserved by the frontal lobes (Colcombe et al. 2006). Previous studies have established that physically more fit older adults have shown greater gray matter density in the frontal areas, preserved connections between the prefrontal cortex to other regions of the brain, and higher level of circulating neurotrophins in the prefrontal cortex, compared to unfit subjects (Guiney & Machado 2013). Furthermore, higher levels of aerobic fitness have shown to express a relationship with better performance in cognitive tasks requiring executive control. It seems that higher fitness can enhance attention, cognitive flexibility and processing speed, altogether accounting for better acquisition of information in a given environment. (Khan & Hillman 2014.) Although most of these findings have been established with older subjects, emerging evidence implies that regular aerobic exercise might also benefit executive functions in young adulthood as well (Guiney & Machado 2013).

Along with the frontal regions, studies in both animals and humans have shown a positive correlation between aerobic fitness and hippocampal volume as well. At least animal studies have shown the correlation clearly, yet the same findings are also established when studying older adults. (Yau et al. 2011.) A study by Erickson et al. (2011), compared an aerobic training group with a stretching group, and discovered that after a one-year intervention period, the aerobic training group had increased the size of their left and right hippocampus by approximately 2%, while the stretching group showed a 1.4% decline in the same period of time. It was established, that the more the aerobic fitness was improved, the more the hippocampal volume increased as well. An interesting finding was also that high initial level of fitness seemed to attenuate the normally occurring hippocampal volume loss in adult individuals, however aerobic exercise was needed for the volume to increase. These findings indicate that the effects of physical activity on brain volume are, at least partly, mediated by improved cardiorespiratory fitness, yet it is not the only influencing factor. (Erickson et al. 2011.)

While cardiovascular fitness can be improved with aerobic training, it improves naturally in youth also due to maturation. The peak VO_2 seems to express a progressive rise from 8 to 13 years in both boys and girls (Figure 3). Boys seem to increase their aerobic fitness even further between ages 13 to 15 years, while girls seem to express a plateau after the age of 14. When controlling the effect of body mass, the boys seem to express an increase in peak VO_2 throughout adolescence up to young adulthood, with girls showing increase at least into puberty. Although cardiovascular fitness improves in adolescence by itself via maturation, trained subjects still express superior aerobic fitness when compared to untrained adolescents. (Armstrong et al. 2011.)

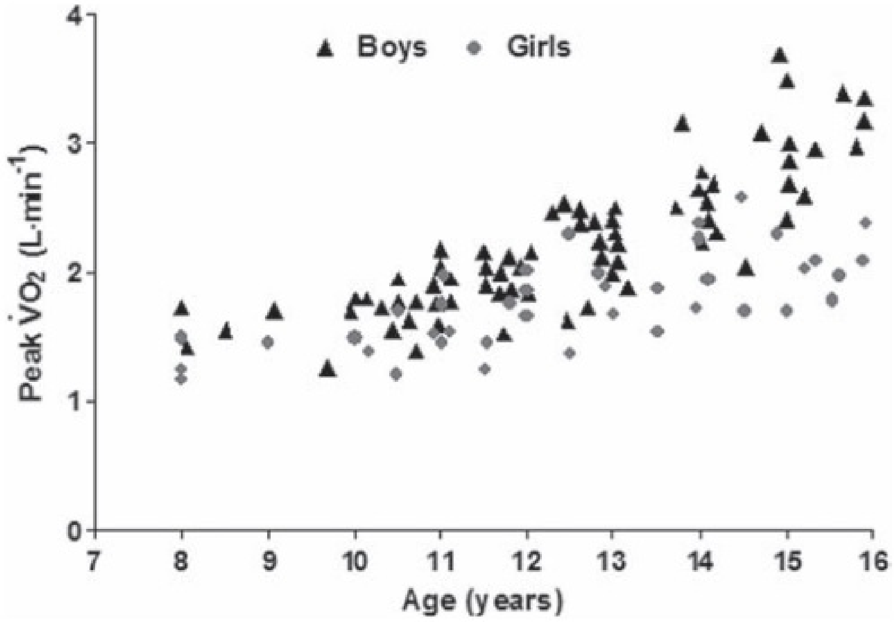

FIGURE 3. Absolute peak oxygen uptake (Peak VO_2, a representation of aerobic fitness), in relation to age (Armstrong et al. 2011).

4.2 Muscle strength and resistance training

Strength is defined as the ability to generate maximal external force. Both peripheral factors; the capabilities of individual muscles, and the central factors; the coordination of muscle activity by the central nervous system, are important for strength. (Zatsiorsky & Kraemer 2006, 21–64.) Most studies on the field have focused on exploring the influence of aerobic exercise on brain morphology and functioning, yet also resistance training and coordination training have given promising results in enhancing cognitive functions and altering the brain structure (Bherer et al. 2013; Hötting & Röder 2013). For example, Koppelmans et al. (2015) found a correlation between grip strength and contralateral gray matter cerebellar volumes, as well as motor cortex volume, when studying healthy older adults. Some evidence supports also the relationship between grip strength and white matter volume (Kilgour et al. 2014). In addition, resistance training has shown to improve executive functions, short-term memory and attention in older individuals. Animal studies have also provided a link between resistance training and spatial memory. (Hötting & Röder 2013.) However, while being less examined, also the possible benefits to cognition are more controversial for resistance training than for aerobic exercise. Some studies have failed to express a relationship between resistance training and cognitive functions, or it has been suggested that the benefits are achieved only when the intensity of the resistance training is high. Furthermore, studies considering the effects of resistance training and strength to brain morphology and functioning in younger subjects remain extremely limited. (Voss et al. 2011.)

A study by Cassilhas et al. (2007) found an increase in the IGF-1 levels concurrent with improved cognitive function in experimental groups doing resistance training compared to the control group. The mechanism behind the possible benefits achieved with resistance training might therefore be explained with higher levels of IGF-1, a growth factor involved in neural plasticity. (Cassilhas et al. 2007.) It has been suggested that while different types of exercise can cause beneficial effects to cognition, they might operate via different kinds of mechanisms and, therefore, have an influence on distinct cognitive capabilities (Hötting & Röder 2013).

In youth, maturation leads, for example, increases in body size, muscle mass and neuromotor control, which all have an effect on the physical abilities as well (Hebestreit & Bar-Or 2005.) Also hormonal changes occur during adolescence (Meylan et al. 2014), and in addition to the increasing body size and mass, the body proportions change during childhood and adolescence, which changes the movement biomechanics as well (Hebestreit & Bar-Or 2005). In females, the relative muscle mass remains quite constant (40–46%) from childhood to adulthood, but in males the relative muscle mass increases from about 42% to 53% during childhood and adolescence. The muscle fiber composition and metabolic properties change during youth as well. It has been studied, that children have a larger proportion of slow oxidative type I muscle fibers compared to fast type II fibers. (Hebestreit & Bar-Or 2005.) These changes occurring during maturation makes the youth an interesting, yet also quite challenging population to examine the relationship between physical exercise and brain morphology.

Although resistance training has been previously considered possibly dangerous and deleterious for children and adolescents, the current guidelines state strength training to be safe and effective also for youth, provided it is well planned, guided and supervised by experienced instructors. Even strenuous strength training can be considered safe, when it is performed with submaximal loads. Resistance training can provide similar positive changes in youth as in adults, including higher strength levels, changes in body composition and improved motor skills. (Barbieri & Zaccagni 2013.)

4.3 Motor skill training

Learning of complex motor skills has been noticed to cause structural changes in the brains. This has been noticed after several weeks of skill learning, yet some studies have discovered changes occurring in just few days. (Gryga et al. 2012; Sampaio-Bapista et al. 2014.) Particularly motor-related brain regions have expressed gray matter increases after motor skill learning, yet structural changes have also been noticed outside the motor cortex (Gryga et al. 2012). In addition to gray matter changes, motor skill training has been linked to white matter changes as well (Scholtz et al. 2009). Whereas endurance training can induce angiogenesis in motor cortex and resistance training can alter spinal motoneuron excitability, only motor skill training seems to be able to alter the organization of neural circuitry within motor cortex. Although every movement pattern requires at least some motor skills, specifically skill training can be defined as the acquisition and practicing of new combinations of movement sequences (Adkins et al. 2006).

