Physical activity and neurodevelopment in children

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“That which we call thinking is the evolutionary internalization of movement”

Llinás R. 2001. I of the vortex: from neurons to self. Cambridge, MA: MIT Press.

Summary

Introduction

The benefits of physical activity on cognitive function are well known; contrarily, the associations with cognitive development and brain maturation require further study. Cognitive development is a relevant outcome in epidemiological research; nevertheless the literature about its determinants and growth trajectories is scarce. This thesis aims to study the determinants and trajectories of cognitive development, as well as the role of physical activity on cognitive and brain development in children aged 4 to 14 years old.

Methods

We used data from two Spanish cohorts (INMA and BREATHE) and one Dutch cohort (Generation R). Teachers reported Attention Deficit and Hyperactivity Disorder (ADHD) symptoms of the participants through questionnaires. Cognitive development, specifically of attention and working memory, was tested by using computerized-based tasks. Growth trajectories were constructed based on four repeated cognitive measurements during a 1-year period in 7- to 11-year-old children. Physical activity was reported by parents through questionnaires. Magnetic Resonance Imaging data was collected in Generation R when children were 6-to-10 years old.

Results

(1) Preschool ADHD symptoms were associated with worse attention function at puberty. (2) Working memory task performance showed developmental trajectories. The cognitive growth was more pronounced at younger ages and in girls, as well as delayed in children with ADHD symptoms. (3) Physical activity levels were positively associated with baseline cognitive performance, although no consistent associations were found with cognitive growth trajectories. (4) Sports participation was related to cortical maturation. (5) Early physical activity was associated with higher working memory performance at school age and adolescence.

Conclusions

Age, gender and ADHD symptoms were identified as important determinants of cognitive development. The use of cognitive growth trajectories in epidemiological research was supported. Physical activity during childhood was positively associated with brain maturation and promoted cognitive development.

Resum

Introducció

Els beneficis de l'activitat física en la funció cognitiva són ben coneguts, per contra, les associacions amb el desenvolupament cognitiu i la maduració cerebral requereixen ser més ampliament estudiades. El desenvolupament cognitiu és una variable important en recerca epidemiològica, tot i això, els estudis sobre els seus determinants i les trajectòries de creixement són escassos. Aquesta tesi pretén estudiar els determinants i les trajectòries del desenvolupament cognitiu, així com el paper de l'activitat física en el desenvolupament cognitiu i cerebral en nens entre 4 i 14 anys.

Mètodes

Vam utilitzar dades de dues cohorts espanyoles (INMA i BREATHE) i una cohort holandesa (Generation R). Els mestres van avaluar els símptomes de Trastorn per Dèficit d'Atenció i Hiperactivitat (TDAH) dels participants a través de qüestionaris. El desenvolupament cognitiu, en concret d'atenció i memòria de treball, es va avaluar amb tasques computeritzades. Les trajectòries de creixement es van generar a partir de quatre mesures cognitives repetides durant un període d'un any en nens de 7 a 11 anys. L'activitat física va ser informada pels pares a través de qüestionaris. Es van recollir dades de ressonància magnètica a Generation R quan els nens tenien de 6 a 10 anys.

Resultats

(1) Els símptomes de TDAH en preescolars es van associar amb una pitjor funció atencional a la pubertat. (2) El rendiment a la tasca de memòria de treball va mostrar trajectòries de desenvolupament. El creixement cognitiu va ser més pronunciat en els nens més joves i en les nenes, així com tardà en nens amb símptomes de TDAH. (3) Els nivells d'activitat física estaven associats positivament amb el rendiment cognitiu basal, però no es van trobar associacions consistents amb les trajectòries de creixement cognitiu. (4) La participació en esports estava relacionada amb la maduració

cortical. (5) L’activitat física primerenca estava associada amb una millor memòria de treball en l’edat escolar i l’adolescència.

Conclusions

L’edat, el sexe i els símptomes de TDAH es van identificar com a determinants importants del desenvolupament cognitiu. L’ús de les trajectòries de creixement cognitiu en recerca epidemiològica va ser recolzat. L’activitat física durant la infantesa es va associar positivament amb la maduració del cervell i va promoure el desenvolupament cognitiu.

Preface

This thesis represents a compilation of the scientific publications led by the PhD candidate, supervised by Prof. Jordi Sunyer Deu, according to the procedures of the Biomedicine PhD program of the Department of Experimental and Health Sciences of Pompeu Fabra University. The book includes an abstract, a general introduction with a review of the relevant literature, the thesis' rationale and objectives, the methods, the research results (five original papers, three of them published), a global discussion and final conclusions. Most of the work, that included data collection, management and analysis, was performed by the PhD candidate at the Center for Research in Environmental Epidemiology (CREAL) in Barcelona (Spain), which is part of the Barcelona Institute for Gobal Health (ISGlobal) since July 2016. One of the publications was performed at Erasmus Medical Center in Rotterdam (The Netherlands).

The thesis aims to improve neurodevelopmental characterization as a process for epidemiological research and to study the effects of physical activity on cognitive and brain maturation in children. The first two articles included in this thesis address the first objective and the other three are related to the second objective. The publications are based on Spanish (INMA and BREATHE) and Dutch (Generation R) child populations. Papers I and V were based on INMA cohort, Papers II and III were performed using BREATHE sample and MRI data from the Generation R cohort was used for Paper IV. We used computer-based neuropsychological instruments. The information of physical activity was reported by parents through questionnaires in the three samples.

Contents

1. INTRODUCTION

The foremost international sports event, the Olympic Games, was originated around 776 B.C. by the Greeks. The Games were held every 4 years for nearly 12 centuries in honour of the god Zeus. In 393 A.D. the Roman Emperor Theodosius ordered that all such "pagan cults" be banned. Baron Pierre de Coubertin of France re-launched the Games in 1896 until today. The importance of physical activity and sports for maintaining health has been expressed since Ancient Greece. One of the first noted physicians, Hippocrates, said, "*If we could give every individual the right amount of nourishment and exercise, we would have found the safest way to health*." However, in 1975 Milton Terris, an American epidemiologist, observed, "*physical fitness and physical education have no respected place in the American public health movement*" (1). Ten years later the U. S. Public Health Service declared "Physical Fitness and Exercise" as 1 of the 15 areas of greatest importance for improving the health of the population (2).

1.1 First section: Physical activity in childhood

a) Definitions

The American College of Sports Medicine (ACSM) defines "physical activity" as any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting energy expenditure. "Exercise" is defined as a type of physical activity consisting of planned, structured, and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness. "Physical fitness" is a set of attributes or characteristics individuals have or achieve that relates to their ability to perform physical activity (3). "Sport" is a subcomponent of exercise, which includes rules, structure, gross motor movements based on strategy and also can have a competitive element (4).

b) Sources of physical activity in children

The most common sources of physical activity in children are school physical education, outdoor play, active transport, and sports participation.

Physical education (PE) does not only provide opportunities for physical activity in children, PE has traditionally pursued objectives in the cognitive, social, and emotional domains (5). Physical activity in schools is associated with academic achievement including lower drop-out rates, better classroom behaviour, higher self-esteem and engagement in school, and on-task behaviour (6,7). Schools are ideal settings to ensure students from all risk groups the recommended amount of physical activity (5,8–12). Although most schools require PE as part of their curriculum, PE classes may occur infrequently and children are often relatively inactive in these classes (5). Increasing the frequency and duration of PE is not always feasible given competing curricular demands.

Children’s unstructured outdoor free-play makes an important contribution to their overall physical activity levels (13–15). McKenzie et al. (16) reported that preschoolers spent 41.1% of their recess time in moderate-to-vigorous-physical activity (MVPA), considering walking as MVPA. More recently, preschool children were found to spend 11.2%-27.4% of outdoor recess time in MVPA (17–19). One longitudinal study found that for every additional hour spent outdoors during cooler months, accelerometer-measured MVPA increased by 27 min/week among 10-12-year-old children (20). Higher baseline reports of time outdoors on weekends were associated with higher MVPA 3 years later, and with a 27-41% lower prevalence of overweight children. Compared with previous generations, children today spend less time playing outdoors within the neighbourhood (21), missing opportunities for physical activity in this domain. Encouraging children to spend more time outdoors during discretionary periods (e.g., after school and on weekends) may be a low-cost and easily implemented strategy to promote physical activity.

Another daily routine that increases total amount of physical activity in children is active commuting to school (22). Santaliestra-

Pasías et al. (23) estimated the prevalence of active and passive commuting to school in children from different European countries. They found that commuting was predominantly passive in the majority of the countries. The highest percentages of active commuting were observed in older (6 to 10 years old) German males and females (51% and 55%, respectively), and both young (2 to 6 years old) and older (6 to 10 years old) Spanish males (54% and 68%, respectively) and females (54% and 64%, respectively). The predictors of active commuting involve characteristics of children and families, schools, communities and the environment. Regarding individual and family characteristics, children from low socioeconomic status (SES) backgrounds are more likely to actively commute than children from high SES backgrounds. Children are more likely to walk or cycle to school when the active commuting does not interfere with parents' work schedules or children's after-school commitments. Regarding school characteristics, distance to school is the most readily identified barrier to children's active commuting. For environmental characteristics, urban neighbourhoods, road and sidewalk infrastructure, and social norms increase the likelihood of active commuting (22). Active commuting to school reduces cardiovascular stress reactivity in children exposed to a cognitive stressor similar to what children might experience during school (24). Active commuting to school has also been positively associated with cognitive abilities, although this effect was only observed in girls (25). The duration of active commuting is key to observe effects on health outcomes (25,26). The evidence suggests that more than 15 minutes of active commuting are required to observe health benefits (24,25).

Sports are considered one specific form of physical activity that contributes to children's and adolescent's overall engagement in MVPA. When compared with other forms of physical activities, sports participation typically involves physical exertion and skill development, and the competition of individuals or teams against one another. School-based sports are more accessible in terms of location and costs, are generally less competitive, and reach those children who are not participating in community sports (27). Extracurricular school-based sports and club sports are characterized for being structured, regular, highly intense, as well as facilitators of social bonding. Sports participation is very popular among children. However, there is evidence that participation in sports peaks at around 11-13 years before declining through adolescence (23,28). Noteworthy, there is research indicating that children who are active through sport are more likely to be physically active in adulthood than those who do not participate in childhood sport (23,28). The psychosocial health benefits of sports participation are evident among children and adolescents, including higher self-esteem, positive social interactions, and a reduction in depressive symptoms (29). Team sports have been more frequently associated with mental health benefits (30,31), although individual sports have been found more effective for improving the symptoms of children with Attention Deficit and Hyperactivity Disorder (ADHD), since they have difficulties in playing team sports (32).

c) The relevance of an active lifestyle

Physical activity is a key determinant of energy expenditure and is therefore fundamental to achieving energy balance and weight control (33). Throughout childhood and adolescence, physical activity is necessary for the development of basic motor skills, as well as musculoskeletal development (33). Appropriate levels of physical activity in children guarantee an optimal physiological development across maturation stages, contribute to the prevention of childhood diseases and decrease the risk of developing chronic diseases later in life (32).

Preschoolers present behaviours like running, jumping or playing in continuous movement in a natural and spontaneous manner. Our ancestors obtained dietary energy and nutrients from the environment through movement, which gave advantage to active phenotypes (34). At the same time, they had also to adapt to extreme conditions, such as long periods of starvation (35). The starvation and abundance cycles would have selected a genotype that allowed a quick fat gain when the food was abundant. These reserves of energy provided survival and reproductive advantages in that context (36). Nowadays, western societies do not need to be active to obtain food, which is available all the time. The population is becoming less active and more sedentary, leading to fat accumulation that increases the prevalence of obesity and cardiovascular diseases in adults and children.

d) Activity patterns across life

There is a trend of decreasing physical activity and increasing sedentary behaviours across lifetime. The changes in these lifestyle patterns have been studied using longitudinal approaches, in which the subjects are followed for a period of time (37–39). Ortega et al. (40) described physical activity decreases from childhood to adolescence and from adolescence to young adulthood, yet with slightly lower rate; whereas sedentary time increases only from childhood to adolescence (Figure 1). However, the magnitude of the change observed in sedentary time was 3-6 times larger than the change observed in physical activity. They suggested that part of the increase in sedentary time was due to more demanding academic requirements in adolescence compared with childhood, also to physiological changes leading to less spontaneous and intermittent physical activity.

