DOCTORAL THESIS

Patterns of sedentary behavior, physical activity and cognitive outcomes in university young adults:

Relationships with academic achievement and working memory capacity

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A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy in Comprehensive Care and Health Services

2017

UNIVERSITAT DE VIC
UNIVERSITAT CENTRAL DE CATALUNYA
Escola de Doctorat

TESI DOCTORAL

Patrons de comportament sedentari, activitat física i paràmetres cognitius en joves-adults universitaris:

Relacions amb el rendiment acadèmic i la memòria de treball

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Programa de Doctorat en Cures Integrals i Serveis de Salut

2017

UNIVERSITAT DE VIC
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Als meus pares,

Abstract

Introduction. The physical health benefits of sitting less and being more active are well documented. However, little is known about how sedentary behavior patterns, alone or in combination with physical activity, influence cognitive outcomes. In young university adults (i.e. 18-25 years old) an age group characterized by optimal cognitive functioning where academic achievement and cognitive control abilities are essential, research is even scarcer. In this context, this PhD thesis investigated the influence of sedentary behavior and physical activity on cognitive outcomes (working memory and academic achievement) in a sample of young university students.

Methods. Three different studies were conducted. Study 1 validated a short working memory task that was subsequently used in studies 2 and 3. In study 1 (n=325) validity evidence was evaluated by comparing participants' scores on the three shortened complex span tasks (Operation, Symmetry and Rotation Span) with two measures of reasoning ability (Raven's Advanced Progressive Matrices and Number Series) and using confirmatory factor analysis. In addition, Cronbach's coefficient alpha was computed for each complex span task as an index of internal consistency. Study 2 (n=371) and Study 3 (n=132) used cross-sectional designs to examine associations between sedentary behavior and physical activity patterns with working memory capacity and academic achievement. In both studies, academic performance was measured via grade point average and working memory capacity was assessed through the validated shortened complex span task. For physical activity and sedentary behavior variables, Study 2 assessed physical activity intensities (min/week of light, moderate and vigorous PA) and min/day of domain-specific sedentary behavior via self-report (International Physical Activity Questionnaire and Last 7 days sedentary behavior questionnaire). Study 3 employed objective assessments (activPAL™) to determine sedentary behavior variables (total sitting/lying time, total number of breaks in sitting/lying time and sedentary bouts duration), standing time, and physical activity variables (light and moderate-to-vigorous intensity physical activity).

Pearson correlations determined which variables were included in the analysis, and separate multiple linear regression models were performed to examine combined associations between sedentary behavior and physical activity variables with cognitive outcomes.

Results. Study 1 indicated that the short version of the Spanish complex span has satisfying psychometric qualities for assessing working memory capacity in Spanish-speaking university students. Study 2 found that performing more than 3h/week of moderate physical activity was related to increases in working memory capacity, but physical activity intensities were not associated with academic performance. Spending >3h/day seated on weekends while performing non-screen leisure activities was related to reduced working memory capacity, after adjusting for physical activity, while spending >3 h/weekday seated in these sedentary activities or in leisure-forms of screen time were inversely associated with academic performance regardless of physical activity level. Study 3 indicated that, independently of physical activity, the amount of time spent in sedentary bouts of 10-20min during weekdays was positively related to academic achievement while sedentary bouts of 20-30min during weekend days were negatively related to working memory capacity. No significant associations were identified for total sitting time.

Conclusions. Time spent in specific leisure domains of sitting time may detract from academic performance and working memory capacity, independently of physical activity intensity and duration. In addition, preliminary results indicated that breaking prolonged sitting time may differentially impact distinct cognitive outcomes by optimizing cognitive operations associated with academic performance and impairing working memory processes.

Resum (Catalan Version)

Introducció. Seure menys i ser més actiu comporta ferms beneficis en la salut física. No obstant, poca evidència científica existeix sobre com els patrons de comportament sedentari, per si mateixos o en combinació amb l'activitat física, influencien paràmetres cognitius. En joves universitaris (18-25 anys), grup d'edat caracteritzat per gaudir d'un rendiment cognitiu en el punt més òptim on el rendiment acadèmic i les funcions executives són essencials, l'evidència és fins i tot més escassa. En aquest context, l'objectiu de la present tesi doctoral ha estat investigar quina és la influència del comportament sedentari i l'activitat física en paràmetres cognitius (memòria de treball i rendiment acadèmic) en una mostra de joves universitaris.

Metodologia. Tres estudis diferents es van dur a terme. L'Estudi 1 va validar una tasca que mesura la memòria de treball la qual va ser utilitzada en L'estudi 2 i 3. En l'Estudi 1 (n=325), es va avaluar la validesa de la tasca per mesurar la memòria de treball comparant les puntuacions de les tres subtasques que la composen (Operació, Simetria i Rotació) amb les puntuacions de dues mesures que avaluen la capacitat de raonament i utilitzant la tècnica d'anàlisis factorial confirmatori. A més a més, es va obtenir el coeficient d'alfa de Cronbach per a cadascuna de les tres subtasques per tal d'obtenir l'índex de consistència interna. L'Estudi 2 (n=371) i 3 (n=132) van emprar dissenys cros-seccionals per examinar les associacions entre patrons de comportament sedentari i activitat física amb la memòria de treball i el rendiment acadèmic. En ambdós estudis, el rendiment acadèmic es va mesurar a través de la nota mitjana acadèmica obtinguda en estudis universitaris, i la memòria de treball es va mesurar amb la tasca descrita en l'Estudi 1. En relació a l'activitat física i comportament sedentari, l'Estudi 2 va mesurar activitat física (minuts/setmana d'activitat física lleugera, moderada o vigorosa) i minuts/dia de temps assegut en cada domini a través de dos qüestionaris. L'Estudi 3 va emprar mesures objectives (activPAL™) per mesurar les variables relatives al comportament sedentari (temps total assegut/estirat, nombre total d'interrupcions en el temps assegut/estirat i el temps assegut en duracions específiques), temps dempeus i activitat física (lleugera i moderada-vigorosa).

Correlacions de Pearson van determinar quines variables van ser incloses en l'anàlisi i es van dur a terme models múltiples de regressió lineals per tal d'examinar les associacions entre les variables de comportament sedentari i activitat física amb els paràmetres cognitius.

Resultats. L'estudi 1 va indicar que la versió de les tasca creada en Castellà posseïa qualitats psicomètriques satisfactòries per mesurar la memòria de treball en població universitària bilingüe català/castellanoparlant. L'estudi 2 va mostrar que >3h/setmana d'activitat física moderada s'associa amb un augment del rendiment de la memòria de treball però no amb el rendiment acadèmic. Passar >3 h assegut en un dia no laborable mentre es realitzen activitats d'oci (que no incloguin estar davant d'una pantalla) es va relacionar amb pitjor rendiment de la memòria de treball després d'ajustar els resultats per l'activitat física. Alhora, >3h assegut en un dia laborable realitzant activitats d'oci (que incloguin o no estar davant d'una pantalla), es van associar inversament amb el rendiment acadèmic, independentment de l'activitat física. L'estudi 3 va indicar que independentment de l'activitat física, passar més temps assegut en períodes de 10-20min en dies laborables es va relacionar amb augments del rendiment acadèmic mentre que passar més temps assegut en períodes de 20-30min en dies no laborables es va relacionar negativament amb la memòria de treball.

Conclusions. El temps assegut destinat a determinades activitats durant el lleure pot comportar disminucions en el rendiment acadèmic i la memòria de treball independentment de l'activitat física que es realitzi. Alhora, els resultats preliminars indiquen que interrompre períodes de temps assegut prolongat pot tenir un impacte distint sobre la cognició, optimitzant processos cognitius associats amb el rendiment acadèmic i reduint-ne aquells associats amb la memòria de treball.