Sampaio-Bapista et al. (2014) established in their study, that larger volumes in the medial occipito-parietal areas lead to faster learning rates in a complex visuo-motor task, and also that learning such a task seemed to increase the gray matter volume of certain brain areas. A positive relationship was found on several motor-related brain areas, including the primary motor cortex. Based on these findings, they suggested that people with good eye-hand coordination have greater gray matter volume, either by genetic factors or due to learning. In addition, individuals with greater gray matter volumes in specific regions were also noticed to maintain the learned skill for longer. (Sampaio-Bapista et al. 2014.) Learning a complex motor task seems not only affect the gray matter volume, but the white matter volume as well. For example, Scholtz et al. (2009) found regional white matter volume increases after training for complex visuo-motor task.

Also Gryga et al. (2012) found bidirectional gray matter changes followed by complex motor skill training. They concluded that individuals who were the best learners and acquired the skill well were also those ones whose gray matter volume showed the most increase. Individuals showing only a small or no improvement in skill performance either showed no change or even decreased gray matter volumes in regional brain areas. The initial level of gray matter volume seemed also to predict how well the introduced motor task would be learned. (Gryga et al. 2012.) In addition, experienced athletes seem to have larger cortical representations in their motor cortex in areas directly connected to the muscles most dominant in their sport. As an example, volleyball players have learned several coordinated shoulder movements and have therefore larger representations of shoulder muscles in their motor cortex when compared to, for example, runners who do not need skilled shoulder movements in their sport. (Adkins et al. 2006.) These findings indicate that in addition to aerobic and resistance training, also motor skill training can induce changes in brain morphology.

5 RESEARCH PROBLEMS AND HYPOTHESIS

The aim of this study was to examine, whether physical activity or physical fitness has a relationship with regional brain volume or cortical thickness in youth. First, the effect of physical activity was examined by comparing brain volume and cortical thickness between active and non-active individuals. Second, the relationship of physical fitness and brain morphology was examined by looking at correlations between different components of physical fitness, brain volume and cortical thickness. Previous studies have shown physical activity and fitness to be linked with increased hippocampal volume (Erickson et al. 2011; Herting & Nagel 2013; Killgore et al. 2013), the frontal regions (Hötting & Röder 2013) and the motor cortices (Gryga et al. 2012). However, the results from previous studies have been established mostly with older individuals, while the number of studies using adolescents as subjects remains extremely limited. The current study is, therefore, one of the first to link the level of physical activity specifically with brain measures during youth. In addition, the study includes also measures of physical fitness, which have not been linked with brain morphology measures in previous studies with adolescents. The hypothesis for the current study is that physically more active and more fit individuals show differences in their brain morphology compared to less active and less fit subjects, presumably in the areas of hippocampus, frontal lobes and/or motor cortices.

6 METHODS

6.1 Subjects

The current study is part of Active, Fit and Smart (AFIS) – research project, which examines the effects of physical activity and fitness on the cognitive prerequisites of learning. From the total of 71 subjects taking part in the brain imaging procedure, two groups were formed based on the amount and intensity of daily physical activity (TOTMVPA, total amount of moderate-to-vigorous physical activity). The *'active'* group consisted of the 18 most active students (mean TOTMVPA = 76.3 ±14.7 minutes, f = 10, m = 8) and the *'non-active'* group of the 17 most inactive students (mean TOTMVPA = 31.6 ±6.9 minutes, f = 13, m = 4), who participated in both the physical activity measurement and the brain imagining procedure. The average of daily physical activity (TOTMVPA) for all the subjects with valid activity data was 52.4 ±21.7 minutes. The 35 subjects (18 active & 17 non-active) included in the study were Finnish elementary school students aged 12–15 years (14.1 ±0.7 years, 23 females & 12 males). Out of the 35 subjects, 32 subjects (16 active & 16 non-active) participated in the physical fitness tests, excluding three subjects who did not take part in the tests. The subjects for this study were recruited from the "Finnish schools on the Move" study (FiscMove). Since the subjects were under 18, their parents' consent was requested for participating in the study.

6.2 Study design

The physical activity and fitness measurements were conducted by LIKES research centre for physical activity and health. The magnetic resonance imaging was organized by the Department of Psychology of the University of Jyväskylä in collaboration with Aalto University. The brain regions of interest were chosen based on previous literature. Volumetric variables included in the study were the total cortex volume, total gray and white matter volumes and the volumes of the left and right hippocampus. Cortical thickness variables included in the study were the thickness of the left and right hemispheres, areas of the motor cortex (pre-, para- and postcentral cortices), parahippocampal cortices and superior frontal cortices (Figures 4 & 5).

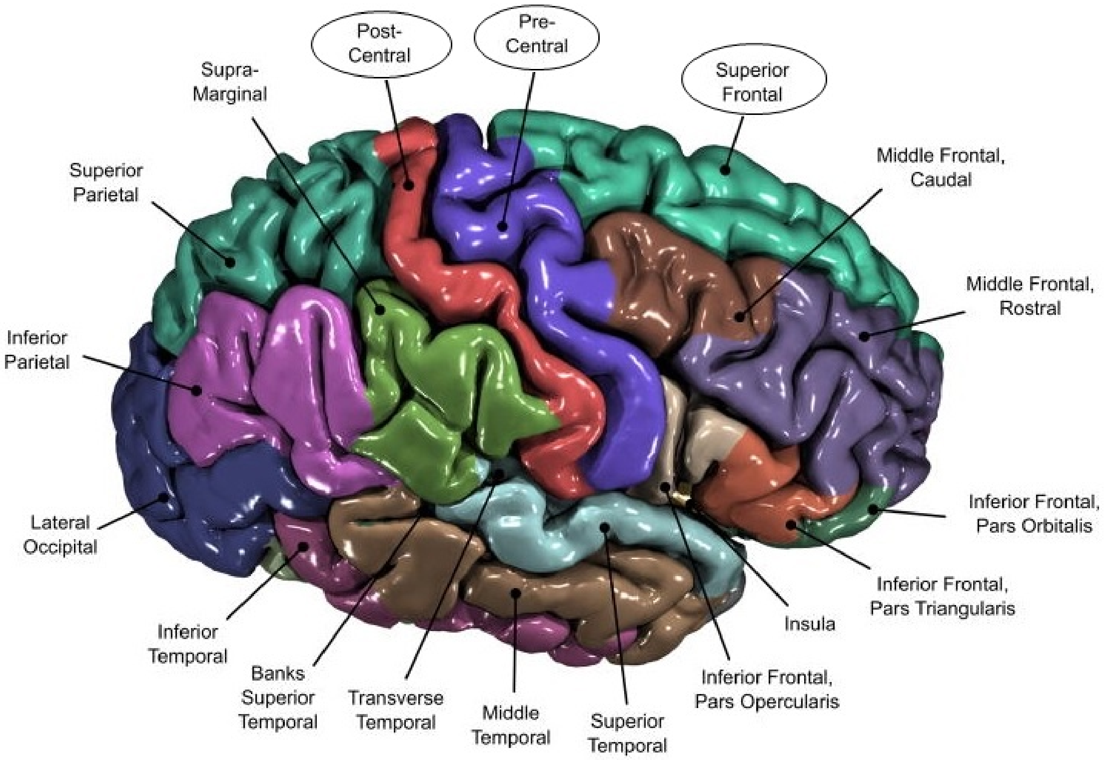

FIGURE 4. Atlas showing the pre- and postcentral cortices and superior frontal cortex. (Modified from Winkler et al. 2010).