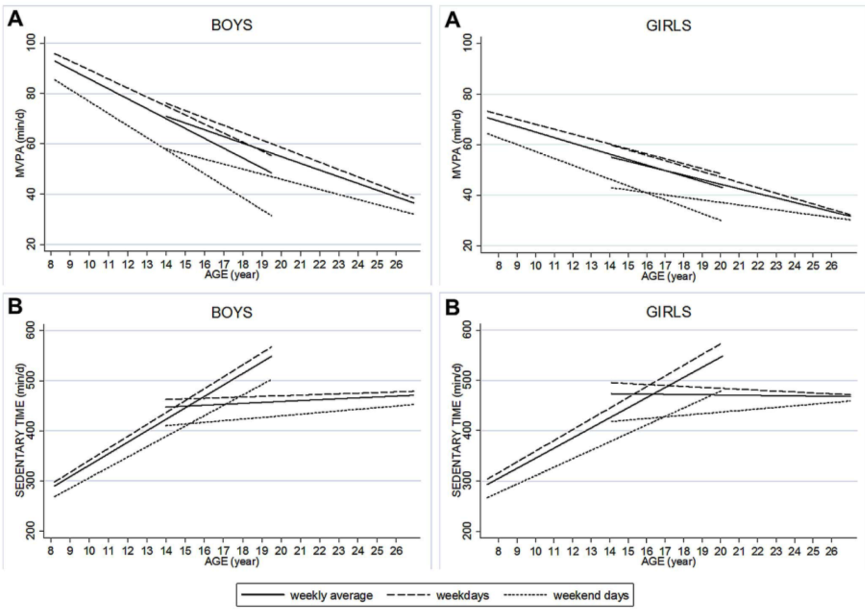

Figure 1. Changes in weekly, weekday and weekend moderate-to-vigorous physical activity and sedentary time. Slopes result from mixed effect models adjusted for age, country, registered time and number of valid days (N = 821 and 989, for boys and girls respectively) (From Ortega et al., 2013)(40)

It is important to encourage physical activity since early childhood to entrench healthy behaviours throughout life, but also plays a role in developmental milestones, such as cognitive functioning, socialization, and emotional well being (41). The National Association for Sport and Physical Education (NASPE) has developed physical activity guidelines for children from birth to the age of 5 years. These guidelines advocate for increasing opportunities for preschoolers (aged 3-5 years) to engage a minimum of 120 minutes of daily physical activity (42). The World Health Organization (WHO) recommends that children and young people accumulate at least 60 minutes of MVPA every day. Adults should undertake at least 150 minutes of moderate-intensity aerobic physical activity each week. A higher level of physical activity is likely to provide additional health benefits for both adults and children (33). The American Academy of Pediatrics recommends parents to limit total media time exposure to less than 2 hours per day (43).

Despite the known benefits of physical activity, there is a worldwide trend towards less total daily physical activity. The increasing rates of physical inactivity among children and adolescents are alarming. In Spain, few children (37.5% of 9-year-old normal-weight and 34.0% of 9-year-old overweight/obese) met the current health-related recommendations of 60 minutes of MVPA daily (44). The percentage of children that reach the recommended 60 minutes spent in MVPA per day descends to only 4.6% of girls and 16.8% of boys at ages 10 to 12 years in Europe (45). Regarding sedentary behaviours, approximately a third of the children between 2 and 10 years old failed to meet the current screen time recommendations of less than 2 hours per day in a study involving different European countries (23). The percentage was even higher on weekend days and in the older group of children (6-10 years old).

In the past, being sufficiently physically active was considered to be the opposite of having a sedentary lifestyle. Nowadays, physical activity and sedentary time are studied as independent behaviours, since a meta-analysis showed that the relationship between them is not significant (46) and they have independent effects on health (47,48).

Maintaining recommended levels of physical activity and sedentary behaviours is becoming more and more difficult. The active transport is being replaced by passive transport, which can be explained by greater distance between homes, workplaces, etc. and low road safety. Children and adolescents spend more time in school due to the increasing academic demands. Therefore, the environment and also the use of technology that makes our life easier contribute to the reduction of physical activity and the increment of sedentary behaviours in our societies.

e) Measurement of physical activity in children

The accurate measurement of physical activity at the population level is important for monitoring trends in physical activity over time, assessing compliance with physical activity guidelines, understanding the dose-response relationship between physical activity and health, and determining the effectiveness of intervention programmes designed to improve physical activity (49).

Physical activity is notoriously difficult to measure. Objective and subjective methods are used for measuring physical activity in children in large-scale research.

Objective measures

These measures include doubly labelled water (criterion method for assessing energy expenditure), indirect calorimetry (measuring energy expenditure from oxygen consumption and CO_2 production), heart rate monitoring, and motion sensors (accelerometers and pedometers) (49).

The most common objective measures are motion sensors. Motion sensors detect body movements and provide an estimate of physical activity. Pedometers detect the number of steps taken over a period of time. Pedometers provide valid assessments of total volume of physical activity, are easy to use and inexpensive, and therefore ideally suited to large-scale studies (50,51). Pedometers are unable to measure intensity of activity or to accurately record activities such as cycling or skateboarding, both common activities in young children. These may affect the validity of the information gathered with young children given the episodic and variable nature of their play. Accelerometers measure accelerations produced by body movement, providing more accurate and detailed physical activity as well as sedentary time data. Accelerometers are valid and reliable instruments for walking and running but less reliable for some sports, since the same count can require different amount of energy expenditure depending on the sport. Some of the limitations of accelerometers relate to the technology itself or the willingness of participants to wear the device, but many relate to how researchers use the technology and interpret the data that is obtained (52).

Objective assessments provide an accurate estimate of physical activity volume and intensity, but they do not provide contextual information of the different types of activity, for instance if the activity is structured or unstructured (53,54).

Subjective measures

The limitations of the objective measures of physical activity regarding the context of the activity can be addressed by using survey instruments. These methods are considered subjective because they rely on responses from someone. Although they are valid tools for providing information about the type and the context of the activity, subjective measures do not provide accurate intensity information. The sporadic nature of children's physical activity makes these activities difficult to recall, quantify and categorise. These measures can be self-completed, interviewer administered, diaries, and proxy reports of physical activity among children by parents, legal guardians or teachers (49).

Proxy measures are used for children aged 10 years or less, where self-report may be inaccurate and unreliable. Proxy measures include parental reports of their children's overall physical activity or occasionally teacher's report of children's activity during school time. These measures are more accurate for capturing structured than unstructured activities of children. Despite that, proxy measures are considered suitable for studies involving large populations of young children, since they are inexpensive and easy to administer (49,55).

Other measures

Aerobic fitness, one element of the physical fitness concept, is often used as an indicator of regular physical activity to study its relation with cognitive development. Aerobic fitness refers to the maximal capacity of the cardiorespiratory system to use oxygen and can be measured by VO_2 max testing, the maximum oxygen consumption elicited during incremental exercise, typically on a motorized treadmill (56,57). Aerobic fitness measures are not suitable instruments for large-scale studies.

1.2 Second section: Cognitive functions in childhood

a) Cognitive development

High physical activity levels in children are associated with enhanced higher-order cognitive processes known as executive functions (EF) (58,59). Early exploratory motor activity places infants in novel situations that train a flexible way of thinking, which becomes the basis of EF. This term is used for the collection of higher-order cognitive processes controlling goal-directed actions. Core EF are inhibitory control (including selective attention and the inhibition of inappropriate or interfering responses), working memory and mental flexibility (60,61) (Box 1). EF play an important role in many aspects of learning during childhood and have a strong impact on academic achievement at school (62–64). EF have been conceptualized as multiple-process related systems that are inter-related, inter-dependent and function together as an integrated supervisory or control system (65). Specific executive processes are thought to be associated with distinct frontal areas, and they show different developmental trajectories (Figure 2).

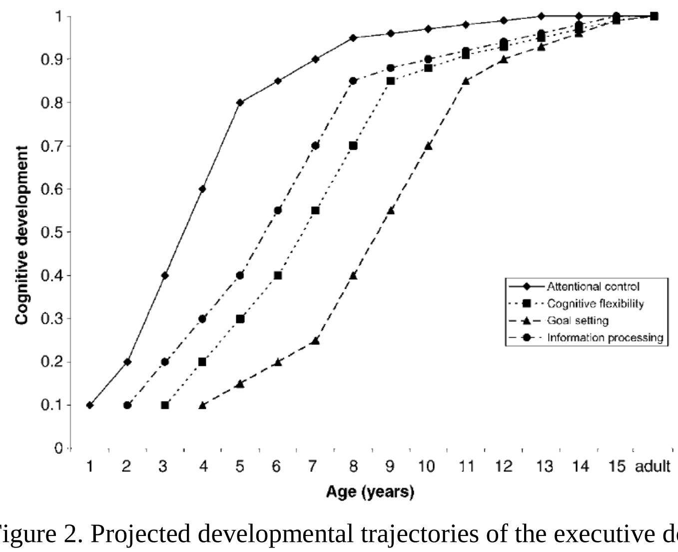

Figure 2. Projected developmental trajectories of the executive domains (from Anderson, 2002)(66)

Box 1. Definitions

Attentional control: the capacity to selectively attend to specific stimuli and inhibit prepotent responses, and the ability to focus attention for a prolonged period of time. The regulation and monitoring of actions so that plans are executed in the correct order, errors are identified and goals are achieved (66).

Goal setting: the ability to develop new initiatives and concepts, as well as the capacity to plan actions in advance and approach tasks in an efficient and strategic manner (66).

Information processing: fluency, efficiency and speed of output. The status of the information processing domain reflects the integrity of neural connections and the functional integration of frontal systems, and can be evaluated by the speed, quantity and quality of output (66).

Inhibitory control: one’s ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary. A prototypical inhibition task is the Stroop task, in which one needs to inhibit or override the tendency to produce a more dominant or automatic response (i.e., name the colour word) (67).

Mental flexibility: the ability to shift between response sets, learn from mistakes, devise alternative strategies, divide attention, and process multiple sources of information concurrently (66).

Working memory: cognitive system that allows us to maintain and manipulate information in mind for short periods of time to guide behaviour (68).

EF develop significantly through childhood and adolescence and occur in growth spurts (61,66). The protracted development of executive domains (Box 1) corresponds with neurophysiological changes, particularly synaptogenesis and myelination, in the prefrontal cortex. Five periods of rapid growth in the frontal lobes have been reported (69). The first growth spurt in frontal lobe is from birth to 5 years of age and is related to the development of attentional control. The other three executive domains (information processing, cognitive flexibility and goal setting) exhibit rapid development between 7 and 9 years of age, which corresponds with the second growth spurt in the frontal lobe. The third growth spurt occurs between 11 and 13 years, the period when all four executive domains approach maturity and "executive control" emerges (66,69). In addition, myelination of prefrontal connections occurs gradually throughout early childhood, middle childhood, and adolescence (70). Progressive myelination results in more rapid and efficient transmission of nerves impulses, improved information processing, as well as enhanced integration of cognitive processes and executive control.

ADHD is characterized by age-inappropriate levels of inattention, impulsivity and/or hyperactivity to a degree that impacts on day-to-day functioning across different settings (e.g. school and home). EF are particularly impaired in children with ADHD (71). Longitudinal neuroimaging data indicates that children with ADHD follow a trajectory of cortical development that is delayed by 2–3 years relative to their typically-developing peers (72). ADHD is estimated to affect 5.3% of children globally (73), becoming a public health concern due to the academic underachievement of these children, and the long-term consequences for the general population (74).

Certain experiences, in this case, physical activity levels of the child, may also influence the development of these cognitive functions. This thesis is particularly focused on two EF: "working memory", the ability to keep information online for a short period of time for cognitive processing; and "attention", a cognitive function involving different processes such as selectively attending to specific stimuli, focusing for prolonged periods of time, or regulating and monitoring of actions.

Working memory undergoes constant change through childhood and adolescence (62), which in turn has an impact on the performance of different complex tasks (75). The developmental changes in working memory are dependent of the improvement in the updating techniques (76–78), in interference control (79), and in focus switching (78). The factors related to storage and speed develop independently (80,81).

The specific measure of attention included in the studies of this thesis is intra-individual variability (IIV). This outcome is based on response consistency throughout cognitive tests. Normally, IIV on cognitive control tasks decreases throughout childhood and adolescence (82,83). Children with ADHD symptoms show alterations in this outcome (84,85), which may be explained by the inability to appropriately modulate very-low frequency fluctuations in neuronal activity (86). Reaction time variability has also demonstrated to be an important measure to study the relation between physical activity and cognitive development (87).

b) Measurement of cognitive functions in children

The measurement of cognitive functions is even more difficult than the measurement of physical activity. Cognitive tasks, questionnaires or scales are used to obtain scores that allow the inference of the "real" cognitive functioning. The performance on a cognitive task can be influenced by different internal and/or external factors, such as physical discomfort, weather or noise. However, the neuropsychological instruments provide reliable and valid measurement of cognitive functions.

In epidemiological studies, the cognitive functions of children are normally assessed using traditional neuropsychological batteries, broad or narrow measures and can be directly or indirectly tested. It is important to use validated tools that allow the comparability between studies (88).

The use of traditional neuropsychological batteries is the most comprehensive assessment of cognitive development in children. This method is also the most time consuming and requires a psychologist who assesses different cognitive domains directly to the child. These batteries have been validated and standardized to specific ages. Two widely used neuropsychological batteries in epidemiological research are Bayley Scales for Infant Development (BSID) and McCarthy Scales of Children's Abilities (MSCA). BSID assesses mental and psychomotor domains in infants between 1 and 42 months (89). MSCA assesses cognitive and motor development in children between 2 and 8 years of age (90).