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List of abbreviations

PA	Physical Activity
LIPA	Light-intensity Physical Activity
MPA	Moderate-intensity Physical Activity
VPA	Vigorous-intensity Physical Activity
MVPA	Moderate-to-vigorous intensity Physical Activity
RCT	Randomized controlled trial
CRF	Cardiorespiratory Fitness
WMC	Working Memory Capacity
SB	Sedentary Behavior
MET	Metabolic Equivalent Task
VO2max	Maximal Oxygen Uptake
IPAQ	International Physical Activity Questionnaire
SIT-Q-7days	Last 7-day Sedentary Behavior Questionnaire
ERP	Event related potentials

List of tables, figures and images

Preamble

"The mind is not immediately affected by all parts of the body but only by the brain - or perhaps just by the small part of it which is said to contain the 'common sense" (Descartes, 1641). Far from the 17th century dualism, where theories defended the body as being independent to the mind, it is currently well accepted that the body affects our brain and vice versa. As we will see through the present PhD dissertation, lifestyle factors such as physical activity and sedentary behavior do not only influence physical health parameters but also the central nervous system.

Public health guidelines and national and international public health policies (e.g. T*he Global strategy on diet, physical activity and health* by the World Health Organization; the Spanish *Strategy for nutrition physical activity and prevention of obesity* – NAOS-; or the *Plan to promote health through physical activity in Catalonia* – PAAS-) highlight the scientific consensus about the benefits of being physically active for maintaining and improving physical health. However, despite the current existing evidence on the importance of physical activity for maintaining and improving brain health – mainly reported on seniors and kids – such brain benefits seem not to be yet considered in public health agendas.

In this context, emerging research aims to change this trend. For instance, the benefits of a physically active lifestyle for brain health are being discussed at the Physical Activity Guidelines for Americans Advisory Committee in the United States, which is currently convening to disseminate the second edition of the Physical Activity Guidelines for Americans in Fall 2018. In addition, other initiatives such as the *Global Council on Brain Health,* which gathers scientists, health professionals, scholars and policy experts from around the world, are developing recommendations on physical activity and brain health specifically for older adults.

Apart from physical activity, current epidemiological studies are revealing increases in the prevalence of sedentary behaviors (i.e. activities in a sitting or reclining posture that require low energy expenditure). Compelling evidence indicates the negative impact of prolonged sedentary behavior on adults´ physical health. A few national guidelines, such as Australia's Physical Activity and Sedentary Behavior Guidelines (2014), the UK guidelines "Start active, stay active" (2011), and the Canadian Sedentary Behavior guidelines (2012), recommend minimizing the time spent being sedentary to reduce physical health risks in children, youth, and adults. In contrast, the association between sedentary behaviors and brain health remains under investigated. Given that sedentary behavior has emerged as a unique determinant of health, it is important to understand the extent to which this behavior can also impact cognition and brain health.

Thesis overview

The first part of the thesis is the background which provides a brief introduction to the research topics. It is divided in four subsections; the first section (A) is focused on the two health-related behaviors that are the key elements of the thesis (physical activity and sedentary behavior); the second section (B) provides a framework for the main outcomes of the study (working memory capacity and academic achievement); the third section (C) summarizes the evidence in regards to physical activity and sedentary behaviors with cognitive outcomes and brain health in children and older adults; while the last section (D) provides a review of the evidence examining physical activity and sedentary behaviors with cognitive outcomes and brain health in young adults. Afterwards, a rationale and the aims of the thesis are outlined. Subsequently, three interrelated papers that are published, in press or under review are presented. The first paper provides validity evidence of a complex span task for Spanish population and is published in the *Psychological Assessment Journal* as a short report. The second paper examined associations between context-specific sitting time and physical activity with working memory capacity and academic achievement in young adults. This study is published *in the European Journal of Public Health.* The third study examined relationships between objectively measured patterns of sedentary behavior, physical activity and academic achievement in college students. This manuscript is currently under review at Journal of Sports Sciences. A complimentary analysis for this last study examining associations between objective measures of physical activity and working memory capacity is also presented. Subsequently, the results obtained along the thesis are analyzed and critically discussed, considerations about the strengths and limitations of the research are outlined, and implications and future research are highlighted. Lastly, the overall conclusions of the research conducted during the thesis are presented.

BACKGROUND

SECTION A. PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

Introduction

This first section of the PhD thesis will clarify key concepts relevant to the topic of the study. Throughout this dissertation, we will use the definitions stated here, which are proposed and supported by the most recent scientific literature (Sedentary Behaviour Research Network, 2017; Garber et al., 2011). Then, the section will present an overview of the prevalence of physical activity (PA) and sedentary behavior (SB) patterns and its relation to physical health outcomes, as well as a description of the existing measurement tools that have been used to quantify patterns of PA and sedentary behaviors.

1. Defining key concepts: Physical Activity and Sedentary Behavior

1.1 Physical Activity

PA is defined as "any bodily movement produced by skeletal muscles that requires energy expenditure above the resting metabolic rate" (Caspersen, Powell, & Christenson, 1985). PA includes many activities that are undertaken in different daily-living domains that include vocation, transportation, household work and leisure time. Although PA is closely related to exercise and physical fitness constructs, these have different meanings. When PA is planned, structured, repetitive and usually performed to improve or maintain physical fitness, the appropriate term is *exercise* (Caspersen et al., 1985). Whereas *physical fitness* refers to a set of attributes that people have or achieve. Cardiorespiratory endurance, body composition and muscular strength are examples of health-related components of physical fitness (Caspersen et al., 1985; Garber et al., 2011). It is PA in its broadest meaning that is the subject of this PhD thesis.

In the context of epidemiology and health, five components of PA are usually considered: duration (total time per day or per week engaged in the activity); frequency (how often PA is undertaken over time, e.g. a day, week, month), type of PA (e.g. aerobic, muscle-strengthening, stretching), setting where the activity is performed (leisure-time, vocation, commuting, etc…) and PA intensity (magnitude of the effort required to perform an activity) (Shephard, 2016a; Bauman, Phongsavan, Schoeppe, & Owen 2006). A recent position statement proposed the standardization of PA intensity in order to gain greater consistency in terminology across studies (Norton, Norton, & Sadgrove, 2010). According to the standard terminology suggested, PA intensity can be categorized into the following descriptive terms:

- Light intensity physical activity (LIPA)
  - An aerobic activity that does not cause a noticeable change in breathing rate.
  - An intensity that can be sustained for at least 60 minutes.
- Moderate intensity PA (MPA):
  - An aerobic activity that can be conducted whilst maintaining a conversation uninterrupted.
  - An intensity that may last between 30 and 60 minutes.
- Vigorous physical activity (VPA) and high intensity PA
  - An aerobic activity in which a conversation generally cannot be maintained uninterrupted.
  - An intensity that may last up to about 30 minutes or high intensity PA when it generally cannot be sustained for longer than about 10 minutes.

Intensity cut-offs are also suggested for distinct types of objectively measured PA intensity, (Garber et al., 2011; American College of Sports Medicine 2013). Objectively measured PA intensity can be either expressed in metabolic equivalent of tasks (METs; a physiological measure that reflects the energy cost of PA), heart-rate parameters (e.g. maximal heart rate, %HRmax, heart rate reserve, %HRR) or in maximal oxygen uptake (VO2max). However, although VO_{2max} parameters can be used to infer PA intensity, it should be noted that this measure is commonly used in exercise research to measure individuals' aerobic capacity as a component of physical fitness rather than PA intensity. Table 1 shows the approximate classification of PA according to the American College of Sports Medicine (2013).