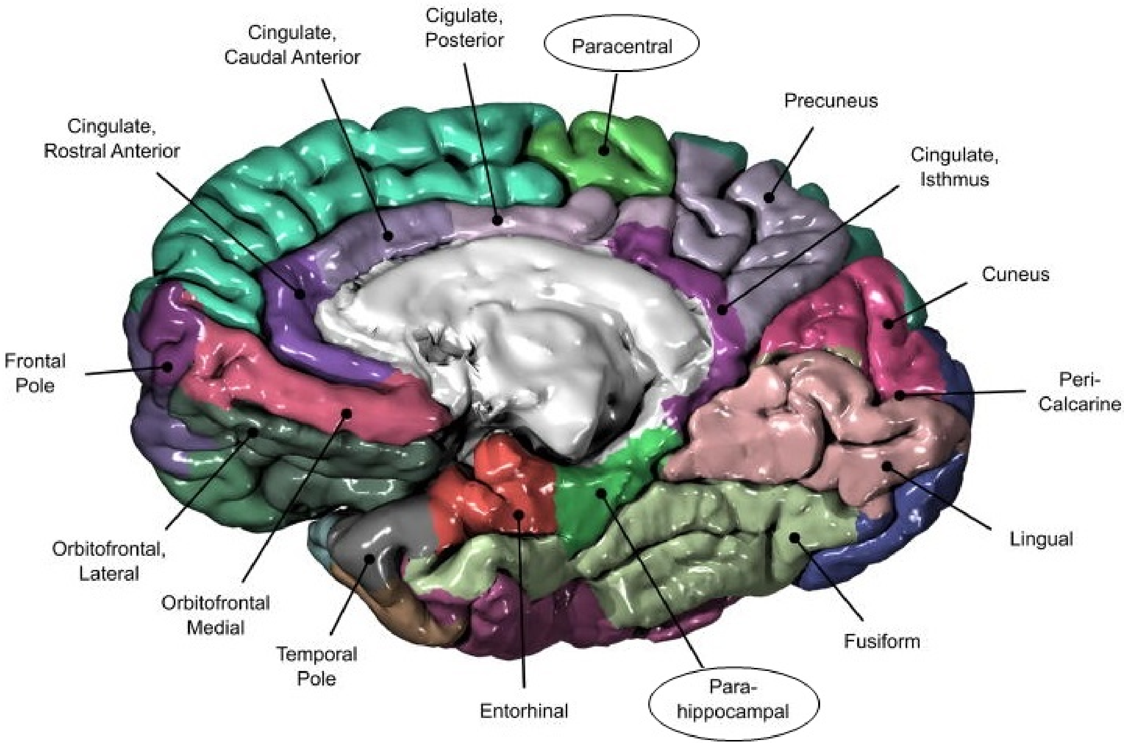

FIGURE 5. Atlas showing the paracentral cortex and parahippocampal cortex. (Modified from Winkler et al. 2010).

6.3 Background measures

Background measures included in the study were age, puberty status and body mass index (BMI) of the subjects. Prior to the brain imagining procedure, the height and weight of the subjects was measured. The BMI was calculated by dividing the body mass (kg) with the height (m) squared. The subjects had also filled out a form assessing their puberty status with the Tanner scale, which is a five-stage scale assessing the physical changes occurring with puberty (Marshall & Tanner 1969; Marshall & Tanner 1970.) An average from the two questions included in the Tanner scale was used to assess the puberty status.

Previous studies have suggested that age or BMI might confound the relationship between physical activity and brain morphology (Erickson et al. 2014), so the effect of those variables was controlled in the analysis. In addition, Goddings et al. (2014) found that pubertal development is related to the structural development of subcortical brain regions, and besides age, also puberty status (Tanner scale) is an important factor to be taken into account when studying adolescent brain development. Therefore, the effects of age, BMI and puberty status were controlled in the analysis of the current study.

6.4 Physical activity and fitness measurements

Physical activity measurements. The subjects' physical activity was measured with hip-worn accelerometers (ActiGraph GT3X+) for seven consecutive days. Subjects were advised to wear the accelerometer during the day and only take it off when sleeping or showering. For the analysis, all activity on the levels of moderate-to-vigorous physical activity was combined to form the activity variable (TOTMVPA, total amount of moderate-to-vigorous physical activity). The variable was formed by dividing the total time of moderate-to-vigorous activity by the number of valid measurement days, thus representing the average time of moderate-to-vigorous activity per day.

Accelerometers have proven to be accurate and relatively reliable tools to assess physical activity. By recording accelerations, they can measure both the duration and intensity of physical activity. Monitors can also be worn on the wrist or ankle, yet hip-worn accelerometers are assumed to provide the most accurate data of normal movement patterns. However, despite the advantages, accelerometers have also limitations, such as lack of sensitivity on sedentary and light-intensity physical activity. In addition, the monitor might not detect activities, where the hip stays relatively still, such as cycling or resistance training. (Ainsworth et al. 2015.)

Physical fitness measurements. The subjects' physical fitness was tested with the *Move!* test battery (Opetushallitus 2017), which is designed for fitness testing in schools. The test battery consists of six different tests, which measure different components of physical fitness, including aerobic capacity, muscular endurance, power, flexibility and motor skills. From the six tests included in the fitness test battery, five were included in the analysis of the current study, leaving out the mobility test. In addition, the push-up and the upper body lift tests were combined to form a single 'strength' variable for further analysis.

The six tests included in the *Move!* test battery:

1. *20 meter line run:* The 20 meter line run test measures endurance and the level of aerobic fitness. In the test, subjects run 20 meters every time they hear a signal from the test tape. The tempo of the signals increases after every minute. The test result is the time one is capable to run 20 meters repeatedly with increasing tempo. The 20 meter line run has proven to be a reliable and valid test to measure aerobic fitness (Güvenç et al. 2013; Paradisis et al. 2014). For example, Paradisis et al. (2014) found a correlation as high as 0.87 (Pearson's r) in their study between the number of successfully completed 20 meter runs and VO_2max measured with an incremental treadmill test at laboratory.

2. *5 continuous jumps:* The 5 continuous jumps test measures strength, power, speed and dynamic balance of the lower limbs. The test is performed by taking five consecutive strides, starting and finishing with joined feet. Test result is the distance covered by these strides.

3. *Upper body lift:* The upper body lift measures the muscular endurance of the abdominal muscles. The test result is the amount of repetitions one is capable to perform in a given tempo. Each repetition must start with head on the ground and heels must remain on the

floor. The movement has to be continuous and repetition is accepted, once fingertips touch the measuring tape on the other side (Figure 6). The maximal result for the test is 75 repetitions.

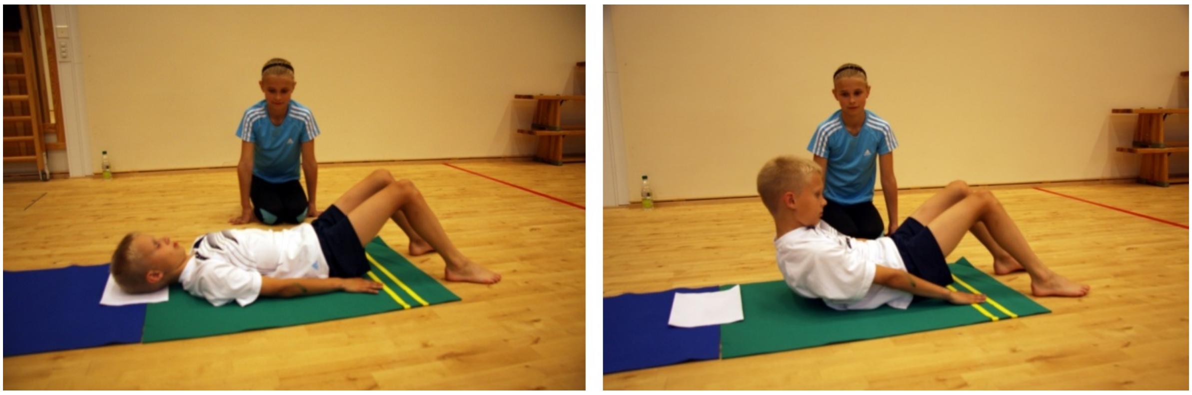

FIGURE 6. Demonstration of the upper body lift test (Opetushallitus 2017).