The measures that are usually included in studies about the cognitive effects of physical activity evaluate directly the cognitive function in the participants. Generally, cognitive tasks that measure specific cognitive processes show associations with physical activity, as opposed to broad measures such as general cognition (91). Tasks that involve EF processes, such as working memory or inhibitory control, are the most sensitive to physical activity effects. These process-specific tests that measure specific components of mental functioning can be based on paper-and-pencil or computerized format. The computerized format is the most common in large studies, since it allows collecting a big amount of data in relatively short time. This method also provides increased objectivity that allows the use of highly precise outcomes. These measures are low cost, easily and rapidly administered, and enables testing of large numbers of people simultaneously (92). Some methodological considerations should be taken into account when cognitive functions are assessed directly. It's important to find a balance between developmental appropriateness of the task and comparability. In other words, the task should be adapted to the age of the participant to detect variability, however this can interfere with the comparison between different age groups. If the primary purpose is within-subjects comparisons looking at trajectories over time, then the good adaptation of the task to the participant's level should by the priority. However, if the aim of the study is to compare different age groups, then a task with a similar difficulty level for all the age groups would be preferable. Another limitation that rises when a cognitive task is administered repeatedly to the same individuals is the practice effect, the improvements on a task simply due to repeated administration (88).

It is relatively common in epidemiological studies the use of indirect measures of cognitive functions, such as rating scales where parents or teachers report the level of cognitive development of their children. An example of this type of measurements is the Behaviour Rating Inventory of Executive Function (BRIEF), which includes the areas of inhibition, shifting, emotional control, initiative, working memory, organization and monitoring (93). However, indirect cognitive measurement is not popular among studies about physical activity. In contrast, academic achievement has been extensively used in this literature as an outcome related to cognitive functioning. This literature is explained with detail in the fourth section.

1.3 Third section: Brain maturation

a) The human brain

The human brain is the most complex organ of the human body. The brain is the command centre for the human nervous system, receiving input from the sensory organs and sending output to the muscles. In addition, it controls the secretions of our glands, our breathing and internal temperature. Our brain creates thoughts, feelings, language, and gives us awareness of ourselves.

The human brain contains about 86 billion neurons (94) connected by trillions of synapses. At an average rate of 6 kcal/day per billion neurons (95), the human brain costs about 516 kcal/day. The ability of using fire to cook foods allowed our ancestors to obtain more calories and nutrients in less time (96), satisfying the daily energy requirements of the brain.

Brain cells can be divided into two groups: neurons and glial cells. Neurons communicate between them through electrical and chemical signalling. A typical neuron consists of a cell body, dendrites that propagate the stimulation received from other neural cells to the cell body, and an axon, a long projection of a neuron that conducts electrical impulses away from the cell body. Glial cells support and protect the neurons. In the brain, there are three types of glial cells: astrocytes, oligodendrocytes and microglia. Astrocytes maintain an appropriate chemical environment for neuronal signalling and modulate neuron behaviour (97). Oligodendrocytes wrap the axons of neurons in the brain to produce the insulation known as myelin. Myelinated axons transmit nerve signals much faster than unmyelinated axons, so oligodendrocytes accelerate the communication speed of the brain. Microglia act much like macrophages by removing cellular debris from sites of injury or normal cell turnover (98).

The tissue of the brain can be divided into two major classes: gray matter and white matter. Gray matter is made mostly of unmyelinated neurons. The gray matter regions are the areas of nerve connections and processing. White matter is made mostly of myelinated neurons that connect the regions of gray matter to each other and to the rest of the body.

The largest part of the human brain is the cerebrum, which is divided into two hemispheres. Underneath lies the brainstem, and behind that sits the cerebellum. The outmost layer of the cerebrum is the cerebral cortex, which consists of four lobes: the frontal lobe, the parietal lobe, the temporal lobe and the occipital lobe. The way the different brain areas function was summarized by the late neurologist and writer Oliver Sacks in the following quoted paragraph:

"The brain is more than an assemblage of autonomous modules, each crucial for a specific mental function. Every one of these functionally specialized areas must interact with dozens or hundreds of others, their total integration creating something like a vastly complicated orchestra with thousands of instruments, an orchestra that conducts itself, with an ever-changing score and repertoire."
― Oliver Sacks

b) The evolution of the human brain

During the evolution of the human brain, the association areas became especially larger, as compared with primary areas. The enlargement of dorsolateral prefrontal cortex allowed the enhanced capacity to inhibit behavioural responses, delay gratification and demonstrate a higher degree of mental flexibility (99). The enlargement of posterior parietal cortex provided additional central visual field representations and greater sensitivity to extract three-dimensional form related to motion (100).

Not only the size, but also the folding pattern characterizes the human brain. The human brain is highly folded, which maximize processing area while minimizing distance. The human prefrontal cortex exhibits more gyrification than expected for an anthropoid primate of the same brain size (101). Furthermore, primary cortex and premotor cortex in humans occupy a smaller proportion of the frontal lobe compared with other primates, suggesting that the remainder is comprised of a relatively large prefrontal cortex (102). Human primary visual cortex is only about one and half times larger in humans than in Great Apes, while the rest of neocortex is about three times larger (103). The relatively small size of primary visual cortex in humans suggests that adjacent areas of the posterior parietal cortex have disproportionately increased in volume (104). Another region that shows extraordinary enlargement in humans is the temporal lobe.

Humans have more neurons than other hominoids in several dorsal thalamic nuclei (105). The human cortico-cerebellar circuit may be distinguished from other primates in having a greater development of the connections with frontal association areas that play a role in cognition and language (106). It is possible that humans have evolved a greater extent of cerebral lateralization in the context of specialization for computationally demanding functions, such as language, to avoid bilateral duplication of circuitry and interhemispheric conflict (107).

Increased neocortex size in humans is not the result of a simple multiplication of uniform processing units. Shariff (108) reported that human cerebral cortex volume is 2.75 times larger than in chimpanzees, but has only 1.25 times more neurons. This suggests that much of the increased mass of the neocortex derives from alterations within the space between neurons.

c) The maturation of the human brain

The maturation of the cortex follows the evolutionary sequence in which these regions appeared. In other words, older cortical regions mature earlier than newer cortical regions. The primary sensorimotor cortices along with the frontal and occipital poles mature first, while the remainder of the cortex develop in a parietal-to-frontal (back-to-front) direction. The superior temporal cortex, which contains association areas that integrate information from several sensory modalities, mature last (109).

The total gray matter volume increases at earlier ages, followed by sustained loss starting around puberty (Figure 3). However, the process of gray matter loss begins first in dorsal parietal cortices, particularly the primary sensorimotor areas near the interhemispheric margin, and then spreads rostrally over the frontal cortex and caudally and laterally over the parietal, occipital, and finally the temporal cortex. Frontal and occipital poles lose gray matter early, and in the frontal lobe the gray matter maturation ultimately involves the dorsolateral prefrontal cortex, which loses gray matter only at the end of adolescence. On MRI, the gray matter density is an indirect measure of a complex architecture of glia, vasculature, and neurons with dendritic and synaptic processes (109).

The exact process underlying the gray matter loss is unknown. Cerebral white matter increases in the first four decades because of axonal myelination (110) and may partially explain the observed gray matter loss (111). It may be driven by the process of synaptic pruning (112) together with trophic glial and vascular changes and/or cell shrinkage (113). Thus, region-specific differences in cortical maturation may result from the underlying heterochronous synaptic pruning and myelination in the cortex (114,115). The age-related trajectories of cortical maturation are influenced by individual differences. Individuals with higher intelligence show increased rate of change in their trajectories and earlier brain maturation (116), while individuals with ADHD show delayed trajectories of cortical maturation (72), as mentioned in the previous section. Alterations either in degree or timing of basic maturational pattern may at least partially underlie the neurodevelopmental disorders (117).

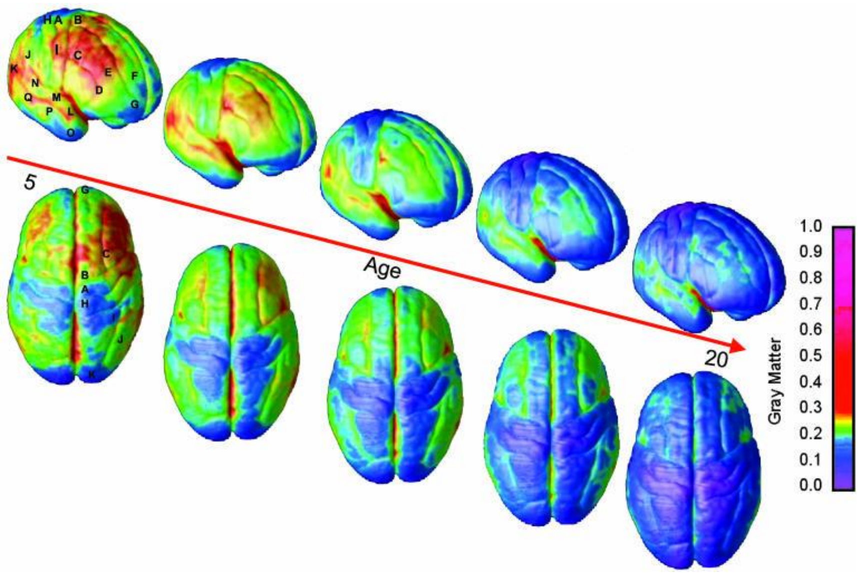

Figure 3. Right lateral and top views of the dynamic sequence of gray matter maturation over the cortical surface. The side bar shows a colour representation in units of gray matter volume (from Gogtay et al., 2004)(109)

1.4 Fourth section: Physical activity and neurodevelopment

a) Physical activity and cognitive functions in children

Extensive literature supports the positive association between physical activity and cognitive functions in children, including cross-sectional, experimental and longitudinal designs, as well as reviews and meta-analyses.

The cross-sectional studies have demonstrated the positive association existing between motion, physical activity or physical fitness and cognitive functioning in children at different ages. In preschoolers, higher levels of movement predicted higher inhibition performance (118). Fitness has been associated with academic achievement in children and adolescents (119–121). Wu et al. (87) found a positive association between fitness and cognitive performance during a task that varies cognitive control demands in 10-year-old children. Raine et al. (122) demonstrated that higher fitness levels were advantageous for learning and memory at 9-10 years of age, and that these fitness-associated performance benefits were largest in most challenging conditions. Van Dijk et al. (123) pointed that objectively measured physical activity was positively associated with executive functioning in adolescents, while executive functioning in turn mediated the associations between physical activity and both academic achievement and mathematics performance. This study also indicated that the association between physical activity and academic achievement is complex and might be affected by academic year, physical activity volume and intensity, and school grade. In addition, high levels of objectively measured MVPA have been associated with faster response to a visual target in 12-year-old children (124). In adolescents, longer time spent in MVPA was positively associated with attention capacity (125).

The experimental studies have provided evidence about the causality of this association. Kamijo et al. (126) studied the effects of a 9-month physical activity intervention on cardiorespiratory fitness and working memory in children between 7 and 9 years old, observing positive effects of the intervention on both outcomes. The benefits were stronger for the task requiring greater working memory demands. Physical activity interventions have been even suggested as a treatment for children with ADHD (127). These exercise-based interventions impacts structural brain growth and functional neurocognitive development, which in turn could have lasting effects on the trajectory of ADHD (127). Few studies have compared distinct age groups in order to test for moderation by age, which showed different results (128,129). Caterino and Polak found an association between a physical activity intervention and selective attention only in the 4th grade age group, while no associations were observed in 2nd and 3rd graders (129). Ellemberg and St. Louis-Deschênes did not detect interactions by age in the association between an exercise intervention and simple and choice response time tasks (128). The differences in the type of physical activity and the cognitive processes measured could explain the discrepancies observed between both studies.

Longitudinal studies suggest that physical fitness could have long-term beneficial effects on cognitive functions. London et al. (130) tracked students longitudinally to examine the ways physical fitness and changes in fitness align with school performance, using matched administrative data and individual growth modelling. They found disparities in both math and English language arts test scores, comparing those who were persistently fit to those who were persistently unfit. Chaddock et al. performed a longitudinal study in which the authors demonstrated that childhood aerobic fitness predicted cognitive performance approximately one year later (131).

The reviews and meta-analyses have concluded that there is enough evidence supporting the positive association between physical activity and perceptual, cognitive, and motor performance (132,133), and that this relationship may be stronger for school age children (134). Moreover, Chaddock et al. (56) also concluded that childhood aerobic fitness is associated with differences in regional brain structure and function. Several reviews have concluded that both chronic and acute aerobic exercise improves executive abilities, most notably inhibitory control (58,59,91,135). Khan and Hillman performed another meta-analysis (136), and they concluded that the current evidence points to the benefits of physical activity and aerobic fitness for cognitive and brain health in childhood. A very recent systematic review (137) provided preliminary evidence that physical activity may have beneficial effects on cognitive development during early childhood.

In general, complex exercise shows stronger effects on EF than simpler exercise. Physical activities that are challenging and goal-oriented and that involve complex movements and strategic behaviour may be more cognitively engaging than repetitive activities, such as jogging, and thus may have a stronger association with cognition (53). Participation in sports is likely to incorporate some of these components and may therefore be more beneficial to cognitive function than less-structured physical activities. However, certain forms of exercise may be more beneficial to EF at one age or another. Younger children may benefit from less structured forms of exercise whereas older children may benefit from more sophisticated activities containing complex rule structures. Thus, the children's developmental level needs to be carefully considered to optimize their cognitive engagement (59).