Table 1. Classification of objectively measured PA intensities

	METS	$\%HR_{max}$	%HRR	VO_{2max}
Very light PA	<2	<57	<30	<37
LIPA	2.0-2.9	57-63	30-39	37-45
MPA	3.0-5.9	64-76	40-59	46-63
VPA	6.0-8.2	77-95	60-89	64-90
Near-maximal to maximal PA	≥8.8	≥96	≥90	≥91

Table adapted from the American College of Sports Medicine (2013) and Garber et al., 2011. PA= physical activity, LIPA= light physical activity, MPA= moderate physical activity, VPA= vigorous physical activity, %HRmax = maximal heart rate, %HRR= heart rate reserve, VO2max= maximal oxygen uptake.

1.2 Sedentary Behavior

SB is distinct from physical inactivity, although they are often used interchangeably in the literature. Physical inactivity refers to those not meeting physical activity guidelines (Sedentary Behaviour Research Network, 2012). In contrast, SB, a term derived from the Latin "sedere", which means "to sit" refer to those waking activities characterized by an energy expenditure of ≤1.5 METs while in a sitting or reclining posture (Sedentary Behaviour Research Network, 2017). Sedentary behaviors occur within different contexts of our daily-living, which can include sitting during commuting, in the workplace and during leisure time. Sedentary behaviors are not merely the absence of PA, as SB and low PA levels represent complementary aspects of human behavior that may entail different physiological effects (Hamilton, Hamilton, & Zderic, 2007). Thus, throughout waking hours, most individuals engage in both PA and SB (see Fig. 1).

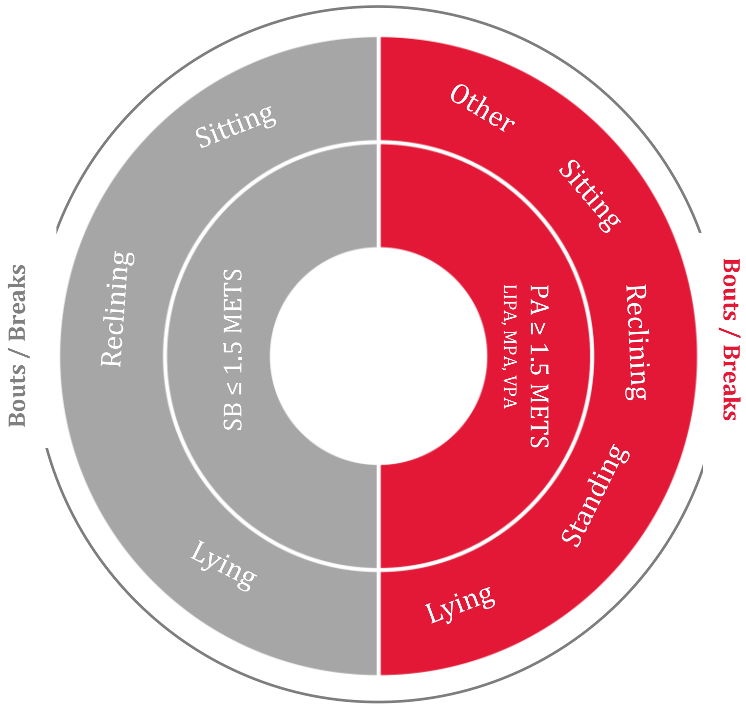

Fig. 1. llustration of how physical activity (PA) and sedentary behavior (SB) constructs fit together and its components. Adapted from SBRN, 2017.

SB patterns refer to the manner in which SB is accumulated throughout the day/week during waking hours. It can be described according to several dimensions: the timing when sedentary behavior occurs (context), duration (hrs/min) and frequency of sedentary bouts and breaks (Sedentary Behaviour Research Network, 2017). As research on SB is increasing rapidly, there is a need to clarify and standardize emerging terminology. The Sedentary Behavior Research Network (SBRN) that in 2012 operationally defined the term "sedentary behavior" (Sedentary Behaviour Research Network, 2012) has recently created a Terminology Consensus to address this issue. Table 2 shows a summary of selected key terms that will be relevant for the present manuscript (Sedentary Behaviour Research Network, 2017).

Table 2. Definition of selected terms for sedentary behavior derived from the Terminology Consensus (Sedentary Behaviour Research Network, 2017).

Term	**Definition**	**Examples**
Sedentary Behavior	Any waking behavior that requires ≤1.5 METs, while in a sitting, reclining or lying posture. Term used when contextual information is available (e.g. questionnaires).	Use of electronic devices while sitting, reclining or lying; reading/writing/ talking while sitting, sitting in a bus, car or train, sitting while doing homework, sitting at school.
Sedentary time	The time spent for any duration or in any context in sedentary behaviors. Term used when contextual information is absent (e.g. activity-monitor devices).	
Sedentary bout	A period of uninterrupted sedentary time.	
Sedentary interruptions/breaks	A non-sedentary bout in between two sedentary bouts.	
Standing	A position in which one has or is maintaining an upright position while supported by one's feet.	Standing in a line, standing for a hallway discussion, use of electronic devices (e.g., television, computer, tablet, phone) while standing.
Standing time	The time spent for any duration or in any context while standing.	
Sitting	A position in which one's weight is supported by one's buttocks rather than one's feet, and in which one's back is upright.	
Reclining	A body position between sitting and lying.	Lounging/slouching on a chair or couch while sedentary.
Lying	Being in a horizontal position on a supporting surface.	Lying on a couch, bed or floor while sedentary.
Sedentary Behavior Pattern	The manner in which SB is accumulated throughout the day/week while awake	Timing, duration and frequency of sedentary bouts and breaks.

All behaviors refer to waking activities.

2. Patterns of physical activity and sedentary behavior in modern societies

2.1 Prevalence of Physical Activity

According to a study that assessed self-reported PA levels from 146 countries, which represents 93.3% of the world's population, 23.3% of adults are physically inactive; not meet the PA guidelines (Sallis et al., 2016). In Europe, a survey conducted of 15 member states in 2002 indicated that two thirds of the adult population did not reach recommended levels of PA (Sjöström, Oja, Hagströmer, & Smith, 2006). Spanish adults reported lower inactivity trends with 33.6% of the population not reaching recommended levels of PA according to the Spanish' national health surveillance system in 2011-2012. In Catalonia, the prevalence of inactivity in 2014 was slightly lower according to a national survey (Departament de Salut 2015), which reported that a 32.2% of adults (15-69 years old) were considered inactive.

In younger populations, the prevalence of physical inactivity is higher. Self-reported data that included 105 countries indicated that the proportion of adolescents (13-15 years old) not meeting PA recommendations of at least 60 minutes/day of moderate-to-vigorous physical activity (MVPA) was 80.3% (Hallal et al., 2012). However, another study that objectively measured PA in 2.200 adolescents (12-17 years old) across nine European countries found that a 59% of adolescents were considered inactive (Ruiz et al., 2011). Similarly, Spanish adolescents showed comparable trends using objectively-measured physical inactivity outcomes (59.2%) (Moliner-Urdiales et al., 2009).

2.2 Prevalence of Sedentary Behavior

Parallel to physical inactivity, epidemiological studies have revealed increases in the prevalence of sedentary behaviors. Studies that examined overall patterns of activity in adults' daily lives, showed that we spend approximately 60% of daily total waking hours in sedentary behaviors, with the remainder mainly distributed to LIPA (35%), and MVPA (5%) –see Fig. 2, (Healy, et al., 2008a; Matthews et al., 2008).