4. *Push-up:* The push-up test measures dynamic strength and endurance of the upper limbs and shoulders. The test is conducted by performing as many push-ups as possible in the time frame of 60 seconds. Hands should be placed at shoulder width and feet cannot be wider than hip width. The movement starts and ends with hands extended. At the bottom position, chest must be lowered to 10cm off the ground or alternatively touch a 10cm high target. Boys perform the movement with their palms and toes on the ground, girls with their palms and knees on the ground (Figure 7).

FIGURE 7. Demonstration of the push-up test (Opetushallitus 2017).

5. *Mobility of the body*: The mobility tests measure the body's normal range of motion with three different tests (squat, lower back extension and shoulder flexibility).

6. *Throw-catch combination:* The throw-catch combination test measures handling skills, perceptual motor skills and upper body strength. The test is performed by throwing a tennis ball with one hand towards a specified 1.5m x 1.5m target 20 times and catching the ball after one ground contact (Figure 8). The throwing distance is 10 meters for boys and 8 meters for girls. Subjects are allowed to try the task a couple times before the actual test. The result is the amount of successful throw-catch combinations out of the 20 trials.

FIGURE 8. Demonstration of the throw-catch combination test (Opetushallitus 2017).

6.5 Brain imaging

The data for the volumetric variables and cortical thickness of the brain was acquired with magnetic resonance imaging (MRI). The MR-imaging technique is based on the principles of nuclear magnetic resonance, the absorption and emission of energy in the radiofrequency range of electromagnetic spectrum. Gray matter, white matter and cerebrospinal fluid, the most common tissue types in brain, all produce different signal intensities, which makes it possible to identify them. (Baars & Gage 2010, 570–573.)

The magnetic resonance imaging was conducted at the Advanced Magnetic Imaging (AMI) -centre of Aalto University, Espoo, Finland. The MR-imaging experiments were performed on a MAGNETOM Skyra syngo MR D13C 3.0T whole-body scanner (Siemens Healthcare, Erlangen, Germany), using a 32-channel head-coil. The maximum field gradient amplitude was

45 mT/m, with slew rate 200 T/m/s. Parent's consent for the imaging procedure was required and all subjects went through a standardized security check routine before scanning. Any contraindications for participating in the study were screened. The scanning took approximately 30–45 minutes and the researcher in charge gave information about the imaging sequences before and during the scanning. Subjects were instructed to keep their head still during the scanning, and pads were used to minimize the head motion. In addition, subjects wore ear plugs to suppress the loud noises of the scanner. All possible disadvantages (i.e. the noisy environment) and the subject's rights were revised before the imaging procedure.

T1-weighted structural images (Figure 9) were acquired in sagittal plane using MPRAGE pulse sequence. Protocol included 176 sagittal slices and the scanning time was 6.02 minutes. The acquisition parameters were set as follows: TI = 1100 ms, TR = 2530 ms, TE = 3.3 ms, voxel size = 1.0 x 1.0 x 1.0 mm, flip angle = 7 °, slice thickness = 1mm, FOV = 256 x 256 x 176 mm 3, bandwidth = 200 Hz/Px, and using GRAPPA parallel imaging technique with acceleration factor PE:2 and with 32 reference lines.

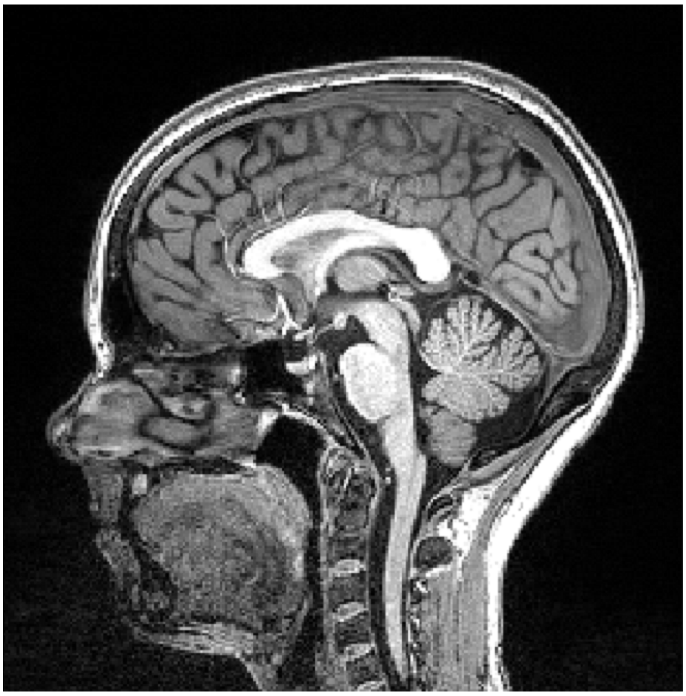

FIGURE 9. Example of a structural MRI scan of the brain (sagittal view).

6.6 MRI data analysis

Cortical reconstruction and volumetric segmentation of the MRI data was performed with the FreeSurfer 5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details of the procedures are described in prior publications (Dale et al. 1999; Dale & Sereno 1993; Fischl & Dale 2000; Fischl et al. 2001; Fischl et al. 2002; Fischl et al. 2004a; Fischl et al. 1999a; Fisch et al. 1999b; Fischl et al. 2004b; Han et al. 2006; Jovicich et al. 2006; Segonne et al. 2004; Reuter et al. 2010, Reuter et al. 2012). In short, the processing includes motion correction and averaging (Reuter et al. 2010) of multiple volumetric T1 weighted images, removal of non-brain tissue (Segonne et al. 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus) (Fischl et al. 2002; Fischl et al. 2004a), intensity normalization (Sled et al. 1998), tessellation of the boundary of the gray and white matter, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the borders of the gray and white matter as well as gray matter and cerebrospinal fluid (Dale et al. 1999; Dale & Sereno 1993; Fischl & Dale 2000).

After the data had been processed with FreeSurfer, each slice of the MRI images for each subject was checked and fixed manually, if needed. To ensure the skull had been properly cut off from the images, both the watershed-tool and manual erasing of voxels were used. The automated separation of gray and white matter was fixed with control points, if needed. Also the automatic parcellation of the cerebral cortex was checked. From the 37 subjects originally involved in this study, two had to be excluded from further analysis because of the poor quality of their MRI data.

6.7 Statistical analysis

Volumetric and cortical thickness values were imported from FreeSurfer to SPSS Statistics 24, which was used to perform all statistical calculations. An independent samples T-test was used to look at the group differences between the ‘active’ and ‘non-active’ groups regarding age, puberty status, height, weight, body mass index (BMI) and the fitness test results. A one-way analysis of covariance (ANCOVA) was conducted to examine the effect of physical activity on brain morphology, controlling the effect of age, puberty status and BMI.

Homogeneity of variances was checked with Levene's test. The push-up test results and the total volume of the gray matter volume displayed a positive result in the homogeneity test of variances, so the between-group differences among the push-up test and gray matter volume was examined with the non-parametric Mann-Whitney U -test. The relationship between physical fitness and the brain variables was examined with Pearson's correlation. For the analysis, all the fitness test results were made comparable between genders by diving each individual value with the mean result of the same gender. The volumetric variables were adjusted to the estimated total intracranial volume to remove the effect of the head size. Significance level of $p<0.05$ was used in all of the statistical calculations, and the effect sizes for Pearson's correlation were considered as small with $r > 0.1$, medium with $r > 0.3$ and large with $r > 0.5$.

7 RESULTS

7.1 Group statistics

The two groups, active and non-active, did not differ from each other in terms of age, puberty status, height, weight, or body mass index (BMI). Detailed information about the basic information of the groups is presented on table 1.

TABLE 1. Mean age, puberty status, height, weight and body mass index (BMI) of the groups.