Similarly, the link between physical activity and EF may be moderated by both age and EF component (59). As mentioned in the second section, EF components are distinct, emerge at different ages, and develop at different rates (61). Thus, whether a specific EF component is sensitive to physical activity and whether physical activity will be cognitively engaging may depend on the children's developmental level.

b) Underlying mechanisms

Physical activity affects cognition through different mechanisms at multiple levels, from cells to social interaction.

The cognitive engagement inherent in physical activity may influence the cognitive functioning in other situations (91,134). Participation in group activities and sports require complex cognitive processes similar to EF tasks, such as cooperation with teammates, anticipation of other's behaviours, planning of strategies, and flexibility to adapt to changing situations. EF tasks require planning, monitoring and mental flexibility to modify the cognitive plan in response to changes in the context (60,61). Motor actions during sports are determined by a myriad of factors that converge at a particular moment; therefore, they are always different. Executive processes such as planning, monitoring and flexibility are necessary to adapt motor actions to particular situations. Social interaction that takes place during participation in group activities and sports provides benefits on cognition itself. Therefore, cognitive skills acquired during participation in group activities or sports may transfer to EF tasks (59).

The neurobiological substrates underlying the protective effects of physical activity on cognitive performance have been studied mainly in animals. Animal research can directly examine the cellular and molecular cascades that are triggered by physical activity in a controlled environment. Both chronic and acute physical activity may facilitate EF but through different pathways. Chronic physical activity induces changes in brain regions critical to learning and memory mediated by upregulation of several growth factors. Physical activity induces immediate neurochemical changes that may prime the central nervous system for either concurrent or subsequent skill acquisition (59).

The specific biological processes that have been related to physical activity are: neurogenesis, synaptic plasticity, growth factors, cerebrovascular remodelling, neuroendocrine function, and inflammation. In humans, brain volume and function have been found influenced by the levels of physical activity or fitness (138).

Neurogenesis

Neurogenesis, the birth of new neurons, has been observed in both animals and humans throughout the lifespan. Neurogenesis occurs exclusively in areas of the brain where specialized vascular endothelium provides the necessary signalling molecules and nutrients. The subgranular zone in the dentate gyrus of the hippocampus is one of the few areas with this specialized environment (139). The hippocampus is a critical structure for learning and memory processes and neurogenesis in the dentate gyrus has been shown to be upregulated by chronic physical activity in rodents (140). It was observed that freewheel running in conjunction with group housing induces neurogenesis in the hippocampus to a greater extent than freewheel running individually

(141). There is also growing evidence that newborn neurons, with the facilitation of various neurotrophins, become functionally integrated into existing neural circuitry as they mature (142,143). This neuronal integration and remodelling may underlie MVPA-induced enhancements in cognitive abilities, as has been observed in animal studies (35,144). The extent to which this occurs in humans, however, remains unclear.

Synaptic plasticity

Physical activity facilitates hippocampal synaptic plasticity in the form of long-term potentiation, which is the creation of new, or strengthening of existing, synaptic connections during learning. Physical activity also increases dendritic complexity and density in the hippocampus (145). In humans, using Transcranial Magnetic Stimulation (TMS) method (Box 2), one study showed that more active adults had greater synaptic plasticity in the left abductor pollicis brevis (APB) muscle motor circuit (146).

Growth factors

Endogenous growth factors play multiple roles that facilitate the survival and maturation of new neurons. These roles are critical for neurogenesis, synaptic plasticity, and angiogenesis, the growth of new blood vessels. Brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF-1) are particularly involved with the positive effects of exercise on the brain and cognition. BDNF is a regulator of the survival, growth, and differentiation of neurons during development. BDNF also translates activity into synaptic and cognitive plasticity in the adult animal. BDNF is able to modulate the efficacy of neurotransmitter release, stimulate the synthesis of vesicle-associated proteins, and regulate transcriptional factors (35).

Physical activity seems to activate the neural circuitry involved in learning and memory, as exemplified by its action on BDNF. It has been shown that quenching the action of endogenous BDNF activated during physical activity can fully block the enhancement of both learning and memory on the Morris water maze task (147).

In humans, BDNF levels mediated the effect of a 1-year walking intervention on executive function in older adults, but only for individuals over the age of 71 (148).

Cerebrovascular remodelling

Healthy brain and cognitive function is critically dependent on the compliance of brain vasculature or the ability to replenish oxygenated hemoglobin following neuronal activity. High metabolic demands from neuronal activity requires tight coupling between neurons and cerebrovasculature. Physical activity-induced cerebrovascular remodelling describes any structural changes (e.g. angiogenesis, or branching of new blood vessels) or functional adaptations (e.g. altered endothelial function) of the arterial vasculature in the brain resulting directly from increasing physical activity (149).

Regional cerebral blood flow (CBF) increases during physical activity, which exposes endothelial cells to shear stress (149). Repeated episodes of elevated shear stress stimulate cell proliferation and vascular remodelling (149). This leads to both increasing the diameter of existing arteries (arteriogenesis) as well as the sprouting of new capillaries from existing vessels (angiogenesis) (149). Angiogenesis coexist with neurogenesis in the hippocampus (150). The role of angiogenesis is to provide nutrients and energy to the new neurons (151) and to integrate them into existing circuits (152). Vascular remodelling is dependent on levels of IGF-1 and VEGF, upregulated by physical activity (132,153).

The context of the physical activity can modulate the vascular remodelling in the brain. A study reported intriguing evidence that whereas individual freewheel running promotes angiogenesis in the hippocampus in comparison to a sedentary condition, an enriched environment promotes angiogenesis in both the hippocampus and prefrontal cortex in adult rats (154).

Another favourable vascular adaptation to regular physical activity is the increased bioavailability of endogenous nitric oxide (NO), which relaxes smooth muscle cells and increases blood flow (149).

Neuroendocrine function

Physical activity is considered a stressor, as it activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (155). The HPA axis is the neuroendocrine pathway that regulates the body's response to stress. Corticotropin-releasing factor (CRF) is released by the paraventricular nucleus of the hypothalamus (PVH) and stimulates the anterior pituitary cortex to release adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal cortex to release glucocorticoids (cortisol in humans). Glucocorticoid receptors in PVH, anterior pituitary, and the hippocampus regulate a negative feedback loop to inhibit HPA axis activation (156). Physical activity can become adverse when it activates the HPA axis for prolonged periods of time, either due to excessive physical activity or to a dysfunctional disinhibition of the axis (155).

Generally, regular MVPA results in favourable adaptation, in which the HPA axis becomes less reactive to stress (155). In the hippocampus, there is an increment of glucocorticoid receptors, which strengths the inhibition of the axis (155). The increased levels of BDNF, neurogenesis and synaptic plasticity may facilitate these adaptive changes.

Inflammation

Physical activity suppresses immune response to inflammation (157). Chronic HPA axis activation can result in chronic low-grade inflammation that increases the risk of chronic disease (158). In contrast, regular MVPA related to adaptive HPA response has positive anti-inflammatory effects (157).

Brain structure

The most common method to study the neurobiological substrates underlying the beneficial effects of physical activity on cognitive performance in humans is non-invasive neuroimaging tools such as magnetic resonance imaging (MRI) (Box 2). The benefits of physical activity on brain structure have been mostly found in the elderly population.

In low-active healthy older adults, a one-year weekly exercise intervention increased the size of the hippocampus (159). Higher levels of fitness and fitness improvements were associated with larger volumes of prefrontal and temporal grey matter as well as anterior white matter volumes (160). Cardiorespiratory fitness was related to white matter integrity in corpus callosum and motor planning regions of the prefrontal cortex (161). Increases in cardiorespiratory fitness following a one-year weekly exercise intervention have been found associated with positive changes in white matter integrity in prefrontal and temporal regions (162). In a longitudinal study, higher amounts of walking was associated with less cognitive impairment and greater frontal, parietal, and temporal lobe gray matter volume 9 years later, compared to less walking (163).

In children, physical activity has been also associated with brain volumetric benefits. Higher cardiorespiratory fitness was associated with larger hippocampal volume in 10-year-old children (164). Moreover, this larger volume mediated the association between fitness and performance on a hippocampal dependent memory task. A similar finding was observed in a population of adolescent children (165). Basal ganglia have been also related to fitness. Higher fit children showed larger volumes in the dorsal striatum, which were associated with a greater ability to inhibit distraction during a compatible congruent and incongruent flanker task (166). In addition, bilateral putamen volumes of the dorsal striatum and globus pallidus volumes predicted flanker performance one year later in a longitudinal study (131). Higher fit children showed decreased grey matter thickness in superior frontal cortex, superior temporal areas, and lateral occipital cortex, coupled with better mathematics achievement, compared to lower fit children (167).

Brain function

Non-invasive techniques have been used to measure brain's electrical activity in real time (EEG and ERPs) and regional changes in blood oxygenation that follow neural activity (fMRI) in relation to physical activity (Box 2).

The neuroelectric findings suggest that individuals with higher aerobic fitness have increased top-down attentional control (168) and reduced response conflict compared to lower-fit peers (169).

Studies have also found differences in regional brain activity depending on physical activity in both children and adults (170–173). Children who completed an exercise intervention performed at a similar level than adults in a flanker task, while showing decreased activation in right anterior prefrontal cortex (170). Aerobic training also improved the functional synchrony within Default Mode Network (DMN) (174). These network is detected by the synchronized activity of different areas of the brain (175,176) and underlie specific aspects of human cognition, behaviour, and neurodegenerative disease (177,178).

Box 2. Non-invasive techniques

Cortical thickness: The closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary.

DTI (Diffusion Tensor Imaging): Method that provides a description of the diffusion of water through tissue. It makes it possible to trace how fibers are connected in the brain, yielding a map of how the brain is wired.

ERP (Event-related brain potential): A time-locked index of neuroelectrical activation that is associated with specific cognitive processes.

fMRI (Functional MRI): Blood oxygenation-level dependent (BOLD) signal reflects the proportion of oxygen-rich and oxygen-poor blood in a given brain region at a given moment. The BOLD signal maps the neural activity in the brain by measuring the change in blood flow.

MRI (Magnetic Resonance Imaging): MRI works by placing the human body in a strong static magnetic field and applying a brief pulse of electromagnetic energy. This pulse produces an oscillating magnetic field that excites hydrogen atoms since they have magnetic properties. The time it takes for the nuclei to "relax" back to their original position is measured by detecting a radio frequency signal emitted by these atoms. The contrast between different tissues is defined by the rate in which excited atoms return to the equilibrium state.

Structural MRI: Provides information about the shape, size, and integrity of gray and white matter structures. MRI signal varies across tissue types. Morphometric techniques measure the volume or shape of gray matter structures and white matter integrity.

TMS (Transcranial Magnetic Stimulation): This non-invasive method is used to stimulate small regions of the brain. With this method synaptic plasticity is operationalized as the increase in reactivity of the hand muscle to activation of the motor cortex following repeated paired stimulations.

2. RATIONALE

Cognitive development is a common and relevant outcome in epidemiological studies. The study of its determinants such as age, gender or ADHD symptoms in the general population is scarce. Moreover, individual trajectories of cognitive development have not been explored in this context as it is usually performed in other health outcomes. The study of cognitive trajectories, based on several measures in short periods of time, would improve neurodevelopment characterization as a process in order to detect alterations in the growth pattern caused by social, environmental and other factors.

Physical activity has been associated with cognitive functions at a cross-sectional level in children. However, it is unknown whether this behaviour is related to cognitive growth trajectories in children. Physical activity in children is also associated with specific brain structural and functional characteristics. The cortical morphology related to sports participation in children has not been studied yet in the general population. In addition, longitudinal studies in the general population of children are needed to establish temporal causality between physical activity at early ages and later development of specific cognitive functions. Understanding the potential of physical activity, in general, and structured physical activity or sports, in particular, for maximizing cognitive and brain development of children has significant public health implications.

3. OBJECTIVES

The two general objectives of this thesis were 1) to study the determinants and trajectories of cognitive development, and 2) to study the role of physical activity on cognitive and brain development in children. The specific aims were:

1. To assess the longitudinal association between preschool ADHD symptoms and attention function at 11 years old in a population-based birth cohort.

2. To characterize developmental trajectories of n-back, a working memory task, using four repeated measures during a 1-year follow-up in schoolchildren.

3. To assess the association between physical activity habits and cognitive growth over one year, including working memory and inattentiveness, in schoolchildren.