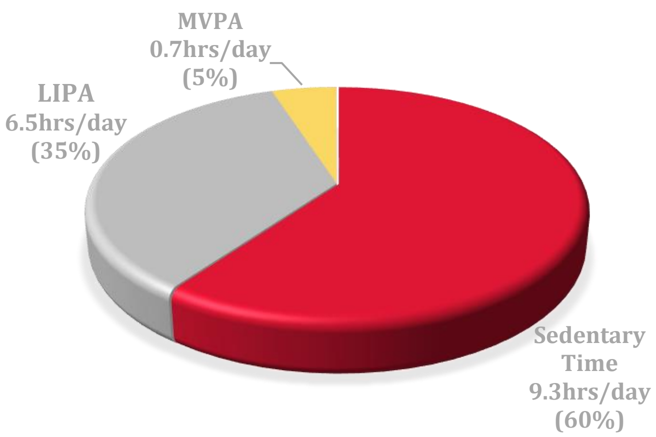

Fig. 2. Distributions of moderate-to-vigorous physical activity (MVPA), light intensity physical activity (LIPA), and sedentary time during adults' waking hours.

American and Australian adults (20-87 years old) spent approximately 8-9 hours/day in objectively-measured sedentary time (Healy, et al., 2008a; Matthews et al., 2008). Objective measures of SB are limited for European adult population (Loyen, et al., 2016a). A recent systematic review of cross-European studies that measured self-reported sitting time in adults (≥18 years old) could not draw conclusions about population levels of sedentary time. Yet, large variations in sedentary time between studies were found. Portugal showed the lowest prevalence of sitting time (2.50hours/day) while United Kingdom obtained the highest prevalence (10.33hours/day) (Bauman et al., 2011; Lakerveld et al., 2015; Loyen, et al., 2016a). In addition, the review identified that the Northern European population reported more time spent sitting than the population of Southern Europe (Loyen, et al., 2016a). For the Spanish population, a study that analyzed data from the Special Eurobarometer 412, indicated that Spanish adults (N=982; mean age of all study sample= 50.1, SD= 17.5) reported a median of 4 hours/day spent seated, and 8.9% spent more than 7.5 hours/day seated (Loyen, van Der Ploeg, Bauman, Brug, & Lakerveld, 2016b). However, another study that assessed prevalence of sitting time indicated that 21.1% of Spanish adults (N= 1549; 18-65 years old) were seated for more than 9hours/day (Bauman et al., 2011). Importantly, both studies estimated total sitting time via a single-item question (Loyen et al., 2016b used a variation of the short version of the International Physical Activity Questionnaire and Bauman et al., 2011 the original version). To the best of our knowledge, studies examining the prevalence of sedentary behaviors specifically in the Catalan population have not been published.

For younger populations, a recent systematic review examined 24 cross-European studies to describe the variation in population levels of sedentary time in children (0-12 years old) and adolescent population (13-18 years old). The authors found that, although the assessment methods for SB were quite heterogeneous between studies, children and adolescents from Eastern-European countries (i.e. Bulgaria, Slovakia, Ukraine) tended to show higher levels of sedentary time compared to the rest of Europe (Verloigne et al., 2016). Another large-scale (N= 2.200) epidemiological study that compared regional differences (Southern Europe –Greece, Italy, Spain vs. Central-Northern Europe –Austria, Belgium, France, Germany, Hungary, and Sweden) in objectively measured sedentary time found that adolescents in Southern Europe had slightly higher sedentary time (2.7%; i.e., 12-15 minutes/day) compared to Central-Northern Europe (Ruiz et al., 2011). In addition, this study showed that European adolescents (12.5-17.5 years old) spent, on average, 9hours/day in sedentary behaviors (Ruiz et al., 2011).

2.3 A focus on young adult population

Young adulthood is an understudied age in which there is an increase in negative health behavior choices (VanKim, Laska, Ehlinger, Lust & Story, 2010). Epidemiological studies state that one of the largest declines in PA levels occur in adolescents and young adults (Dumith, Gigante, Domingues, & Kohl, 2011), while high sitting times are also reported in this stage of the lifespan (Bauman et al., 2011; Bennie et al., 2013). Specifically for college students, 30% of Spanish undergraduates accumulated 30min/day at least five days a week of objectively determined MVPA (Arias-Palencia et al., 2015) while 10 hours/day were spent in sedentary behaviors (Arias-Palencia et al., 2015; Felez-Nobrega, Hillman, Cirera, & Puig-Ribera, 2017a). Increased sedentariness at work is an international concern (Ng & Popkin, 2012) as the predominant mode of working is office-based, and as a result many people spend their work-day seated (Church et al., 2011; Straker & Mathiassen, 2009). In addition, college students spend considerable time in a setting that promotes SB and it has been suggested that environments which require long periods of physical inactivity may contribute to establishing long-term SB patterns that persist throughout adulthood (Leslie, Sparling, & Owen, 2001; Owen, Salmon, Fotheringham, & Leslie, 2000). Higher levels of education are associated with higher levels of sitting time and college students will probably occupy sedentary jobs (Bennie et al., 2013; Sjöström et al., 2006). Thus, decreasing PA levels and increased sedentariness in this age group are of special concern.

3. Epidemiology of physical activity and sedentary behavior in relation to physical health: an overview

According to the World Health Organization (2010), health promotion is “the process of enabling people to increase control over, and to improve, their health. It moves beyond a focus on individual behaviour towards a wide range of social and environmental interventions”. Health promotion and disease prevention are not only important to improve societies’ quality of life, but also to keep economies healthy. Clearly, populations’ low levels of phyisical activity leads to governments’ higher health care expenditure. In 2016, the PA (Series 2) Executive Committee, published an article in which they examined the economic burden of physical inactivity on five major non-comunicable diseases (coronary heart disease, stroke, type 2 diabetes, breast cancer, and colon cancer) (Ding et al., 2016). Based on data from 142 countries (which represents 93.2% of world’s population), they conservatively estimated that in 2013, total economic burden of physical inactitvity was more than 67.5 billion dollars (accounting for health-care and productivity losses). Examining specific regions in more detail, the direct cost attributable to physical inactivity ranged from 0.6 billion dollars in Africa to 25.7 billion dollars in North America (11.7 nillion dolars in Europe). These values represented (on average) a total health-care expenditure ranging between

0.22% in Southeast Asia to 0.84% in North-America (0.55% in Europe) (Ding et al., 2016). Concretely in Spain, the direct cost attributable to physical inactivty were estimated to be more than 2 billion dollars in 2013, where 70.4% of total direct costs were paid by the public sector, 6.8% by private sectors and 22.8% by households (Ding et al., 2016).

3.1 Physical activity, physical inactivity and physical health

Beneficial effects of being physically active on physical health have been examined for years. Current PA recommendations for health in the adult population include participation in 150 minutes of aerobic MPA or 75 minutes of aerobic VPA per week, performed in bouts of at least 10 minutes in duration. In addition, two or more days per week of muscle-strengthening activities should be incorporated (World Health Organization, 2010). Engaging in PA regularly, reduces the incidence of hypertension, arthritis, stroke (Warburton, Nicol, & Bredin, 2006), and it is estimated that 6 to 10% of major non-communicable diseases including coronary heart disease, type 2 diabetes, and specific types of cancer could be avoided if physical inactivity was eradicated (Lee et al., 2012). Thus, achieving PA recommendations would reduce the risk of all-cause mortality and major causes of death (e.g. cardiovascular disease and cancer) in adults (Kruk, 2007; Lee, Folsom, & Blair, 2003; Rockhill et al., 2001; Sofi, Capalbo, Cesari, Abbate, & Gensini, 2008; Thune & Furberg, 2001).

Epidemiologic longitudinal studies also acknowladge the long-term health benefits of PA. A systematic review that included fifteen longitudinal studies (>5-year follow up) in more than 500 healthy adults (18-85 years old) concluded that PA seems to have a positive long-term influence on coronay heart disease, type 2 diabetes mellius, weight gain and obesity (Reiner, Niermann, Jekauc, & Woll, 2013).