	Active	**Non-active**
N	18 (10 females)	17 (13 females)
Age (years)	14.0 (±0.8)	14.3 (±0.6)
Puberty status	3.2 (±0.9)	3.5 (±0.6)
Height (cm)	161.7 (±8.7)	164.9 (±8.6)
Body mass (kg)	53.4 (±10.1)	54.5 (±8.6)
BMI	20.1 (±2.4)	20.5 (±2.1)

The *'active'* group outperformed the *'non-active'* in three of the five fitness tests (Table 2). A significant difference between the groups was noticed in the 20m line run test ($t(30) = 3.997$, $p<0.001$) (Figure 10), upper body lift test ($t(30) = 2.148$, $p<0.05$) and the push-up test ($p<0.01$, using a Mann-Whitney U -test) (Figure 12). Also the difference between 5 continuous jumps test was close to significant level ($t(30)=2.012$, $p=0.053$) (Figure 11). The throw-catch combination test did not show a significant difference between the groups ($t(30) = 1.488$, $p=0.15$) (Figure 13). Adjusted values (individual results divided by the gender mean) for the active and non-active were 1.21 and 0.80 for the 20m line run test, 1.04 and 0.96 for the 5 continuous jumps test, 1.26 and 0.79 for the push-up test, 1.22 and 0.83 for the upper body lift test and 1.11 and 0.98 for the throw-catch combination test, respectively.

TABLE 2. Mean results and standard deviations of the groups from the fitness tests.

	Active	**Non-active**
20m line run (minutes)	6.9 (±1.9)***	4.2 (±1.5)***
5 continuous jumps (meters)	9.6 (±0.9)	8.7 (±1.2)
Push-up (repetitions/min)	28.8 (±14.3)**	19.8 (±7.8)**
Upper body lift (repetitions)	49.2 (±24.6)*	31.5 (±17.9)*
Throw-catch combination (repetitions/20)	12.9 (±4.1)	11 (±5.3)

***p<0.001, **p<0.01, *p<0.05 significant difference between the groups

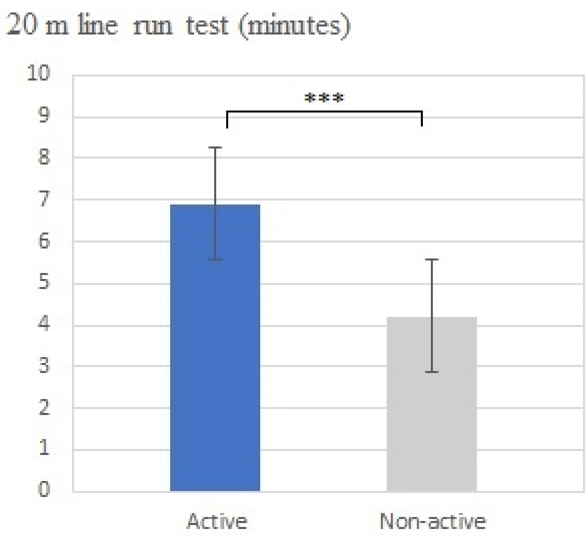

FIGURE 10. Mean results (with standard deviations, ±SD) for the active and non-active groups in the 20 meter line run test, ***p<0.001 significant difference between the groups.

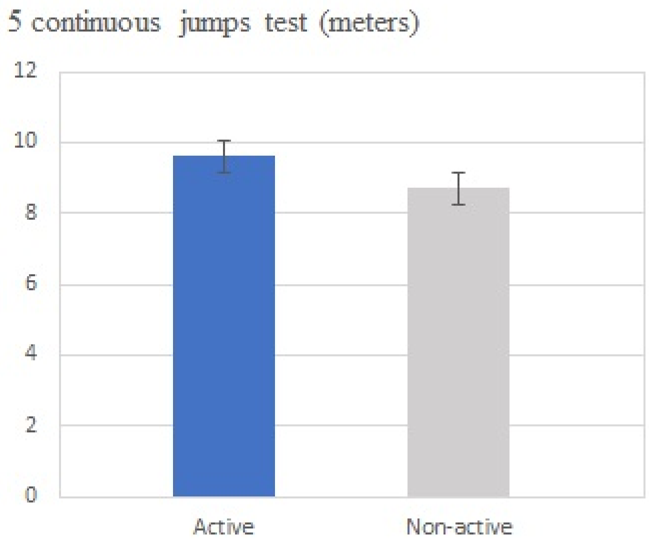

FIGURE 11. Mean results (±SD) for the active and non-active groups in the 5 continuous jumps test, no significant difference between the groups (p=0.053).

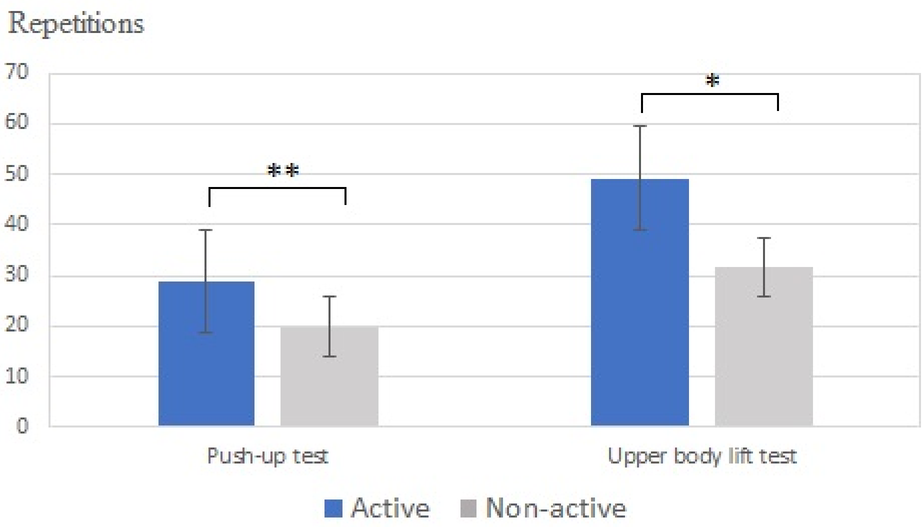

FIGURE 12. Mean results (±SD) for the active and non-active groups in the push-up test and upper body lift test, **p<0.01 and *p<0.05 significant differences between the groups.

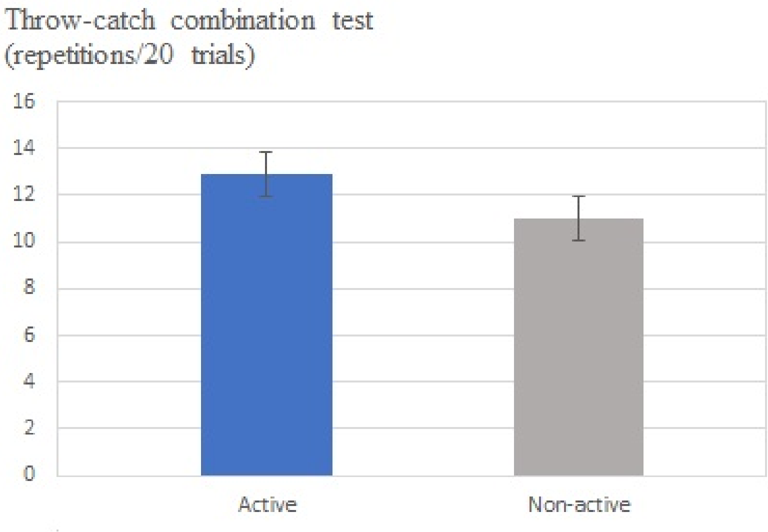

FIGURE 13. Mean results (±SD) for the active and non-active groups in the throw-catch combination test, no significant difference between the groups (p=0.15).

7.2 Physical activity and brain morphology

There were no significant relationships observed between the level of physical activity and the volumetric variables inspected. No between-group differences were found in the total volume of the cortex, gray matter volume, white matter volume, or the hippocampal volumes (right and left). Detailed information is presented on table 3 below.

TABLE 3. Results for the volumetric variables, representing the differences between the active and non-active group (no significant differences).