4. To study cortical morphology in relation to sports participation and type of sport in healthy children.

5. To study the effect of early physical activity and sedentary behaviours on working memory at 7 and 14 years of age.

4. METHODS

4.1 Participants

a) INMA

The INMA-INfancia y Medio Ambiente-(Environment and Childhood) Project is a network of population-based birth cohorts in Spain that aim to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development (179). In this thesis, 4 regions were included: Menorca (n=530), Sabadell (Catalonia) (n=657), Valencia (n=855), Gipuzkoa (Basque Country) (n=638). In Menorca, women attending antenatal care were recruited over a 12-month period starting in mid-1997, while in Valencia, Sabadell and Gipuzkoa the recruitment took place between 2003 and 2008.

b) BREATHE

The BREATHE-Brain development and air pollution ultrafine particles in school children- project aims to analyse the association between air pollution and cognitive development of schoolchildren (180). This project was conducted from January 2012 to March 2013 in 36 schools of Barcelona, and 3 in Sant Cugat del Vallès, a smaller city near Barcelona (Catalonia, Spain) (n=2897). All the families of children attending these 39 schools in the 2nd, 3rd and 4th primary grades (aged from 7 to 10 years) were invited to participate via mail and/or project presentations in the schools. Children were evaluated in the schools every 3 months over four repeated sessions using computerized neuropsychological tests.

c) Generation R

Generation R is a population-based birth cohort in Rotterdam (The Netherlands) that aims to investigate children's development from fetal life onward (181). In total, 9778 mothers with a delivery date from April 2002 until January 2006 were enrolled in the study. Response at baseline was 61%, and general follow-up rates until the age of 6 years exceed 80%. From the age of 5 years, regular detailed hands-on assessments were performed in a dedicated research center including advanced imaging facilities such as Magnetic Resonance Imaging. The neuroimaging wave included 1070 children aged 6-to-10 years who were scanned between September 2009 and July 2013.

4.2 Neuropsychological instruments

a) ADHD-DSM-IV

The ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (ADHD-DSM-IV) (182) form list is comprised of 18 symptoms categorized in two separate symptom groups. These are inattention (nine symptoms) and hyperactivity/impulsivity (nine symptoms). Teachers rated each ADHD symptom on a 4-point scale (0 never or rarely, 1 sometimes, 2 often, or 3 very often) for each child. We recorded the option 0 and 1 as “symptom absent”, and ratings of 2 and 3 as “symptom present” (183).

b) Continuous Performance Test II (CPT-II)

CPT-II is a computerized measure of vigilance/attention control and inhibition response for children aged 6 years and older (184). Participants were shown successive letters on a computer screen and were required to press the space bar or click the mouse button when any letter except “X” appeared on the screen. Stimuli were presented in six blocks, with three sub-blocks each containing 20 trials (i.e., letter presentations). Interstimulus intervals varied between 1, 2, and 4 s, while the display time was held constant at 250 ms. During the CPT-II, there was a total of 360 trials (324 targets and 36 nontargets). The CPT-II took 14 min to complete.

c) N-Back task

In the n-back task the subjects were required to monitor a series of stimuli presented in the centre of the laptop’s screen and they had to respond whenever a given stimulus is the same as the one presented *n* trials previously (1-, 2-, and 3-back) (185). These different conditions are known as loads and in the highest cognitive load (i.e., 3-back) the demands on working memory are stronger. Stimuli were presented in a fixed central location on a white background for a 1500-ms duration with a 1000-ms interstimulus interval. All participants were required to press a specific keyboard button when the target appeared in the screen. Participants completed three levels (1-, 2-, and 3-back) for each stimulus. In the 1-back level, the target was any stimulus that matched the stimulus immediately preceding it. In the 2-back level, the target was any stimulus that matched the one presented two trials previously. In the 3-back level, the target was any stimulus identical to the presented three trials previously. Each level consisted of 25 trials. The first three trials of each level were never targets, and 33% of stimuli of the following trials were targets. After each level, a short break (5–20 s) was provided to allow participants some rest. Upon completion of each target, children heard a motivational recorded sample ("woo hoo!") and a smiling face appeared at the top left of the screen.

d) Attentional Network Task (ANT)

In the ANT, a row of five yellow fish appearing either above or below a fixation point is presented (186). Children were invited to "feed" the central fish as quickly as possible by pressing either the right or the left arrow key depending on the direction in which the fish in the middle was pointing while ignoring the flanker fish, which pointed in either the same (congruent) or opposite (incongruent) direction than the middle fish. Each trial began with a fixation period, in which a cross appeared in the centre of the screen for a duration defined as a random variable between 400 and 1600 ms. Subsequently, a warning cue was given by presenting an asterisk on the screen for 150 ms. Another brief fixation period of 450 ms occurred following the disappearance of the cue, and this was in turn followed by the appearance of the row of five yellow fish. The ANT comprised a total of 16 practice trials and four experimental blocks of 32 trials each (a total of 128 trials).

4.3 Questionnaires

a) INMA

Physical activity and sedentary behaviour information was collected through questionnaires administered face-to-face to parents, generally the mother, at 4 years of age in the younger subcohorts (Valencia, Sabadell and Gipuzkoa), while this information was collected when the children were 6 years old in Menorca. Parents reported extracurricular physical activity of their children through the question “During a typical week, how long does your child perform extracurricular exercise every day, i. e. dance/swimming lessons, or just playing, running, cycling, skating, swimming, etc.?” The parents were able to specify more than one activity in Gipuzkoa and Sabadell. TV watching was studied separately because of the known different effects of this behaviour on cognitive outcomes as compared to other sedentary behaviours. In all regions, TV watching was assessed by the question “How many hours does your child watch TV per week?” Other sedentary behaviours were reported using the question “Outside school, how long does your child dedicate to games or sedentary activities (i. e. puzzles, books, dolls, homework, computer/video games)?” (See Paper V).

b) BREATHE

We collected information about extracurricular physical activity frequency and commuting (mode and duration) through a questionnaire completed by parents during the first visit (See Paper III). Parents reported extracurricular physical activity of their children through the question “How often does your child exercise until breathless or sweating, outside of school?” and they completed a table indicating the transport used usually by the child to go to school and the time spent in the trip. We used the data about the one-way route from home to school as a proxy of commuting.

c) Generation R

Information about sports participation was obtained through a parent-reported questionnaire administered when the child was 6 years old (See Paper IV). Parents completed the following question "Does your child take part in sports (for example, football, judo, gymnastics, jazz ballet, tennis, etc.)?" Parents were able to report up to three different sports, including information regarding frequency and duration of each sport.

4.4 Magnetic Resonance Imaging

Magnetic resonance images were acquired using a GE Discovery MR750 3.0 T scanner (GE Healthcare Worldwide, USA) with an eight-channel head coil. The high resolution T1-weighted image was collected using an inversion recovery fast spoiled gradient recalled sequence with the following parameters: TR (repetition time)=10.3 ms, TE (echo time)=4.2 ms, TI (inversion time)=350 ms, NEX (number of excitations)=1, flip angle=16°, readout bandwidth=20.8 kHz, matrix 256×256, imaging acceleration factor of 2, and an isotropic resolution of 0.9×0.9×0.9mm^3.

We performed image quality assurance in two steps. The first step was a visual inspection of the image quality of the T1 sequence prior to preprocessing the data. The next step of quality assurance took place after the images were processed through the FreeSurfer pipeline, and consisted of a visual inspection of the segmentation quality of the data. Scans that were rated as unusable or poor were excluded.

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) version 5.1. The technical details of these procedures are described in a prior publication (187). Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface. The surface-based map was smoothed using a 10mm full-width half-maximum Gaussian kernel prior to whole-brain, surface-based analyses.

5. RESULTS

Paper I. Continuous Performance Test II Outcomes in 11-Year-Old Children with Early ADHD Symptoms: A Longitudinal Study

Paper II. Developmental Trajectories in Primary Schoolchildren Using n-Back Task

Paper III. Physical Activity and Cognitive Trajectories in Schoolchildren

Paper IV. Cortical Structures Associated with Sports Participation in Children: A Population-Based Study

Paper V. Longitudinal effects of physical activity and sedentary behaviours on working memory in children

5.1 Paper I

López-Vicente M, Sunyer J, Forns J, Torrent M, Júlvez J. Continuous Performance Test II outcomes in 11-year-old children with early ADHD symptoms: A longitudinal study. Neuropsychology. 2014 Mar;28(2):202–11. DOI: 10.1037/neu0000048

5.2 Paper II

López-Vicente M, Forns J, Suades-González E, Esnaola M, García-Esteban R, Álvarez-Pedrerol M, et al. Developmental Trajectories in Primary Schoolchildren Using n-Back Task. Front Psychol. 2016 May 13;7:716. DOI: 10.3389/fpsyg.2016.00716

5.3 Paper III

López-Vicente M, Forns J, Esnaola M, Suades-González E, Álvarez-Pedrerol M, Robinson O, et al. Physical Activity and Cognitive Trajectories in Schoolchildren. Pediatr Exerc Sci. 2016 Aug;28(3):431–8. DOI: 10.1123/pes.2015-0157

5.4 Paper IV

López-Vicente M, Tiemeier H, Wildeboer A, Muetzel RL, Verhulst FC, Jaddoe VW V, et al. Cortical Structures Associated With Sports Participation in Children: A Population-Based Study. Dev Neuropsychol. 2017 Feb 17;42(2):58–69. DOI: 10.1080/87565641.2017.1309654

5.5 Paper V

López-Vicente M, Garcia-Aymerich J, Torrent-Pallicer J, Forns J, Ibarluzea J, Lertxundi N, González L, Valera-Gran D, Torrent M, Vrijheid M, Sunyer J. Longitudinal effects of physical activity and sedentary behaviours on working memory in children.

Longitudinal effects of physical activity and sedentary behaviors on working memory in children

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Abbreviations: PA: physical activity, SB: sedentary behavior, WM: working memory

Abstract

Background

Low levels of physical activity and high levels of sedentary behaviors are linked with poorer cognitive function in infancy and childhood, but lack of prospective studies limits inference about the directionality of these associations. We aimed to study the effects of early physical activity, TV watching and other sedentary behaviors on working memory at 7 and 14 years of age.

Methods

This study was based on four subcohorts of the Spanish population-based birth cohort INMA. In the younger three subcohorts (n=1,093) parents reported lifestyle habits and socio-demographic information through a questionnaire at child age 4, and children performed a computerized working memory task at age 7 years. In the older subcohort (n=307), the questionnaire was completed at 6 years of age and working memory was tested at 14 years.

Results

Low physical activity levels at 4 years old were associated with a reduction of 23 points (95% CI: -45, -1.6) in working memory task at age 7 only in girls. Low physical activity levels at 6 years of age were associated with a reduction of 96 points (95% CI: -179.3, -12.9) in the working memory task in adolescent boys. TV watching and other sedentary behaviors were not associated with working memory. These results were robust to the adjustment for socio-economic factors and sensitivity analyses.

Conclusion

Children with low levels of physical activity in two periods of vulnerability had worse cognitive function later in school-aged girls and in adolescent boys.

Introduction

Healthy lifestyle habits, such as adequate levels of physical activity (PA) and sedentary behaviors (SB), are a fundamental prerequisite for the development of basic cognitive, motor and social skills in children.[1,2] U.S. guidelines recommend 120 minutes of PA daily in preschoolers.[3] In children, it has been recommended to participate in at least 60 minutes per day moderate-to-vigorous physical activity (MVPA), however only 4.6% of girls and 16.8% of boys between 10 and 12 years old in Europe reach these recommendations.[4] Approximately a third of the children between 2 and 10 years old fail to meet the current screen time recommendations of less than 2 hours per day (American Academy of Pediatrics).[5] PA decreases from childhood to adolescence and from adolescence to young adulthood; whereas SB, including screen time and other activities such as reading or doing homework, increase from childhood to adolescence.[6] Low PA and high SB are not necessarily correlated[7] and their health effects should be examined independently.[4] Cognitive functions such as attention[8] and higher-order cognitive processes, particularly working memory (WM), the ability to keep information online for a short period of time for cognitive processing, have important implications for learning and school achievement.[9,10] These functions develop significantly across childhood and adolescence and have been related to PA and SB.[8,11] Positive cross-sectional associations have been observed between PA and cognitive functions in preschoolers[12] and in school age children.[11,13–16] Regarding SB, while TV watching and playing videogames have been inversely associated with executive functions, reading was associated positively with different cognitive outcomes in preschoolers[17,18] and schoolchildren.[11,19] Contrarily, other studies have observed that videogames can enhance executive functions.[20–22]

An important limitation of existing research on PA, SB and cognitive functions is the cross-sectional design[11,13,18,19,23–25] that limits the possibility to infer directionality of the association. Furthermore, it is unknown whether this association extends to subsequent developmental periods. The effect of these lifestyle behaviors on cognitive outcomes may change at different periods, since the type of activities vary across ages.[6] Similarly, the link between PA or SB and cognitive functions may be moderated by both the age and the specific cognitive process, since they develop at different rates.[26] The current literature indicates that the preschool and school years are important for establishing healthy lifestyle behaviors,[27] and that WM undergoes constant change through childhood and adolescence, which makes this specific cognitive function a good indicator of cognitive development at these periods of life.[9,28] We therefore aimed to evaluate, in a prospective study design, the effect of PA and SB on WM development in two key periods of cognitive maturation in two separate populations. We focused on extracurricular PA because this behavior is more variable among children than school PA, which is highly standardized. Moreover, extracurricular PA is the best indicator of the engagement in PA later in life.[5] The type of PA included in each of the populations was adapted to children's age, as certain forms of PA may be more beneficial to cognitive development at one age or another.[26] The specific objectives of this study were to analyze 1) the effect of PA habits, TV watching and other SB at preschool age on WM at primary school age, and 2) the effect of PA habits, TV watching and other SB at primary school age on WM in adolescence. In addition, we evaluated differences by sex, since lifestyle patterns are different between girls and boys.[4]

Methods

Design and study population

This study was based on the population-based birth cohort INMA, including 4 Spanish regions: Menorca (n=530), Valencia (n=855), Sabadell (Catalonia) (n=657), and Gipuzkoa (Basque Country) (n=638).[29] In Menorca (the oldest subcohort), women attending antenatal care were recruited over a 12-month period starting in mid-1997, while in Valencia, Sabadell and Gipuzkoa (the younger subcohorts) the recruitment took place between 2003 and 2008. The number of participants in this study was 1,093 children for the younger subcohorts, and 307 for the oldest subcohort. Only subjects with information about lifestyle habits and cognitive task were included in the current analysis (Figure 1). The study was approved by the Hospital Ethics Committees in the participating regions and informed consent was signed by parents.