Probably because some diseases associated with physical inactivity manifest in adult years (Andersen, Riddoch, & Kriemler, 2011; Hardman & Stensel, 2009), a greater number of studies regarding the beneficial effects of PA on health status has been conducted in adult population. However, epidemiological studies also support the positive link between higher levels of PA and better health in youngers' population. PA recommendations for health in youth include the accumulation of at least 60 minutes of MVPA every day (mainly aerobic activity). And muscle and bone strengthen activities at least 3 times per week (World Health Organization, 2010). Scientific evidence shows that PA helps in developing a healthy cardiovascular system (i.e. heart and lungs), which prevents the risk factors of cardiovascular diseases (Andersen, Riddoch, Kriemler, & Hills, 2011), helps developing healthy musculoskeletal tissues (i.e. bones, muscles and joints), neuromuscular awareness in terms of coordination and movement control (World Health Organization, 2010) and protects againts obesity (Jiménez-Pavón, Kelly, & Reilly, 2010).

3.2 Sedentary behavior and physical health

The concept of SB and its impact on physical health is not novel. Back in 1950s Jeremy Morris' work set the historical roots of the relation between SB and health (Morris, Heady, Raffle, Roberts, & Parks, 1953). However, in the recent years, sedentary behaviors, their biological mechanisms and their impact on health have emerged as a new focus for research.

Multiple systematic reviews and meta-analysis have concluded that SB is linked to an increased risk of cardiovascular diseases, type 2 diabetes incidence, certain types of cancer incidence and premature mortality in adults (Biswas et al., 2015; Chau et al., 2013; Lynch, 2010; Proper, Singh, van Mechelen, & Chinapaw, 2011; Rezende, Rodrigues Lopes, Rey-López, Matsudo, & Luiz, 2014; Thorp, Owen, Neuhaus, & Dunstan, 2011; Wilmot et al., 2012). To further clarify the causal relationships between SB and health outcomes, future prospective studies using higher methodologic quality are needed. In addition, more efforts should be placed on better understanding the specific properties of SB that relate to diminished health outcomes.

Relatively new epidemiological evidence indicates that apart from the duration of sedentary behaviors, the manner in which it is accumulated may be important for health outcomes (Healy, et al., 2008b). Breaking up prolonged sitting time has been associated with enhanced adults´ cardiometabolic health (Bailey & Locke, 2015; Chastin et al., 2015); however, the optimal and most beneficial type, intensity and frequency of PA to interrupt SB remains unclear (Bailey & Locke, 2015; Benatti & Ried-Larsen, 2015). While interrupting sitting time with frequent brief bouts of LIPA (activities that require an energy expenditure of <3METs; Norton et al., 2010), but not standing, have enhanced the cardiometabolic profile of healthy adults (Bailey & Locke, 2015), other research pointed out that replacing SB with LIPA PA and standing may be enough to improve metabolic parameters in physically inactive and type 2 diabetes individuals, but not in young habitually physically active subjects for whom higher intensities (MVPA) may be needed (Benatti & Ried-Larsen, 2015).

In youth, research that has examined associations between SB and health outcomes is less conclusive (Carson, Hunter, Kuzik, Gray, Poitras, Chaput, Saunders, Katzmarzyk, Okely, Connor Gorber, Kho, Sampson, Lee, & Tremblay, 2016; Chinapaw, Altenburg, & Brug, 2015; Chinapaw, Proper, Brug, van Mechelen, & Singh, 2011; Cliff et al., 2016; Tremblay, LeBlanc, Kho, Saunders, Larouche, Colley, Goldfield, Gorber, et al., 2011). A recent systematic review suggested that there is an association between higher amounts of screen time/TV viewing and physical health outcomes such as higher clustered cardiometabolic risk scores, lower fitness and unfavourable body composition (Carson, et al., 2016). However, specifically for body composition, another recent systematic review of reviews that also conducted an analysis of causality concluded that associations between SB and adiposity in children and adolescents are small to very small and there is little to no evidence that this association is causal (Biddle, García Bengoechea, & Wiesner, 2017). Yet, when accounting for MVPA or focusing on studies with low risk of bias, another recent meta-analysis concluded that there is limited evidence that SB is associated with health in children and adolescents (Cliff et al., 2016). It is important to note that the vast majority of current evidence is based on cross-sectional studies and on self or parent reported TV viewing time, thus, higher quality studies using reliable and valid SB measures should confirm observational evidence.

3.3 Interactions of physical activity and sedentary behavior with physical health parameters

A key question that remains to be answered is whether the associations between sedentary behaviors and health outcomes are independent of PA levels. The meta-analysis by Biswas et al. (2015) suggested that prolonged sedentary time was independently associated with deleterious health outcomes, regardless of PA (i.e. all-cause mortality, cardiovascular disease, diabetes). Nonetheless, other studies found that PA can attenuate the association between sedentary behaviors and health outcomes (Chau et al., 2013; Ekelund et al., 2016). The most recent systematic review and meta-analysis by Ekelund and colleagues (2016) found that the mortality risk related to more than 8h per day of sitting can be counteracted by high levels of MPA (60-75min of MPA per day). However, this high activity level attenuates, but does not eliminate the increased risk associated with high TV-viewing time (Ekelund et al., 2016).

4. Measuring physical activity and sedentary behavior in free-living conditions

Due to the importance of sedentary behaviors and PA as health-related behaviors, their precise measurement in free-living environments is critical to surveillance and epidemiological studies investigating trends and associations with health and disease. PA and SB can be assessed through different techniques that can mainly be categorized into subjective and objective measures.

4.1 Self-reported measures of physical activity and sedentary behaviors

Self-reported measures, which include self/interviewed administered questionnaires and activity diaries, are considered subjective measures as they measure a persons' ability to recall their behavior either from a specified time-frame (past day, past 7 days, past month, past year), throughout the day or about typical patterns of behavior (Healy et al., 2011; Sallis & Saelens, 2000; Helmerhorst, Brage, Warren, Besson & Ekelund, 2012).

Recall questionnaires are the most common form of assessing self-reported PA and SB because they can be implemented on a large scale, they are relatively inexpensive, do not alter the behavior under study and they provide additional information about the context/domain where the behavior takes place, which is not obtained when using objective measurements (Healy et al., 2011; Sallis & Saelens, 2000). However, self-reported instruments present some limitations. Questionnaires are susceptible to random and systematic reporting errors as recalling behaviors that are sporadic or intermittent in nature may be challenging (Atkin et al., 2012) and they are exposed to social desirability bias (Jago, Baranowski, Baranowski, Cullen, & Thompson, 2006). Also, especially for reporting PA, confusions may appear when categorizing time spent in MPA and VPA as these terms may be ambiguous, and categorization is based on subjective perceptions that are influenced by participants' physical fitness and duration of the activity (Bouchard, Shephard & Stephens, 1994). Thus, as validity and reliability of questionnaires to assess PA and SB remains questioned, further efforts should be directed towards developing accurate methods for obtaining the highest quality of information (Atkin et al., 2012; Bauman, Phongsavan, Schoeppe, & Owen, 2006; Shephard & Vuillemin, 2003).