Variable	Sig.	df	F	Partial Eta Squared
CortexVol	0.778	1, 30	0.081	0.003
GM[1]	0.443	-	-	-
WM	0.344	1, 30	0.923	0.030
Hippocampus (right)	0.595	1, 30	0.289	0.010
Hippocampus (left)	0.464	1, 30	0.550	0.018

Sig. = significance/p-value, df = degrees of freedom, F = F-test value, Partial Eta Squared (η^2) = measure of effect size, CortexVol = total volume of the cortex, GM= total gray matter volume, WM = total white matter volume

[1]*differences between GM was examined with a non-parametric Mann-Whitney U -test*

From the cortical thickness variables, the level of physical activity had a significant relationship with the thickness of the parahippocampal cortex of the right hemisphere. This relationship was positive; physically more active subjects expressed a thicker right parahippocampal cortex when compared to less active subjects. A relationship between physical activity and the left paracentral cortex was also discovered, even though the significance of this connection was lost after controlling the effect of age. The relationship of physical activity and the left paracentral thickness was positive, whereas age and the thickness of the left paracentral cortex displayed a negative relationship. No other significant relationships were observed, including the total thickness of the right and left hemispheres, precentral cortices, right paracentral cortex, postcentral cortices, superior frontal cortices and the parahippocampal cortex of the left hemisphere. Detailed information is presented on table 4 and figure 14 below.

TABLE 4. Results of the analysis of covariance (ANCOVA) for the thickness variables, representing the differences between the active and non-active group.

Variable	**Sig.**	**df**	**F**	**Partial Eta Squared**
Right hemisphere	0.450	1, 30	0.586	0.019
Left hermisphere	0.461	1, 30	0.557	0.018
Precenral (right)	0.665	1, 30	0.192	0.006
Precentral (left)	0.295	1, 30	1.136	0.036
Paracentral (right)	0.506	1, 30	0.453	0.015
Paracentral (left)	0.124	1, 30	2.500	0.077
Postcentral (right)	0.223	1, 30	1.549	0.049
Postcentral (left)	0.231	1, 30	1.494	0.047
Parahippocampus (right)	**0.044***	**1, 30**	**4.440**	**0.129**
Parahippocampus (left)	0.195	1, 30	1.757	0.055
Superior frontal (right)	0.875	1, 30	0.025	0.001
Superior frontal (left)	0.993	1, 30	0.000	0.000

*significance at the level of p<0.05

Sig. = significance/p-value, df = degrees of freedom, F = F-test value, Partial Eta Squared (η^2) = measure of effect size

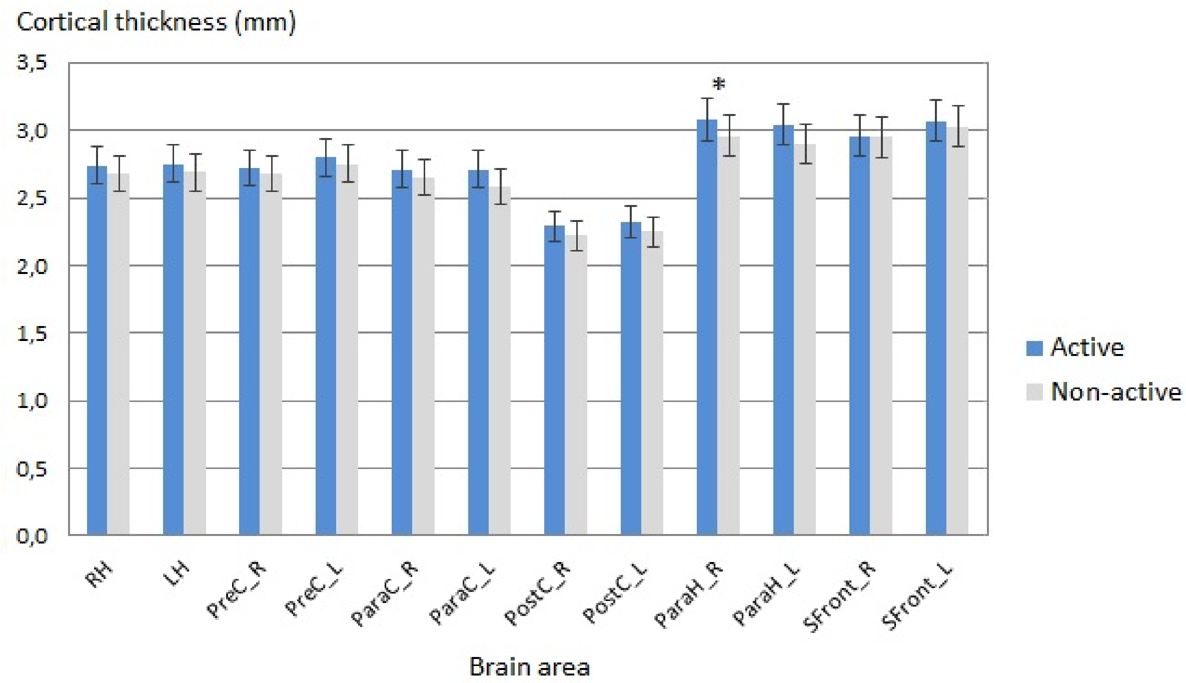

FIGURE 14. Mean cortical thickness in examined brain areas of the groups.

RH = Right hemisphere, LH = Left hemisphere, PreC_R = Right precentral cortex, PreC_L = Left precentral cortex, ParaC_R = Right paracentral cortex, ParaC_L = Left paracentral cortex, PostC_R = Right postcentral cortex, PostC_L = Left postcentral cortex, ParaH_R = Right parahippocampal cortex, ParaH_L = Left parahippocampal cortex, SFront_R = Right superior frontal cortex, SFront_L = Left superior frontal cortex.
*significance at the level of $p<0.05$

7.3 Physical fitness and brain morphology

From the volumetric and cortical thickness variables examined, no brain area showed a significant correlation with the physical fitness tests; the 20 meter line run test, the 5 continuous jumps, the strength tests (push-up & upper body lift) or the throw-catch combination test. However, despite not reaching the significance level, various fitness tests and brain areas showed correlation of small effect size ($r > 0.1$) in relation to each other, and some variables showed also correlation close to the medium effect size ($r > 0.25$). A positive, however statistically non-significant, correlation close to the medium effect size was found between the throw-catch test and the hippocampal volumes (right: r=.296, p=1.00, left: r =.261, p=1.49), strength and the thickness of the left paracentral cortex (r=.266, p=0.141) and between strength and the thickness of the left superior frontal cortex (r=.271, p=1.34). A negative, yet statistically non-significant, correlation close to the medium effect size was found between the 20m line run test and the total volume of the cortex (r=-.292, p= 0.105), 20m line run test and the total gray matter volume (r=-.253, p=0.163), 5 continuous jumps test and the thickness of the right precentral cortex (r=-.279, p=0.123), 5 continuous jumps test and the thicknesses of the postcentral cortices (right: r=-.289, p=0.108, left: r=-.260, p=0.151) and between the throw-catch test and the thickness of the right postcentral cortex (r=-.299, p=0.096). Correlations (Pearson's r) are presented on tables 5 and 6 below.

TABLE 5. Correlations between physical fitness tests and volumetric variables of the brain.

	20m run	**5-jump**	**Strength**	**Throw-catch**
CortexVol	-.292	-.233	-.046	-.128
GM	-.253	-.147	.003	-.056
WM	-.143	-.118	-.116	-.017
HC (right)	.002	.176	.120	.296
HC (left)	.097	.133	.077	.261

CortexVol = total volume of the cortex, GM = total gray matter volume, WM = total white matter volume, HC = volume of the hippocampus

TABLE 6. Correlations between physical fitness tests and cortical thickness variables.