Measurement of physical activity and sedentary behaviors

PA and SB information was collected through questionnaires administered face-to-face to parents, generally the mother, at 4 years of age in the younger subcohorts (Valencia, Sabadell and Gipuzkoa), while this information was collected when the children were 6 years in Menorca. Parents reported extracurricular PA of their children through the question "During a typical week, how long does your child perform extracurricular exercise every day, i. e. dance/swimming lessons, or just playing, running, cycling, skating, swimming, etc.?" The variable "extracurricular PA" excluded outdoor playing, walking and cycling in Menorca, since structured PA may be more beneficial to cognitive development at this age than unstructured PA.[26] The parents were able to specify more than one activity in Gipuzkoa and Sabadell (Supplemental Material).

TV watching was studied separately because this behavior has different effects on cognitive outcomes as compared to other SB. In all regions, TV watching was assessed by the question "How many hours does your child watch TV per week?" Other SB was reported using the question "Outside school, how long does your child dedicate to games or sedentary activities (i. e. puzzles, books, dolls, homework, computer/video games)?" As the questions were not identical in all the regions (Supplemental Material), the answers were harmonized a posteriori. Categorical variables were transformed to continuous variables (Supplemental Material). The continuous variables in minutes were transformed to hours per day and then, added to hours per week. In Menorca, TV watching was excluded from SB question by subtracting the value obtained in TV watching specific question.

Neuropsychological testing

Baseline cognitive function was assessed by trained psychologists at 4 years of age using the McCarthy Scales of Children's Abilities (MSCA).[30] The general cognition score, which is the sum of all cognitive tasks that MSCA assesses, has a good internal consistency (Cronbach's alpha coefficient = 0.82). The general cognition score was standardized to a mean of 100 with a standard deviation of 15.
WM was tested individually using computerized n-back task[31] at 7 years of age in the younger subcohorts and at 14 years of age in Menorca. This instrument has been validated with brain imaging,[32] and in the general population.[33] The duration of the sessions was 25 minutes. Briefly, in the n-back task, participants have a sequence of stimuli on the computer screen (i.e. a number), one at a time, and they have to respond (i.e. hit a button) only when the current stimulus matches the one presented *n* steps before. The specific visual n-back task used consisted of a series of numbers, and three levels of difficulty or loads (1-, 2-, and 3-back). Stimuli were presented in a fixed central location on a white background for a 1500-ms duration with a 1000-ms interstimulus interval. Participants completed three blocks (1-, 2-, and 3-back) consisted of 25 trials each block. The first three trials of each block were never targets and 33% of stimuli of the following trials were targets. In the present study, we only analyzed the 2-back task because it showed better properties than the 1- and 3-back tests (e.g. clear age-dependent slope and little learning effect).[34] We measured *d prime* (*d'*), a measure of detection subtracting the normalized false alarm rate from the hit rate: (Z hit rate - Z false alarm rate) x 100. A higher *d'* indicates more accurate test performance and thus better WM.

Socio-demographic variables

Birth date and child's sex were collected after delivery. Age was calculated based on birth date and neuropsychological testing session date. We used maternal education as a proxy of social class; this information was collected during the first trimester of pregnancy through a questionnaire. This variable was categorized in three levels for the analysis (1: Primary or without education; 2: Secondary; 3: University).

Statistical analyses

We used categorical lifestyle variables split by the median value in each subcohort. We performed Tobit regression models[35] to take into account that the 2-back *d'* was truncated at 391 score due to the ceiling effect in this task (12.2% censored observations in the younger subcohorts, and 59% in the older subcohorts). We performed independent models for each lifestyle behavior (extracurricular PA, TV watching, and other SB). Separate models were performed for Menorca and younger subcohorts. Pooled analyses were performed to combine the younger subcohorts (Valencia, Sabadell and Gipuzkoa). The confounders included in our models were sex, age in years, maternal education, and baseline cognitive function (MSCA), as previous literature has indicated that these variables could be associated with both lifestyle habits and cognitive performance.[4,6,25,36] Final models were additionally adjusted for subcohort in the pooled analyses. We also performed stratified analyses for boys and girls to study possible effect modification by sex in the association between early lifestyle habits and later WM.

Statistical analyses were done using R (3.0.2; R Foundation for Statistical Computing) and Stata 12.1 (Stata Corporation, College Station, Texas).

Results

The characteristics of the participants by region are described in Table 1. Boys and girls were similarly distributed in all the regions. Children from Sabadell and Gipuzkoa reported the higher levels of PA, spending 14 to 15 hours per week in extracurricular PA, respectively. Younger subcohorts spent 9 to 11 hours per week watching TV and 7 to 10 in other SB. In Menorca, children spent 3 hours per week in structured PA; they spent 7.6 hours per week watching TV and 13.5 hours per week in other SB. The mean n-back score was higher in the oldest subcohort (Menorca) and lower in the youngest subcohort at follow-up (Sabadell).

Table 2 shows the percentage of children in each category of the lifestyle behaviors by sex and maternal education. In the younger subcohorts (Valencia, Sabadell and Gipuzkoa) boys spent more time doing PA and watching TV, while girls spent more time in other SB. In Menorca, the percentage of boys was slightly higher in the high PA and high TV watching group, while the percentage of girls was higher in the group of high other SB levels. Children whose mothers had lower education spent more time watching TV than those of higher educational background, both in the younger and older subcohorts.

Low levels of extracurricular PA at 4 years of age were associated with a reduction of 23 points (95% CI: -45, -1.6) in WM task at age 7 years in girls compared to those with high levels of extracurricular PA (median *d'* score in girls=167) (Table 3), whereas no association was detected in boys (p for interaction=0.105). In Menorca (the older subcohort), we found a reduction of 62 points (95% CI: -119.9, -4.8) in the WM task in adolescents who were less active at age 6 years compared to those who were more active (median *d'* score=392). The stratified analyses showed a clear association in boys (coef.: -96.1; 95% CI: -179.3, -12.9) but did not reach statistical significance in girls (coef.: -28.6; 95% CI: -107.3, 50.9) (p for interaction=0.282). No statistically significant longitudinal associations were observed between TV watching or other SB and WM function at either age or in either sex.

Discussion

In this study, girls with low levels of extracurricular PA at 4 years of age had worse cognitive function (i.e., performance in a WM task) later at age 7. Boys with low PA levels at 6 years of age had worse WM task performance at age 14 years in an independent study population. No associations were observed between early SB and later WM performance.

Many studies have observed the positive cross-sectional relationship between PA and cognitive functions in children,[12,23,24] especially executive functions.[8,11,14] In line with our results, Chaddock et al. (2012)[37] demonstrated that childhood fitness (a variable closely related to PA) predicted cognitive abilities one year later in a longitudinal study. PA may enhance attentional processes and executive functions through different mechanisms at multiple levels, from cells to social interaction. Cognitive skills acquired during PA may transfer to cognitive functioning in other situations.[26] Chronic PA has been associated with larger brain volume in regions supporting memory and executive functions,[38–40] improvement in the connectivity of brain networks,[41,42] higher levels of brain-derived neurotrophic factor (BDNF)[36,43] and enhanced cerebrovascular function.[44]

Regarding our results in the younger children, we found a positive association between PA levels at 4 years of age and WM performance at 7 years. The question included different types of PA, such as playing, walking, cycling and sports. Previous literature has supported the idea that any type of PA, measured using accelerometers, is associated with better cognitive capacities using a cross-sectional design.[11] This is particularly true for younger children, who may benefit more from unstructured forms of PA than older children.[26] The longitudinal approach of our study highlights the importance of early PA habits for maximizing cognitive development of children. Interestingly, in line with previous studies,[45,46] the positive association between PA and WM performance was only found in girls. This finding can be explained by different levels of activity, as the greater benefits of PA on cognition are observed at lower frequency levels of PA, by different type of activity or different metabolic pathways between boys and girls.[45]

Regarding older children (Menorca subcohort), our results indicated that time spent in extracurricular PA at 6 years predicted WM performance of the same children 8 years later, with differences by gender. In Menorca (the oldest subcohort), the variable of extracurricular PA included mainly structured PA, such as sports. Although PA levels starts to decrease through late childhood,[6] it is known that sports participation increases at school age, since preschool children do not normally participate regularly in organized PA[5] and habitual PA is rarely intensive.[47] Sport usually occurs regularly, is highly intense, with a strong social component.[48,49] Children engaged in sports are more likely to be physically active during adolescence and adulthood.[50] Thus, this study showed that structured PA during childhood might have long-term positive effects on cognitive development. In this sample, the effect was strong in boys, not reaching statistical significance in girls. It is possible that the intensity of the structured PA at school age was higher in boys than in girls, which would be more beneficial for later WM development.

We did not observe any association between SB and WM. We analyzed separately TV watching and other SB, since opposite effects have been observed for each of these behaviors.[17,18] However, both variables were probably too general to detect some effect. We had no information about the content of the TV programs, which may be detrimental or beneficial for cognitive functions. For instance, early exposure to age-appropriate programs designed around an educational curriculum is associated with academic enhancement, whereas exposure to violent content is associated with poorer cognitive development.[25,51] The variable of other SB included a large variety of behaviors, such as solving puzzles, reading, playing with dolls, doing homework or playing video games. All these activities could affect cognitive development in different ways.[11,17] According to our results, early SB may have no influence in later cognitive maturation at any of the studied age periods. The null results could be explained by the heterogeneity of activities included in this question, which may dilute any possible association.

This study has some limitations. First, some questions were not identical between subcohorts. In order to account for these differences by region, categorical variables split by cohort specific medians were used in the analyses, which could lead to imprecise results. Second, half of the initial sample was lost at follow-up, which made selection bias possible. Our sample may be more predisposed to participate in activities than the general population, driving to underestimated effects. Third, the reduced sample size in the stratified analyses by sex in Menorca restricted the interpretation of our results; with our data we were unable to confirm or discard any association in adolescent girls. Fourth, the associations found in this study can be explained by residual confounding by unmeasured variables, such as household income. The inclusion of other covariates related to social class could reduce the effects observed in our study. Fifth, the content of the TV program, key for the cognitive consequences of screen time in the children,[25] was not asked to parents. Moreover, the general questions regarding SB (i.e., TV program content, type of sedentary activity, etc.) may dilute possible longitudinal associations between specific sedentary activities and WM. Finally, the lifestyle habits included in this study were not objectively measured, on the contrary, this information was reported by parents, which may imply misclassification, recall bias or perceived desirability of responses. Furthermore, parents tend to overestimate the level of activity of their child.[52]

The main strength of this study is the long period between measurements. We extended the results obtained by Chaddock et al. (2012)[37] by showing that early PA habits predicted WM performance at school age and adolescence. In addition, the different ages of the samples in this study allowed us to compare different age periods. We adjusted the models for baseline cognitive function, which represented an advantage towards cross-sectional studies. Our sample was part of a population-based birth cohort including different Spanish regions, which increased the external validity of the study, as the results can be generalized to the general population of children. Furthermore, this cohort allows studying the longitudinal effects of healthy lifestyles with longer time lapses, as the follow-ups assessing different health and cognitive outcomes are being carried out consecutively. The cognitive instrument used in the present article to measure WM was validated in the general population.[33] While less comprehensive than formal neuropsychological assessment, the standardization of the computerized format can provide increased objectivity.[53]

Conclusions

In conclusion, this study has shown that low PA levels at preschool age were associated with poorer WM performance at school age in girls and that low PA levels at school age did so in adolescent boys. These data suggested that PA habits at early ages influence the WM at school age, which may impact academic achievement. Our results also showed that highly intense and structured physical activities are especially relevant for WM development in adolescence. Further studies should include larger sample sizes to compare the effects by sex at different ages, longer time periods between the exposure and the cognitive outcomes, specific SB questions and/or objective activity measurement such as accelerometers.