4.1.1 Physical activity questionnaires

Several questionnaires are available for measuring PA (Helmerhorst et al., 2012). Recent reviews have estimated that there are 85 validated questionnaires for assessing PA in adults (van Poppel, Chinapaw, Mokkink, van Mechelen, & Terwee, 2010), 61 for youth (Chinapaw, Mokkink, van Poppel, van Mechelen, & Terwee, 2010) and 13 for older adults (Forsén et al., 2010). From those questionnaires, the International Physical Activity Questionnaire (IPAQ) may be one of the most widely used in adults. In 1998-1999, a consensus group of PA experts developed eight initial pilot versions of the instrument, − four long and four short versions − that could be either self-administered or administered by phone interview. Validity and reliability of the instruments were first tested in twelve different countries (Craig et al., 2003) and subsequently, short and long versions of the IPAQ have been translated into several languages and these versions are supported by psychometric studies conducted across different countries (e.g. Hagströmer, Oja, & Sjöström, 2006; Roman-Viñas et al., 2010; Román Viñas, Ribas Barba, Ngo, & Serra Majem, 2013).

The International Physical Activity Questionnaire (IPAQ)

The IPAQ is designed to assess the levels of habitual PA in adults (i.e. 18–65 years old; Craig et al., 2003). The questionnaire assesses min/week of walking, MPA and VPA across different domains (i.e. work, domestic and gardening activities, transport and leisure).

A recent study that examined the level of agreement between the IPAQ-long form and objective accelerometry across eight different countries observed relative agreement between measures (r=0.05-0.37) with participants over-reporting total PA and total time in MVPA (Cerin et al., 2016). The short form of the IPAQ showed similar correlations between total PA level and objective assessments (r= 0.09 to 0.39) and overestimated physical activity levels by 36 to 173% (Lee, Macfarlane, Lam, & Stewart, 2011).

Psychometrical properties of the Spanish and Catalan versions of the IPAQ have been examined using accelerometers as a criterion (Roman-Viñas et al. 2010; Román Viñas et al. 2013). The Spanish long form version of the questionnaire showed acceptable validity for total PA and for time spent in VPA ($r=0.29$, $p<0.05$; $r=0.30$, $p<0.05$). However, the questionnaire showed poor validity for reporting MPA, as no significant correlation was found between measures. The long form of the IPAQ showed good reliability coefficients for total PA, VPA and MPA (r=0.82; r=0.79; r=0.89). Similar psychometric properties were obtained with the short Catalan version of the IPAQ (Román Viñas et al. 2013).

4.1.2 Sedentary behavior questionnaires

SB questionnaires asses global measures of sitting time via a single item question of total daily sitting time, multiple sedentary behaviors that occur in different domains such as at work, commuting, leisure-time, exclusively daily TV-viewing, or work-place sitting time.

Evidence regarding questionnaire validity for assessing SB is somewhat equivocal. While some evidence indicates that sitting time is over-reported compared to objective criterion measures (Besson, Brage, Jakes, Ekelund, & Wareham, 2010; Busschaert et al., 2015; Wijndaele et al., 2014) other studies report that questionnaires underestimate sitting time (Chinapaw, Slootmaker, Schuit, van Zuidam, & van Mechelen, 2009; Gardiner et al., 2011; Marshall, Miller, Burton, & Brown, 2010).

The Last 7-day Sedentary Behavior Questionnaire (SIT-Q-7d)

One of the most comprehensive self-reported questionnaire is the Last 7-day Sedentary Behavior Questionnaire -SIT-Q-7d- (Wijndaele et al., 2014). This tool is designed to assess volume and patterns of sedentary time in adults. The questionnaire assesses total and domain-specific SB with a reference frame of the last week (last 7 days). It provides estimations for week and weekend–specific sitting time (minutes/day) across five different domains: meals, transportation, occupation, leisure screen time and time spent sedentary in other activities.

The SIT-Q-7days has relatively strong validity correlations for the total sitting time (English version: rho 0.22; Dutch version: rho 0,52) and domain-specific sedentary time (rho 0.21-0.76) while test-retest reliability for total sedentary time is fair to good (English version: rho 0.53; Dutch version: 0.68) and poor to excellent for domain-specific sedentary time (English version: 0.45 - 0.76; Dutch version: 0.36 - 0.66). More importantly, unlike other studies that validated questionnaires in specific populations (Clark et al., 2013; Kozey-Keadle, Libertine, Staudenmayer, & Freedson, 2012; Rosenberg et al., 2010), psychometric properties of the SIT-Q-7days were assessed in general adult population (English sample: 49.5 ± 7.3 years old; Flemish sample: 39.4 ± 11.1 years old) (Wijndaele et al., 2014).

Compared to the number of available PA questionnaires validated for Spanish-speaking population (Guirao-Goris, Cabrero-García, Moreno Pina, & Muñoz-Mendoza, 2009), Spanish versions of SB questionnaires and studies examining their psychometric properties are scarce. To our knowledge, only two studies examined validity of self-reported sitting time in Spanish-population. Roman-Viñas et al. (2010) examined validity of the Spanish version of the IPAQ (long-form) which assesses total daily sitting time via a single item question, and Rey-Lopez et al. (2012) designed and examined psychometric properties of the HELENA sedentary behaviors questionnaire in adolescent population. Thus, more research is needed to develop specific questionnaires for different age-population groups (e.g. adolescents, adults, older adults) and further examine their validity and reliability for Spanish-speaking populations.

4.2 Objective monitoring of physical activity and sedentary behaviors: Motion sensors

In the past few years, the number of papers published in the scientific literature as well as the range of commercially available objective monitors has increased rapidly (Troiano 2005; Shephard 2016b). Objective monitors such as pedometers and accelerometers offer greater validity and reliability compared to self-reported data as they can provide more accurate assessments (Troiano 2005; Shephard 2016b).

4.2.1 Measuring physical activity via accelerometry

Accelerometery-based monitors have been widely used to measure PA in free-living environments in both observation and interventional studies (Wijndaele et al., 2015). To illustrate this point, it has been estimated that accelerometry data has been collected from more than 275.000 adults across 36 countries (Wijndaele et al., 2015).

Accelerometers (e.g. ActiGraph GT3X, GENEA) measure body accelerations. Through proprietary algorithms, these accelerations are converted in activity counts occurring in a specific time interval, which is referred as an epoch (Chen & Bassett, 2005). The analysis of these counts allow researchers to estimate parameters of PA such as intensity, with greater accelerations providing more counts, frequency and duration (Shephard 2016b; Warren et al. 2010).

Although the use of accelerometers provides valid and objective estimates of individuals' PA in free-living conditions, these activity monitors are not without their limitations.

Several variables in terms of monitors' calibration, data collection and data processing criteria must be considered as the interpretation of the resulting data may differ (Migueles et al., 2017; Troiano, 2005). In addition, although accelerometers are accurate for measuring locomotor movement, which accounts for a great amount of adults' daily PA (Welk, 2002), these monitors are not able to measure all type of physical activities. In particular, they cannot account for upper body movements (mostly because the instrument is commonly positioned at the waist), they cannot capture load-carrying activities, (because they do not require changes in acceleration patterns), cyclic movements or water-based activities (Warren et al., 2010). Another limitation of PA monitors is that there is little consensus about the number of days of monitoring necessary to reflect a valid measurement of habitual PA (Keadle et al., 2017; Trost, Pate, Freedson, Sallis, & Taylor, 2000). In addition, short periods of recording may also be biased by response to activity measurement, weekly or seasonal changes (Kristensen et al., 2008). Lastly, while objective measurements provide more accurate measures of PA compared to structured questionnaires, they cannot gather domain specific information which is important for public health surveillance and for context-specific interventional studies (Bauman et al., 2006).

4.2.2 Measuring sedentary behavior via accelerometry

Due to the initial interest in understanding the relationship between MVPA and health outcomes (Haskell, Lee, Pate, Powell, & Blair, 2007; Powell, Paluch, & Blair, 2011) research efforts were placed to accurately capture dynamic components related to motion (Chen & Bassett, 2005; Chen, Janz, Zhu, & Brychta, 2012; Plasqui, Bonomi, & Westerterp, 2013). However, another research focus has emerged emphasizing the importance of non-motion behaviors.