	20m run	**5-jump**	**Strength**	**Throw-catch**
Right hemisphere	-.092	-.237	.031	.111
Left hemisphere	-.040	-.125	.122	.175
Precentral (right)	-.080	-.279	-.078	-.006
Precentral (left)	-.128	-.182	.019	.041
Paracentral (right)	-.027	-.044	.234	-.090
Paracentral (left)	.166	.043	.266	-.164
Postcentral (right)	-.164	-.289	-.055	-.299
Postcentral (left)	-.126	-.260	-.029	-.164
Parahippocampus (right)	.101	.163	.237	.235
Parahippocampus (left)	.079	-.089	.222	.136
Superior frontal (right)	-.235	-.229	-.037	.045
Superior frontal (left)	-.053	-.007	.271	.175

8 DISCUSSION

The aim of this study was to examine, whether physical activity or physical fitness has a relationship with brain morphology in youth. Physical activity expressed a positive relationship with the thickness of the right parahippocampal cortex, after controlling the effect of age, puberty status and body mass index. Physically more active individuals had thicker right parahippocampal cortex, when compared to less active individuals. A positive relationship was also found between physical activity and the thickness of the left paracentral cortex, even though this finding was not significant after controlling the effect of age. Whereas physically more active individuals expressed a thicker left paracentral cortex compared to less active individuals, older subjects had thinner left paracentral cortex compared to younger subjects. These results add understanding to the associations between physically active lifestyle and brain morphology in youth.

8.1 Physical activity and brain morphology: the hippocampal area

A relationship between physical activity and the thickness of the right parahippocampal cortex (PHC) of the right hemisphere was found. Physically more active individuals seemed to have thicker right PHC compared to less active subjects. The hippocampal area and medial temporal lobe are essential for human cognition and memory (Shohamy et al. 2013). Adjacent to hippocampus, the parahippocampal cortex has been shown to have an important role especially in visuospatial processing and episodic memory. The parahippocampal area seems to respond strongly to visual scenes, and it is thought to be involved in functions like spatial representation and navigation. These functions seem to be dependent on the posterior part of the PHC, hence the name ‘parahippocampal place area’ (PPA). In addition to the strong associations to scene stimuli, the PHC is involved in episodic memory, specifically in contextual associative processing. The PHC is, therefore, also important in binding different objects, places and relations into a single representation in memory. (Aminoff et al. 2013; Baumann & Mattingley 2016.) Since physical activity seems to have an effect on the anatomy of the parahippocampal cortex, it might also have an effect on PHC related cognitive functions, such as visuospatial and contextual processing.

Differences between brain volumes can be explained by various factors, including neurogenesis, synaptogenesis, myelination, angiogenesis or changes in axon or glia cell number and size (Zatorre et al. 2012). In the current study, the specific underlying cause for the greater cortical thickness in the active group remains unknown, however a recent research by Bracht et al. (2016) showed that physical activity in young healthy adults was linked to greater myelination of the right parahippocampal cortex. In other words, it was discovered that physical activity was connected to the white matter microstructure of the right PHC (Bracht et al. 2016). Myelination has been noticed to increase linearly up to age 20 (Houston et al. 2014), yet this evidence supports the idea physical activity might increase the process even further. Although the current study cannot conclude the cause for the larger volume of the right parahippocampal cortex of the physically active individuals, higher myelination might be a plausible explanation.

Apart from the right parahippocampal cortex, no other brain area expressed a significant relationship with the level of physical activity, after controlling the effects of age, puberty status and BMI. Especially hippocampus has been linked to physical activity induced changes in several previous studies, although the findings have mainly been established with elderly (Hillman et al. 2008). However, a study by Rottensteiner et al. (2015) compared active and non-active young adults and found no differences in hippocampal volumes between the groups. It was suspected that all the subjects' hippocampal-dependent memory functions were already at so high level that exercise did not have an effect on hippocampus or the effect was so small, it could not be detected (Rottensteiner et al. 2015). A similar explanation might apply to the findings of the current study as well. The lack of discovered connections between physical activity and hippocampal volume might also be explained by the large-scale MRI data processing of the current study. Previous studies have shown the dentate gyrus of the hippocampus to be especially sensitive to physical activity induced changes and to display neurogenesis (Yau et al. 2014), yet the current study did not examine hippocampal subfields, which would have given more detailed information about the brain morphology.

8.2 Physical activity and brain morphology: motor cortices and frontal brain regions

A relationship between physical activity and the left paracentral cortex was found, yet the result was not significant after controlling the effect of age. Whereas physical activity and the thickness of the left paracentral cortex had a positive relationship, age displayed a negative relationship with the thickness of the left paracentral cortex. In other words, physically more active individuals had thicker left paracentral cortex compared to less active subjects, and older subjects had thinner left paracentral cortex compared to younger subjects. Cortical thinning has been noticed to take place in almost all brain areas due aging, with the greatest changes occurring in adolescence (Tamnes et al. 2010). The decrease in cortical thickness can, therefore, be considered as a normal phase in brain development, even though the process might be influenced to some extent by external factors, such as physical activity. In addition, physical activity has been noticed to decrease during adolescence (Kokko et al. 2016), contributing also to the effect of age on brain morphology.

The primary somatomotor cortex is located in the central parts of the paracentral cortex, and the paracentral area has somatosensory representations of the foot and leg (Spasojević et al. 2013). Since the motor cortex is crucial for the execution of voluntary movement (Shenoy et al. 2013), it is quite logical for physical activity to express a relationship with the area. Although higher level of physical activity seemed to predict thicker left paracentral cortex, the connection was overpowered by the effect of age. Since the adolescent brain seems to express cortical thinning to a great extent (Tamnes et al. 2010), it would be interesting to assess the connection between physical activity and the thickness of the paracentral cortex in adults, whose brains have reached a more stable developmental phase and might, therefore, express the changes induced by external influences more clearly. In addition, further research should assess the relationship between physical activity and cortical thickness in a longitudinal study. For example, Schnack et al. (2015) established that intelligence was in fact connected to the change in cortical thickness, rather than with thickness itself. They concluded that faster thinning of the left cortex was connected to higher intelligence in children, whereas after the age of 21, the reverse was true. These findings suggest that thicker cortex might be either positive or negative, depending on the developmental phase of the brain. In the current study, physically more active individuals seemed to express a trend of thicker cortex among all the examined brain areas compared to less active ones, although only one area reached a significant difference. It seems, that the thickness of the cortex is a highly equivocal variable, especially in youth, when developmental changes are occurring simultaneously with possible changes caused by external factors. Therefore, further research would be necessary to examine the behavioral and cognitive consequences the cortical thickness reflects.

In contrast with previous findings, physical activity did not express a relationship with the frontal brain regions. Physical activity and exercise have previously been linked with increased gray matter volume and changes in activation of the frontal regions (Hötting & Röder 2013). However, in the current study, the focus was only on the structure of the brain. Therefore, nothing can be said about the activation patterns of frontal regions and the possible differences between the active and non-active subjects. In addition, previous studies have shown physical activity to benefit especially executive functions dependent from the frontal regions (Guiney & Machado 2013). However, differences in cognitive functions are not necessarily expressed in the structural level, which might also explain the lack of observed connections between physical activity and the frontal regions in the current study. In addition, the only frontal area examined in the current study was the thickness of the superior frontal cortex. For more precise results, also the MRI data processing would have required more precision.

8.3 Aerobic fitness and brain morphology

The active group outperformed the non-active group in three of the five fitness tests, with the biggest difference established in the 20m line run test. This implies that physically active lifestyle is strongly connected to higher level of aerobic fitness. However, previous literature has suggested only moderate correlations between aerobic fitness and regular physical activity (Schutte et al. 2016). In fact, Schutte et al. (2016) established in their study, that genetic factors explain 55% of total variance in relative VO_2max (ml/min/kg) in adolescent population. Therefore, in addition to physically active lifestyle, also genetics can have a major effect on the level of aerobic fitness. Although previous studies have presented contrary results, the present study did not find significant relationships between aerobic fitness and brain morphology, but there was a relationship between physical activity and cortical thickness in specific regions.

This indicates that physical activity does not necessarily have to improve physical fitness to influence brain morphology in youth.