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Table 1. Characteristics of the participants

	Younger subcohorts			Older subcohort
	Valencia (n=437)	Sabadell (n=492)	Gipuzkoa (n=164)	Menorca (n=307)
Baseline				
Sex (n, % females)	217 (49.7%)	232 (47.2%)	83 (50.6%)	157 (51.1%)
Age (mean, SD)	4.3 (0.12)	4.4 (0.19)	4.5 (0.25)	6.1 (0.08)
Maternal education (n, %)				
Primary or low	116 (26.5%)	111 (22.6%)	21 (12.8%)	150 (48.9%)
Secondary	188 (43.0%)	208 (42.3%)	60 (36.6%)	90 (29.3%)
University	133 (30.4%)	158 (32.1%)	83 (50.6%)	46 (15.0%)
Missings	0 (0%)	15 (3.1%)	0 (0%)	21 (6.8%)
Extracurricular PA (h/w) (mean, SD)	4.6 (5.5)	14.4 (6.1)	15.1 (3.8)	3.1 (2.5)
TV (h/w) (mean, SD)	10.0 (5.4)	11.4 (7.0)	9.0 (6.1)	7.6 (4.3)
Other SB (h/w) (mean, SD)	8.9 (6.0)	10.1 (6.0)	7.5 (4.8)	13.5 (5.2)
Follow-up				
Age (mean, SD)	7.6 (0.20)	6.7 (0.45)	7.9 (0.13)	14.6 (0.21)
Working Memory (2-back, *d'*) (mean, SD)	172 (124)	159 (114)	226 (108)	327 (88)

PA: physical activity, TV: television; SB: sedentary behavior; SD: standard deviation

Table 2. Percentage of participants in each category (low/high) of lifestyle activities by sex and maternal education categories

	Extracurricular PA (%)			TV watching (%)			Other SB (%)		
	Low	High	p value[a]	Low	High	p value[a]	Low	High	p value[a]
Younger subcohorts (Valencia, Sabadell and Gipuzkoa)									
Sex (%)									
Female	50.8	46.6		52.4	44.2		43.9	54.4	
Male	49.2	53.4	0.092	47.6	55.8	0.004	56.1	45.6	<0.0001
Maternal education (%)									
Primary	22.3	22.7		18.9	27.6		22.3	23.8	
Secondary	42.9	42.3		40.9	44.4		42.2	42.4	
University	34.9	35	0.977	40.2	28	<0.0001	35.5	33.7	0.775
Older subcohort (Menorca)									
Sex (%)									
Female	52.3	48.9		54.6	45.4		48.7	56	
Male	47.7	51.1	0.338	45.5	54.6	0.079	51.3	44	0.137
Maternal education (%)									
Primary	52.2	52.6		49.5	57.4		54.7	48.1	
Secondary	32.4	29.5		28.9	34.7		30.9	32.7	
University	15.5	18.0	0.815	20.7	7.9	0.017	14.4	19.2	0.453

[a] Fisher's exact test; PA: physical activity, TV: television; SB: sedentary behavior

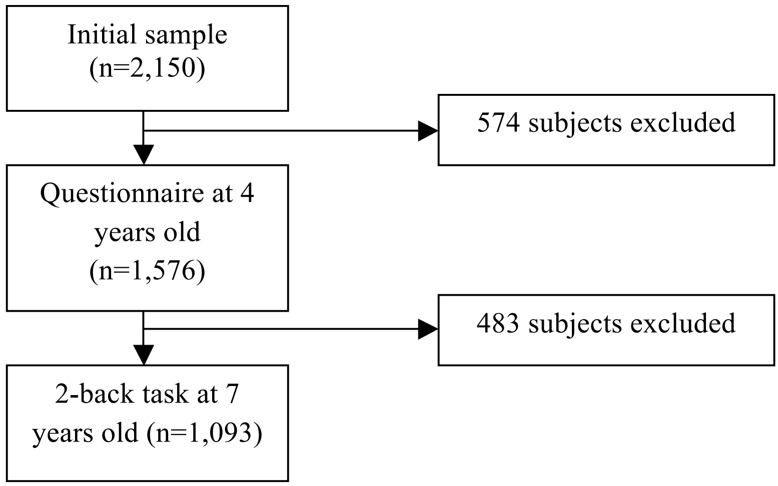
Table 3. Adjusted associations between preschool and school age lifestyle habits and 2-back performance (*d'*) at childhood (Sabadell, Valencia and Gipuzkoa) and adolescence (Menorca)

	Younger subcohorts (Valencia, Sabadell and Gipuzkoa)	Older subcohort (Menorca)
	Coef.[1] (95% CI)	Coef.[2] (95% CI)
Extracurricular PA (ref. high activity)		
All	-8.93 (-24.65, 6.78)	-62.34 (-119.90, -4.79)
Girls	-23.31 (-45.01, -1.62)	-28.60 (-107.29, 50.09)
Boys	6.21 (-16.49, 28.91)	-96.05 (-179.26, -12.85)
TV (ref. low TV watching)		
All	6.21 (-9.93, 22.35)	-8.91 (-60.93, 43.11)
Girls	10.75 (-11.78, 33.27)	9.99 (-63.32, 83.30)
Boys	0.77 (-22.33, 23.88)	-17.43 (-91.48, 56.62)
Other SB (ref. low SB)		
All	3.79 (-12.07, 19.67)	-21.74 (-73.08, 29.61)
Girls	-1.47 (-23.31, 20.37)	17.69 (-53.12, 88.50)
Boys	9.44 (-13.56, 32.44)	-57.93 (-132.64, 16.77)

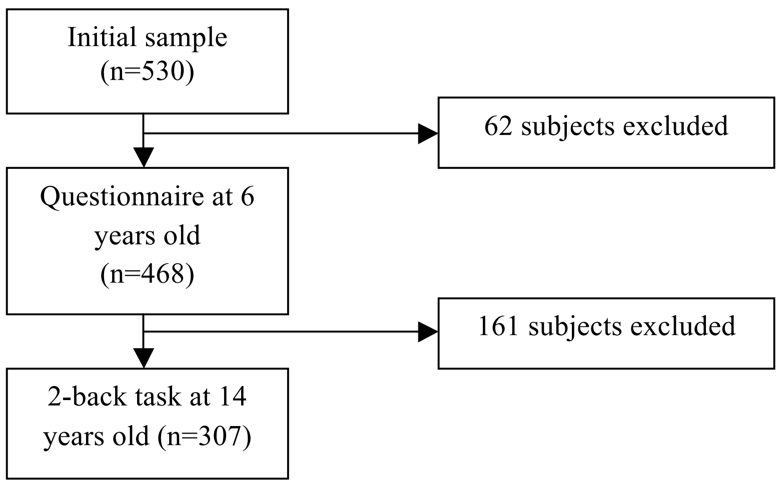
Coef.: coefficient; CI: confidence interval; PA: physical activity; TV: television; SB: sedentary behavior. [1] Tobit models adjusted for age, sex, maternal education, baseline cognitive function and subcohort. [2] Tobit models adjusted for age, sex, maternal education and baseline cognitive function.

Figure 1. Flowchart of the study population

Younger subcohorts (Valencia, Sabadell and Gipuzkoa)



Older subcohort (Menorca)



Supplemental Material: Questionnaires

Extracurricular PA
Menorca: In his/her free time, including extracurricular sport activities, how long does your child spend exercising or playing sports? Less than ½ hour/day, ½ to 1 hour/day, 1 hour/day, 2 hours/day, 3 hours/day, 4 or more hours/day[a]
Gipuzkoa and Sabadell: During a typical week, how long does your child usually practice extracurricular physical activity every day, (e.g. dance/swim lessons) or simply play, run, cycle, skate, swim, etc. (To exclude Wii and trip to school). Specify the activities.
Valencia: How long does your child usually practice extracurricular organized physical activity (e.g. dance/swim lessons) or non-organized as playing outdoors, cycle, run, jump, skate, swim, gym, etc. (To exclude Wii and trip to school).

TV watching
Menorca: How many hours does your child watch TV per week?
Gipuzkoa and Sabadell: How many hours does your child watch TV/videos per day? a-During week days: hours and minutes b-Weekends: hours and minutes
Valencia: How many hours does your child watch TV/videos per day? a-During week days: never or almost never, less than ½ hour per day, between ½ and less than 1 hour/day, 1 hour/day, 2 hours/day, 3 hours/day, 4 or more hours/day[b] b-Weekends: never or almost never, less than ½ hour per day, between ½ and less than 1 hour/day, 1 hour/day, 2 hours/day, 3 hours/day, 4 or more hours/day[b]

Other sedentary behaviors
Menorca: In his/her free time, how long he/she spend watching TV, videos, sedentary games, reading or playing in the computer? Less than 1 hour/day, 1 hour/day, 2 hours/day, 3 hours/day, 4 hours/day, 5 hours/day, 6 or more hours/day[c]
Gipuzkoa and Sabadell: Out of school, how long per day does your child spend in sedentary games or activities (e.g. puzzles, books, dolls, homework, computer/video games)? Exclude TV/videos and Wii-sports. During week days: hours and minutes During weekend: hours and minutes
Valencia: Out of school, how long per day does your child spend in sedentary games or activities (e.g. puzzles, books, dolls, homework, computer/video games)? Exclude TV/videos and Wii-sports. a-During week days: almost never, 1 hour/day, 2 hours/day, 3 hours/day, 4 hours/day, 5 hours/day, 6 or more hours/day[d] b-Weekends: almost never, 1 hour/day, 2 hours/day, 3 hours/day, 4 hours/day, 5 hours/day, 6 or more hours/day[d]

Transformations categorical variables to continuous variables:

[a]Less than ½ hour/day	20 min/d
½ to 1 hour/day	45 min/d
1 hour/day	1 h/d
2 hours/day	2h/d
3 hours/day	3h/d
4 or more hours/day	4h/d

[b]Never or almost never	0.1 h/d
Less than ½ hour per day	20 min/d
Between ½ and less than 1 hour/day	45 min/d
1 hour/day	1 h/d
2 hours/day	2h/d
3 hours/day	3h/d
4 or more hours/day	4h/d

[c]Less than 1 hour/day	30min/d
1 hour/day	1 h/d
2 hours/day	2 h/d
3 hours/day	3 h/d
4 hours/day	4 h/d
5 hours/day	5h/d
6 or more hours/day	6 h/d

[d]Almost never	0.1 h/d
1 hour/day	1 h/d
2 hours/day	2h/d
3 hours/day	3h/d
4 hours/day	4h/d
5 hours/day	5h/d
6 or more hours/day	6 h/d

6. GENERAL DISCUSSION

6.1 Contributions and implications for public health

In the first study, we found longitudinal associations between preschool ADHD symptoms in a population-based birth cohort and worse performance in a cognitive task measuring attention function at 11 years of age. The most altered outcome was speed consistency across the task or HRT-SE. These associations were not confounded by sociodemographic factors.

In the second study, we demonstrated that n-back task is able to detect developmental trajectories in children from 7 to 11 years old from the general population through four repeated administrations in a period of 1 year.

The third study showed that the most active children, in this case based on extracurricular physical activity and commuting to school, obtained better scores in the cognitive tasks at baseline than less active children. All the models were adjusted for sex, maternal education, socioeconomic vulnerability index, and home air pollution. Physical activity levels had no clear effects on cognitive growth trajectories.

In the fourth study, we found associations between sports participation and the cortical morphology in a population-based sample of children. We showed a positive relationship between sports participation and the thickness of brain areas involved in motor control, as well as evidence for the role of team sports versus individual sports participation in the development of brain areas involved in the regulation of behaviours. These associations remained after adjusting the regression models for age, gender and maternal education.

In the fifth study, girls with low levels of extracurricular physical activity at 4 years of age had worse cognitive function (e.g., performance in a WM task) later at age 7. Boys with low physical activity levels at 6 years of age had worse WM task performance at age 14 years in an independent study population. In this study, these associations were obtained after adjusting the statistical models for age, sex, maternal education, and baseline cognitive function.

The first two studies have important implications for the measurement of cognitive development in the context of epidemiological research. The influence of different individual factors such as age, gender or ADHD symptoms in the general population has to be taken into account when the outcome is cognitive development in epidemiology, especially in environmental epidemiology discipline. Environmental epidemiology is characterized by studying the effect of environmental factors on different health outcomes. The results of our first study, in line with previous literature, indicated that speed consistency across a neuropsychological task is the most stable altered cognitive measure in children with ADHD symptoms. We also found other alterations less severe in children with ADHD symptoms, such as increased number of omission errors and delayed HRT in the last block of the task, which indicated a dysfunction of the sustained attention domain. This longitudinal perspective lets us observe the evolution of incipient problems and their consequences in the long term. The second study provided the epidemiological research with a novel methodology to use individual trajectories of cognitive development as an outcome using n-back task. This improvement in neurodevelopment characterization as a process would allow the detection of alterations in the growth pattern caused by social, environmental and other factors. We observed a rapid improvement in d prime (d') score, a measure of signal detection, at younger ages and more pronounced in 2-back than 3-back. The cognitive growth was more pronounced in girls as compared to boys and similar in children with and without ADHD symptoms, although the baseline performance in children with ADHD symptoms was lower. Our results showed delayed cognitive development in children with ADHD symptoms. No improvement of response speed was observed in children with ADHD symptoms with age. This study has implications for basic neuropsychology research, since offers the possibility of testing theories about WM development (188,189). Therefore, with these two studies we showed the importance of including individual cognitive trajectories in epidemiological research and the influence of age, gender and

ADHD symptoms on cognitive measures, in one time point and trajectories.