Accelerometers can be broadly classified into those that mainly provide an approximation of energy expenditure (e.g. Actigraph) or those that primarily aim to classify posture (e.g. activPAL) (Granat, 2012). While energy-expenditure devices provide accurate measurements for PA, their ability to capture static behaviors has been questioned (Kozey-Keadle, Libertine, Lyden, Staudenmayer, & Freedson, 2011).

Energy-expenditure devices categorize SB based on periods of inactivity. A <100 counts per minute criteria has been widely used as a cut-off threshold for SB (Healy et al., 2008a; Matthews et al., 2008). However this criterion has not been selected from empirical studies and conclusions of sitting time using such thresholds must be interpreted cautiously (Atkin et al., 2012). Some studies reported overestimations of <100 accelerometer cut-point for estimating total sitting time in free-living conditions (Hart, Ainsworth, & Tudor-locke, 2011) while others reported underestimations of sitting time using <100 threshold (Kozey-Keadle et al., 2011). It has been suggested that a threshold of <150 counts per minute could be more appropriate to accurately measure sitting time (Kim, Barry, & Kang, 2015; Kozey-Keadle et al., 2011). More importantly, energy-expenditure devices are not sufficiently sensitive to distinguish between sitting/lying and standing time as both behaviors produce <100 counts per minute. This is an important limitation as standing is not considered a SB (Sedentary Behaviour Research Network, 2012).

The activPAL™: the golden standard for measuring SB

The activPAL™ (PAL Technologies Ltd., Glasgow, UK) was developed to overcome these limitations (see image 1). This accelerometry-based device uses accelerations and body inclinations to accurately capture body positions and it has been currently considered the gold standard for measuring sedentary behaviors in detail (Byrom, Stratton, Mc Carthy, & Muehlhausen, 2016). Concretely, recent evidence indicates that the activPAL™ is more accurate than waist- and wrist-worn accelerometers in objectively measuring sitting and standing activities (An, Kim, & Lee, 2017). Moreover, it is important not to only examine total accumulated sedentary time as it may not provide all features of SB. In that sense, the activPAL also captures sedentary breaks and bouts information (Lyden, Kozey Keadle, Staudenmayer, & Freedson, 2012) which has been found to influence health outcomes (Benatti & Ried-Larsen, 2015; Chastin, Egerton, Leask, & Stamatakis, 2015; Healy et al., 2008b). A part from SB, the activPAL also provides accurate estimated times of free-living PA intensity categories in adults and adolescents (Dowd, Harrington, & Donnelly, 2012; Lyden, Keadle, Staudenmayer, & Freedson, 2016).

Image 1. activPAL™ placement

Despite these significant improvements in SB measurements, there is still a lack of consensus regarding the wear period – in terms of number of days necessary to estimate habitual sedentary patterns and wearing hours – and protocols for data processing (Atkin et al., 2012; Edwardson et al., 2017). In addition, posture-based devices are usually worn for 24 hours (Edwardson et al., 2017), so, differentiating between sleep and wakeful lying/sitting is important. However, this is out of the scope of accelerometers' algorithms and, although this is an emerging area, empirical accepted waking time identification protocols have not yet been developed (Byrom et al., 2016; Edwardson et al., 2017). Despite these limitations, there is no doubt that accelerometer-devices are a valuable tool to measure health-related behaviors in free-living conditions.

Summary of key issues. Section A

- Inactivity is a distinct concept than sedentary behavior.
- Psychometric properties of sedentary behavior questionnaires are comparable to those obtained with self-reported measures of physical activity.
- Spanish versions of sedentary behavior questionnaires and studies examining their psychometric properties are scarce.
- Objective monitors provide more accurate assessments, but they cannot gather domain specific information.
- To measure sedentary behavior patterns in detail, accelerometers that primarily aim to classify posture have been currently considered the gold standard.
- 30% of Spanish undergraduates accumulated 30min/day at least five days a week of objectively determined MVPA while 10 hours/day were spent in sedentary behaviors.
- Physical activity has many benefits for adults' physical health and for youngers' population.
- Sedentary behavior is linked to deleterious health effects in adults, but in research is less conclusive in younger populations.
- A key question that remains to be answered is whether these associations between sedentary behaviors and health outcomes are independent of physical activity levels.

SECTION B. HIGHER-ORDER COGNITIVE ABILITIES: SPOTLIGHT ON WORKING MEMORY

Introduction

When thinking about the self, Marvin Minsky made these reflections:

"It often does more harm than good to force definitions on things we don't understand. Besides, only in logic and mathematics do definitions ever capture concepts perfectly. The things we deal with in practical life are usually too complicated to be represented by neat, compact expressions. Especially when it comes to understand minds, we still know so little that we can't be sure our ideas about psychology are even aimed in the right directions. In any case, one must not mistake defining things for knowing what they are. You can know what a tiger is without defining it. You may define a tiger, yet know scarcely anything about it"

(Minsky, 1986).

These thoughts can be applied to define the term "cognition". Cognition, a term derived from the Latin "cognoscere" (get to know), is a complex phenomenon, which words cannot easily characterize. The Oxford dictionary of English defines cognition as "the mental action or process of acquiring knowledge and understating through thought, experience, and the senses". Similarly, the American Psychological Association defines cognition as "processes of knowing, including attending, remembering, and reasoning; also, the content of the processes, such as concepts and memories". To better understand the cognitive system, cognition can be divided in different neuropsychological processes or cognitive abilities (e.g. language, perception, cognitive control, etc.).

This section of the manuscript, will conceptualize key cognitive constructs relevant to the topic of the study (i.e. cognitive control, working memory) as well as describe their implications for everyday life. Methods for measuring working memory capacity will also be covered and explanations of the PhD variables of interests will be provided.

1. Cognitive control

1.1 The concept of cognitive control and its implications for everyday functioning

Research on cognitive control (also known as executive function or executive control) set the historical roots in neuropsychological studies of patients with frontal lobe damage back in the XIX century. One of the most well-known case was the patient Phineas Gage, who demonstrated severe problems in controlling and regulating his behavior, having difficulties in managing his everyday life functioning after a large iron rod broke though his skull and destroyed much of his left frontal lobe, following an explosion (Harlow 1848).

One of the first authors that initially defined the term cognitive control was the neuropsychologist Muriel Lezak. Lezak introduced the term as "the dimension of human behavior that deals with "how" behavior is expressed" (she mentioned executive functions instead of cognitive control; Lezak, 1983). The complexity of the term is reflected in the difficulty for operationally defining it. A few selected examples of definitions of cognitive control/executive functions proposed in the literature are:

"Cognitive control is the ability to orchestrate thought and action in accordance with internal goals".

(Miller & Cohen, 2001).

"Executive functions are a generic term that refers to a variety of different capacities that enable purposeful, goal-directed behavior, including behavioral regulation, working memory, planning and organizational skills, and self-monitoring".

(Stuss & Benson, 1986).

"A collection of top-down control processes used when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible".

(Diamond, 2013).