In line with the previous finding by Herting and Nagel (2013), aerobic fitness was not related to either total gray or total white matter volume. This reinforces the suggestion that aerobic fitness has an influence on specific brain areas, which are not expressed in larger scales. However, in contrast to previous studies, aerobic fitness did not show connections to any specific brain areas either, including the hippocampal area and frontal brain regions. Aerobic exercise and improved cardiovascular fitness have been noticed to increase the volume of the hippocampus in both adolescents and older adults (Erickson et al. 2011; Herting & Nagel 2013), but this could not be represented in the current study. This reinforces the assumption, that physical activity does not necessarily have to increase aerobic fitness to cause changes in brain anatomy. In their review about the benefits of physical exercise on cognition, Hötting and Röder (2013) conclude, that cardiovascular fitness explains only a fraction of the variation in the cognitive variables, which might reflect the changes in the brain morphology as well.

Although previous studies have suggested a relationship with aerobic fitness and the frontal brain regions (Chaddock et al. 2012; Colcombe et al. 2006), this could not be represented in the current study. Possible reasons for this might include the age of the subjects or the undetailed processing of the MRI data. The connections between aerobic fitness and frontal brain regions have previously been discovered with either children (Chaddock et al. 2012) or older participants (Colcombe et al. 2006), suggesting that adolescents and young adults might not express similar benefits due to higher fitness as in childhood or with aging. The adolescent brain might also express such great anatomical and functional changes, that the possible effects of external influences, such as physical activity or fitness, cannot be observed. In addition, the current study looked at only one area of the frontal brain regions without more precise examination. Finally, the current study cannot conclude, whether the frontal lobe mediated cognitive functions would have been better in the more active group, since only the anatomical between-group differences were examined. Several previous studies have found a better performance in executive tasks in highly active or more fit subjects (Guiney & Machado 2013), yet here the focus was merely in the morphology of the brain.

Williams et al. (2016) established that higher peak VO_2, an estimate of aerobic fitness, was connected to thinner cortex in young adults. In addition, a study by Chaddock-Heyman et al. (2015) found decreased gray matter thickness in superior frontal cortex in higher-fit children. Whereas larger brain volumes have often been connected with higher intelligence, it has been suggested that the relationship might be reversed in youth. In their extensive study, Schnack et al. (2015) found that faster cortical thinning of the left cortex was connected to higher intelligence in adolescents. The correlation between aerobic fitness and the total volume of the cortex, as well as the correlation between aerobic fitness and total gray matter volume were slightly negative also in the current study, even though these findings did not reach significance. It is, however, possible that individual differences in aerobic fitness can affect some brain areas showing considerable changes in cortical volume and thickness during development, leading to positive changes in cognitive processing and intelligence (Chaddock-Heyman et al. 2015; Schnack et al. 2015).

8.4 Strength, motor skills and brain morphology

The active group outperformed the non-active also in the strength tests, linking physical activity to better muscular endurance. Also the 5 continuous jumps test, measuring power and strength of the lower limbs, showed a slight difference between the groups, although this result did not reach significance. No between-group difference was detected from the throw-catch combination test. This implies that perceptual motor skills and handling skills are independent from the level of physical activity.

Although no significant correlations were found between the physical fitness tests and brain variables, there were several variables showing a connection close to moderate effect size. The throw-catch combination test, measuring handling and perceptual motor skills, displayed a slight positive, however non-significant, correlation with the volumes of both right and left hippocampus. Animal studies have suggested, that physical skill training can increase the number of newly-born neurons in the hippocampus in both adolescents and adults (Curlick et al. 2013; DiFeo & Shors 2017). Although results from animal studies should always be implied to humans with extreme caution, they might however offer plausible explanations that would otherwise be impossible to confirm in humans. Even though the connection between motor skills and hippocampal volume established here was only moderate and did not reach significance, it can still be regarded as a possibility that better performance in a motor skill task is connected to either increased neurogenesis or survival of the newly-born neurons, therefore leading to a larger hippocampal volume.

A modest non-significant positive correlation was found between strength and the thicknesses of the left paracentral cortex. The thickness of the left paracentral cortex displayed a connection also with the level of physical activity, making it an interesting brain area for further research considering the effects of both physical activity and fitness. Previous studies have found a link between grip strength and motor cortex volume, as well as with white matter volume (Kilgour et al. 2014; Koppelmans et al. 2015). However, the strength tests in the current study did not measure maximal strength, and further research would be necessary to examine, whether muscular endurance could have similar influences on brain morphology.

Slight negative, yet non-significant, connections were found between the fitness test variables and the motor cortex regions, especially the right precentral cortex and the postcentral cortices. Contrary to the results from previous studies, also the throw-catch combination test result showed a slight negative non-significant connection with the thickness of the right postcentral cortex, although previous studies have discovered rather larger volumes in the motor cortex areas (Gryga et al. 2012; Sampaio-Bapista et al. 2014). These findings might, however, reflect merely the normally occurring cortical thinning in the adolescent brains (Tamnes et al. 2010).

8.5 Strengths and limitations of the study

Previous studies examining the relationship of physical activity and fitness to brain morphology have mostly been animal studies (Yau et al. 2014), whereas this study offered additional information on the topic using human subjects. In addition, the study was conducted with less examined population, the youth. An objective measurement of physical activity was used instead of less reliable self-evaluation questionnaires and also the brain imaging was performed on a high-technology equipment, providing high-quality MRI data. Both of these add reliability to the acquired results of the present study.

Limitations of the current study include a modest number of subjects, the cross-sectional nature of the study and possible inaccuracies in the physical activity and fitness measurements. With a larger study sample, the results could be generalized with higher reliability. However, including both males and females in the age range of 12 to 15 years, the results can be reliably generalized to other healthy Finnish adolescents of that age group. Being a cross-sectional study, the cause or consequence cannot be implied from the results. However, previous studies have already suggested that brain morphology could be altered with physical activity and exercise (Colcombe et al. 2006; Erickson et al. 2011), so the level of activity can be assumed to be the cause in the findings of this study as well. Possible inaccuracies in the physical activity and fitness measurements should also be taken into account. For example, measured physical activity from the sample week is merely assumed to represent a normal pattern of behavior, and there are also some technical limitations concerning the hip-worn accelerometers. Activities, where the hip stays in one vertical plane (i.e. cycling) or where the hip stays relatively still despite of heavy loading on muscles (i.e. resistance training), are often underestimated in how vigorous the activity is (Ainsworth et al. 2015; Hansen et al. 2014). In addition, the physical fitness measurements used in the current study were field tests instead of highly standardized, objective laboratory tests. Possible inaccuracies concerning the fitness tests results might be due to varying movement standards, lack of motivation or simply errors in counting the repetitions or measuring the results. The differences in the test protocols among girls and boys is also an issue to be considered, even though the results were adjusted to eliminate the gender differences. Finally, although the effect of age, BMI and puberty status was controlled, there might have been other variables to interfere with the relationship of physical activity and brain anatomy that were left out of the analysis.

8.6 Conclusions

The current study established a positive relationship between the level of physical activity and the thickness of the right parahippocampal cortex. Physically more active individuals had thicker right parahippocampal cortex when compared to non-active individuals. A relationship between physical activity and the thickness of the left paracentral cortex, a part of the motor cortex, was also found, although this finding lost significance after controlling the effect of age. Whereas physical activity and the thickness of the left paracentral cortex had a positive relationship, age displayed a negative relationship with the thickness of that area. However, in contrast to our hypothesis, no significant connections were found between the level of physical fitness and brain morphology.

These findings imply that the area of the right parahippocampal cortex might be especially susceptible to physical activity induced changes in youth, and that physical activity does not necessarily have to improve physical fitness to cause changes in brain morphology. Further research could focus on whether physical activity can enhance also parahippocampal mediated cognitive functions, such as visuospatial and contextual processing. In addition, further research should focus on longitudinal studies on the topic, since the brain morphology changes might reflect different causes depending on the developmental phase of the brain.

The current study was one of the first to link physical activity and fitness specifically to brain variables in adolescents, and thus offered additional information about the relationship of physically active lifestyle and brain morphology in youth. The findings imply that physical activity can influence brain morphology in adolescents and, therefore, promoting physical activity in youth is important not only for physical health, but for brain health as well.

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