The remaining three papers highlighted the importance of the promotion of physical activity habits in children. In the third study, we used repeated-measurement design to study the association between physical activity and neurodevelopmental trajectories. We showed that exercising twice per week or more was associated with better 2-back, 3-back and inattentiveness scores at baseline, as compared to "once per week or less" category. Active commuting for more than 50 minutes was associated with better 3-back scores at baseline, as compared to passive commuting. No consistent associations were found between physical activity and cognitive growth trajectories. Overall, our results suggest an earlier maturation of highly active individuals. In the fourth study we explored the cortical morphology related to sports participation. We found that sports participation was associated with increased cortical thickness in areas involved in motor control in healthy children. In addition, we observed morphological differences between team and individual sports. Children enrolled in team sports showed cortical thickness reductions in brain areas related to behavioural regulation. The fifth and last study included in this thesis was a longitudinal study, which aimed to find the long-term effects of lifestyle habits at early ages, such as physical activity and sedentary behaviours, on later cognitive development (i.e., performance in a WM task). The novelty of this study was the inclusion of two different age groups. This study showed that low physical activity levels at preschool age were associated with poorer WM performance at school age and that low physical activity levels at school age did so in adolescence. These data suggested that physical activity habits at early ages influences the WM at school age, which may impact academic achievement. Our results also showed that highly intense and structured physical activities are especially relevant for WM development in adolescence. Overall, these three studies stress the role that an active lifestyle during childhood has in the development of the brain and specific cognitive functions that are of key importance for academic achievement.

Therefore, understanding the potential of physical activity for maximizing brain and cognitive development of children has significant implications for educators and policy makers. Increasing the level of physical activity of children would lead to substantial benefits for the health and fulfilment of the population. EF, which are highly influenced by physical activity in children, are critical for learning, academic achievement, as well as emotional and behavioural regulation. In addition, there could be improvements in the environment, the individual quality of life, community social participation and resilience. More walking and cycling could help reduce greenhouse gas emissions, air pollution, and noise.

6.2 Strengths

The samples of three studies included in this thesis were population-based birth cohorts (INMA and Generation R). Regarding INMA cohort, we used longitudinal data, which allowed inferring the causal relationship between physical activity and the cognitive test performance. All the studies were performed using large sample sizes drawn from the general population, which increased the external validity of the results.

The dimensional perspective of ADHD we used was appropriate in population-based studies. This approach may mitigate the limitation related to the reduced number of children with more severe symptoms, as compared to clinical samples (190).

The neuropsychological tests used have good psychometric characteristics, were administered directly to the children, which reduced the error of the observer, and were computerized. The computerized format of the instruments was essential to our studies, while less comprehensive than formal neuropsychological assessment, the standardization of the computerized format can provide increased objectivity and allows the use of highly precise outcomes such as response speed measured in milliseconds.

The developmental approach we took in these studies, first to improve the neurodevelopmental assessment, and second to disentangle the relationship between physical activity and cognitive growth in children, was the main contribution of this thesis. For the first time, the cognitive trajectories of children with different activity levels have been explored. Regarding the longitudinal study, it has shown the long-term association between physical activity and cognitive function in two critical periods of development.

The second novelty of this thesis was the inclusion of children MRI data from a large cohort with information about sports participation and other important confounding factors. This provided the unique opportunity to test differences in brain morphology associated with sports in healthy children.

6.3 Limitations

The studies included in this thesis have some general weaknesses.

Teachers reported information about ADHD symptoms, thus we lack information about the occurrence of these symptoms in other settings, such as home. We chose teachers for reporting these symptoms because they have a wide knowledge of children's behaviours (191).

The use of cognitive trajectories has intrinsic limitations due to repeated administration of the same task, known as learning or practice effect. Although little practice effect has been shown in n-back task (192), we did not observe important learning of the task across sessions. It was difficult to determine this effect, since we adapted the level of the task to the age of the children because the priority of the study was to compare individual performance. Therefore, the comparison between different age groups to examine the possible practice effect was not fully reliable. Anyway, we decided to assume any possible learning of the task throughout the sessions, so what we considered cognitive growth could also include some practice effect. In our models, the adjustment by session did not remove the age effect; therefore practice did not fully explain the improvement.

Major limitations related to the questionnaires completed by parents exist. Physical activity is difficult to measure in children due to its sporadic nature. Although subjective measures allowed us to obtain information about the context and the type of physical activity, the type of instruments used do not provide accurate intensity information, as opposed to objective measures. It may also imply misclassification, recall bias, perceived desirability of responses, or overestimated levels of activity. Moreover, the questionnaires were completed only once, so we lack information about the evolution of the physical activity habits. In general, we ignore for how long the sport or the physical activity reported has been practiced. So, we are unable to distinguish the effects of different patterns (regarding onset, duration, etc.) on cognitive development. Particularly, our longitudinal study had profound limitations, since the questions about physical activity and sedentary behaviours were different between regions. This heterogeneity in the exposure data complicated the interpretation of the results, although a big effort was done trying to harmonize the answers of the questionnaires. Even though, the harmonization was not the ideal method, which could compromise validity. Another limitation of this study was the different sample size between the younger and the older subcohorts, which could make difficult the interpretation of the results.

A general limitation of all the studies presented here is the selection bias originated not only at the beginning of each project, but also at the follow-up. Therefore, the final samples may be more predisposed to participate in activities than the general population, and this could drive to underestimated effects.

Although the external validity was high in all the studies, it should be mentioned that the prevalence of high social class is higher than in the general population and the studies were carried out in western societies, which can influence both the exposure and the outcome in our studies. The sports and the physical habits of the population not only depend on the social class and the cultural background; the geographical region also influences it. As a consequence, our results were not fully applicable to other contexts.

The associations found in these studies can be explained by residual confounding, such as household income. The inclusion of other covariates related to social class could reduce the effects observed in our studies.

6.4 Future research

Further research should include longitudinal data in adolescents to observe the consistency of our findings across a longer time period of neuropsychological development. A study more focused on WM development from a theoretical point of view is warranted. It has been suggested that WM development is caused by changes in speed (188), while other authors (189) have found that speed and WM changes are related but the relation is not causal. Having almost 3000 children tested four times in a year is extremely rare in developmental psychology. All this data could be used to try to disentangle the relationship existing between the development of response speed and the development of WM.

More studies are needed in order to better understand the role of physical activity in the development of different cognitive domains, specifically EF, at a longitudinal level. This knowledge would provide evidence about the sensitivity of specific cognitive functions to physical activity at different ages. At the same time, this research would highlight the importance of promoting policies related to healthy habits in children.

Regarding our findings in the cortical structure related to sports participation, longitudinal studies should be carried out in order to establish causality and further explore the effect of team versus individual sports on differences in brain development. It would be interesting to add a control group of children who do not participate in sports to study the brain areas related to team sports in comparison to the control group as well as the areas related to individual sports in contrast to the same control group. The inclusion of neuropsychological assessment of specific EF would provide functional correlates of the brain regions that were thinner in children enrolled in team sports in our study. Moreover, a larger sample size is necessary to confirm our results. A larger sample of girls is needed in order to perform the same analysis as we did in boys and compare the results between boys and girls. The inclusion of older participants could help in increasing the number of girls enrolled in sports, since participation in sport peaks at around 11-13 years. The acquisition of longitudinal MRI data would allow studying the effect of physical activity on the cortical thickness change across development, which is better related to high cognitive skills than cortical thickness *per se* (116). Furthermore, longitudinal data of physical activity, in general, and sports participation, in particular, would provide information about the lifestyle trajectories. This information would allow studying the effect of different physical activity temporal patterns on the brain, for example, when it is constant across time, when it is interrupted or when it is started at older ages. In other words, repeated measures of physical activity are needed to figure out the effects of duration, the age at enrolment and the long-term effects on brain maturation, since this habits change considerably across life (40). The objective measurement of physical activity would be useful to get information about intensity, since a more intense activity has increased potential to cause molecular changes in the brain, such as vascular remodelling due to higher cerebral oxygenation.

Further studies should include larger sample sizes to compare the effects of physical activity on WM development by gender at different ages, longer time periods between the exposure and the cognitive outcomes, specific questions about sedentary behaviours and/or objective activity measurement such as accelerometers. Moreover, it is still to be elucidated through mediation analyses whether the effect of early physical activity habits on later WM development is by a direct pathway or, on the contrary, the effect is indirect, by current physical activity habits. The direct pathway would imply that the physical activity at early ages has beneficial effects on later cognitive development that are independent of current levels of physical activity. The mechanisms underlying this association might include neurogenesis and synaptic plasticity, providing a more complex brain at early ages that would increase the potential to form more efficient networks. Otherwise, the mediated pathway would imply that the early life acquisition of healthy habits influences the current levels of physical activity, which in turn increases the cognitive capacities through the different mechanisms described in the introduction. Anyway, both theories highlight the importance of promoting physical activity habits early in life.

7. CONCLUSIONS

The main conclusions of this thesis are:

1. The presence of ADHD symptoms in preschool children was longitudinally associated with a lower performance on the CPT-II. Omission errors seemed to be partly explained by early social and cognitive competences. Slower HRTs showed a direct association with inattention symptoms, particularly in the latest CPT-II blocks. HRT (SE) was strongly related to hyperactivity symptoms.

2. N-back task detected age-related trajectories in primary schoolchildren from the general population. In addition, this task showed different developmental patterns by sex and ADHD symptoms. The repeated administration of this task can be used to study the factors that may alter the cognitive development during childhood.

3. Although medium and high levels of physical activity could be related positively to baseline cognitive performance in schoolchildren, physical activity levels may not have an effect on cognitive trajectories.

4. Sports participation was associated with thicker cortex in areas that are involved in motor control. Children enrolled in team sports versus individual sports showed a more mature cortex in areas related to behavioural regulation.

5. Low physical activity levels at preschool age were associated with poorer WM performance at school age and low physical activity levels at school age did so in adolescence.

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GLOSSARY

ACTH	Adrenocorticotropic hormone
ADHD	Attention Deficit and Hyperactivity Disorder
ANT	Attentional Network Task
BDNF	Brain derived neurotrophic factor
BOLD	Blood oxygenation-level dependent
CBF	Cerebral blood flow
CPT-II	Continuous Performance Test (II)
CRF	Corticotropin-releasing factor
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
ERN	Error-related negativity
ERP	Event-related brain potential
fMRI	Functional Magnetic Resonance Imaging
HPA	Hypothalamic-pituitary-adrenal axis
HRT	Hit Reaction Time
HRT-SE	Hit Reaction Time (Standard Error)
IGF-1	Insulin-like growth factor
IIV	Intra-individual variability
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MVPA	Moderate-to-vigorous-physical activity
NO	Nitric oxide
PA	Physical Activity
PE	Physical Education
PVH	Paraventricular nucleus of the hypothalamus
SB	Sedentary Behaviours
SES	Socioeconomic status
TMS	Transcranial Magnetic Stimulation
VEGF	Vascular endothelial growth factor
WM	Working Memory

ANNEX

Apart from the original papers included in the present thesis, the PhD candidate has also published other papers as a co-author and, apart from INMA, BREATHE and Generation R, she has participated in other projects:

Participation and collaboration in research projects

- INMA (Infancia y Medio Ambiente)
  Role: Participation in neuropsychological testing coordination, protocol design, and data cleaning and processing.

- BREATHE (Brain development and air pollution ultrafine particles in school children)
  Role: Neuropsychological testing protocol and questionnaires design, and fieldwork during 15 months consisting in four visits to the 39 schools for neuropsychological testing of the almost 3,000 participants.

- GENERATION R
  Role: Data cleaning of the questionnaire about sports participation.

- HELIX (The Human Early Life Exposome): Novel tools for integrating early-life environmental exposures and child health across Europe
  Role: Participation in neuropsychological testing coordination and protocol design; cleaning of raw neuropsychological data.

- WALNUTS: Intervention study in adolescents
  Role: Participation in neuropsychological testing coordination and protocol; questionnaires design.

Other papers as a co-author

Marcella Marinelli, Irene Pappa, Mariona Bustamante, Carolina Bonilla, Anna Suarez, Carla M Tiesler, Natalia Vilor-Tejedor, Mohammad Hadi Zafarmand, Mar Alvarez-Pedrerol, Sture Andersson, Marian J Bakermans-Kranenburg, Xavier Estivill, David M Evans, Claudia Flexeder, Joan Fons, Juan R Gonzalez, Monica Guxens, Anke Huss, Marinus H van IJzendoorn, Vincent W V Jaddoe, Jordi Julvez, Jari Lahti, Mónica López-Vicente, Maria-Jose Lopez-Espinosa, Judith Manz, Viara R Mileva-Seitz, Markus Perola, Anu-Katriina Pesonen, Fernando Rivadeneira, Perttu P Salo, Shayan Shahand, Holger Schulz, Marie Standl, Elisabeth Thiering, Nicholas J Timpson, Maties Torrent, André G Uitterlinden, George Davey Smith, Marisa Estarlich, Joachim Heinrich, Katri Räikkönen, Tanja G M Vrijkotte, Henning Tiemeier, Jordi Sunyer: *Heritability and Genome-Wide Association Analyses of Sleep Duration in Children: The EAGLE Consortium*. Sleep 08/2016

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