"Executive functions encompass metacognitive processes that enable efficient planning, execution, verification, and regulation of goal directed behavior. There is no single agreed upon definition of executive functions"

(Oosterlaan, Scheres, & Sergeant, 2005)

Despite diversity of definitions, currently there is general agreement that cognitive control involves three main components: inhibition, cognitive flexibility and working memory (e.g. Diamond, 2013; Miyake et al., 2000). Inhibition refers to the ability to inhibit dominant, automatic or prepotent responses or selectively attend to relevent information among a field of non-relevant information in the stimulus environment (Miyake et al., 2000). Cognitive flexibility, also known as mental set shifting, is conceptualized as the ability to multitask, change perspectives and adjust to new demands, rules or priorities (Diamond, 2013). Working memory allows individuals to hold information in mind and manipulate it (Baddeley & Hitch 1994) (see section B. Part 2. *Working Memory* for an extended conceptualization and further information on working memory). Whether these components constitute distinct but related processes, or there is a single underlying ability that can explain all the components is a question that remains under debate (de Frias, Dixon, & Strauss, 2006; Duncan, Emslie, Williams, Johnson, & Freer, 1996; Friedman & Miyake, 2017; Miyake et al., 2000). Recently, the most accepted postulate is that cognitive control show both unitary and diversity, as different cognitive control abilities correlate with one another sharing a common underlying ability, but also show some separability (see Friedman & Miyake, 2017 for review).

Cognitive control skills are useful in many different contexts of life. They are relevant for school and vocational success (Cowan & Alloway, 2008; Bailey, 2007) and creativity (Dietrich, 2004). Cognitive control abilities are shown to be compromised across mental health disorders including schizophrenia, major depressive disorder, attention deficit, bipolar and obsessive compulsive (see Snyder, Miyake, & Hankin, 2015 for review). In addition, cognitive control has significant implications for physical health (Allan, McMinn, & Daly, 2016; Williams & Thayer, 2009), for succeeding in the community and for ethical behavior (e.g. Denson, Pedersen, Friese, Hahm, & Roberts, 2011).

1.2 Development of cognitive control and neural underpinnings

In early observations, because people with severe lesions in the frontal lobe had low performance on tests that traditionally measured cognitive control (e.g. Milner, 1963), it was suggested that cognitive control abilities uniquely depended on the frontal lobes. Currently, it is widely accepted that the prefrontal cortex (Brodmann areas 8–11, 24, 25, 32, 45–47) plays a critical role in cognitive control, but it is also supported by other brain regions (e.g. subcortical and posterior areas, thalamic pathways) (see Alvarez & Emory, 2006; Royall et al., 2002 for review).

Through the course of evolution, the frontal lobes are the brain region that developed the last and the most extensively in human beings. It reaches its greatest development in the human brain occupying approximately one-third of the neocortex (Fuster, 1980). Ontogenetically, the frontal lobes are the regions that maturate the last (i.e. late adolescence), which concurs with the improvement of cognitive control abilities during childhood and adolescence (Anderson, 2002; Best & Miller, 2010). Moreover, the frontal lobes are one of the brain areas most vulnerable to the effects of aging (Jurado & Rosselli, 2007) and cognitive control abilities seem to decline earlier when compared with other cognitive domains (De Luca et al., 2003). However, it is important to note that the development and the decline of cognitive control is heterogeneous, since some cognitive control abilities develop and decline earlier than others (see Jurado & Rosselli, 2007 for review).

2. Working Memory

Working memory[1] is the component of cognitive control that this PhD thesis will focus on. Briefly, the rationale for studying working memory lies in its implications for school and vocational success as well as for everyday functioning. In addition, working memory capacity (WMC) is one of the few cognitive control components that is highly related to fluid intelligence (Friedman et al., 2006; Shipstead, Harrison, & Engle, 2016) (see Section B part 2.2). Lastly, considering the complexity of the construct, an accurate assessment of cognitive control abilities is not simple, and no goal standard exist. However, compelling evidence has demonstrated validity, reliability and standardized procedures for measuring WMC (see Section B part 2.4).

2.1 What is working memory and its implications for everyday functioning

Working Memory is one of the core concepts of cognitive control. It refers to a complex system that allows for the holding and manipulation of information in mind to access goal-relevant information and supports complex cognition (Baddeley & Hitch, 1994; Broadway & Engle, 2010). Individual differences in WMC have been extensively examined in clinical, educational, personality, and developmental research disciplines. WMC plays a fundamental role in predicting performance on a broad range of higher order capabilities (i.e. reasoning, problem solving, decision making; for reviews, see Conway, Jarrold, Kane, Miyake, & Towse, 2007; Unsworth, Redick, Heitz, Broadway, & Engle, 2009) and it is highly correlated with intelligence (Oberauer,

1 According to Wilhelm, Hildebrandt & Oberauer (2013), in this manuscript we use working memory to refer to “a hypothetical cognitive system responsible for providing access to information required for ongoing cognitive processes”, and working-memory capacity to refer to “an individual differences construct reflecting the limited capacity of a person's working memory”.

Schulze, Wilhelm, & Süß, 2005; Shipstead et al., 2016). In addition, studies showed that WMC is strongly related to learning, note taking in class, overall academic achievement, and further children's reading, writing, mathematics, and science performance (St Clair-Thompson & Gatercole, 2006; Cowan & Alloway, 2008; Kiewra & Benton, 1988; Cowan et al., 2005, Palladino, Cornoldi, De Beni, & Pazzaglia, 2001, Abu-Rabia, 2003; Gathercole, Pickering, Knight, & Stegmann, 2004; Yuan, Steedle, Shavelson, Alonzo, & Oppezzo, 2006). WMC is also related with the ability to prevent mind wandering during tasks requiring focus (Kane & McVay, 2012). In clinical settings, working memory has a significant role as lower levels of WMC have been considered a core cognitive deficit in theories of aging, Alzheimer's disease, reading disability and schizophrenia (Snyder et al., 2015).

2.2 Working memory in relation to fluid intelligence

Fluid intelligence (Gf) is defined as the ability to understand complex relationships allowing to flexibly adapt thinking to solve novel problems or situations (Cattell, 1941). Gf is influenced by biological factors on intellectual development and allows one to act independently of previous acquired knowledge (Cattell, 1941; Horn & Cattell, 1967). In contrast, crystallized intelligence is influenced by formal and informal educations factors and cultural assimilation (Cattell, 1941; Horn & Cattell, 1967). Both fluid and crystalized intelligence develop rapidly during childhood. However, while fluid intelligence increases until neural maturation is reached (adolescence) and declines thereafter, crystallized intelligence increases during adulthood (Baltes, Staudinger, & Lindenberger, 1999; Cunningham, Clayton, & Overton, 1975).

Results from several latent variable analyses suggest that although not identical constructs, WMC is highly correlated with fluid intelligence (Kane, Hambrick, & Conway, 2005; Shipstead et al., 2016), accounting for one-third to one-half of variance in fluid intelligence (Conway, Kane, & Engle, 2003).

2.3 A focus on young adult population

Emerging adulthood (18-25 years) is a life period replete of developmental challenges. It is the age of possibilities, the age of identity explorations, instability, and the self-centered age (Arnett, 2004). In addition, risky behaviors may be most tolerated or even promoted during emerging adulthood (Sussman & Arnett, 2014). Cognitive control abilities in general, and working memory in particular, become crucial in this stage as they are important skills for facing the challenges of the XXI century society, for managing everyday life functioning, as well as for achieving life goals and career progress (e.g. troubleshooting in unexpected situations, maintaining discipline, resist temptations, creating structure and schedules).

2.4 Measuring working memory capacity

A wide variety of cognitive tasks are used to measure WMC. They can be mainly categorized in N-back tasks, simple and complex span tasks. N-back tasks have been more frequently used to study the neural underpinnings of working memory (e.g. Cunningham et al., 1975), because stimulus presentation and response requirements are less complex, while simple and complex span tasks are commonly used to examine individual-differences in WMC (e.g. Palladino et al., 2001). Yet, although all three measures are considered WM tasks, they share little variance (Redick & Lindsey, 2013). N-back task (Kirchner, 1958), require participants to indicate whether a stimulus (e.g. letter) presented on a screen matched the stimulus previously presented. Simple span tasks (Turner & Engle, 1989) (i.e. digit span, word span, or visuospatial span tasks) require holding in mind a brief list of words, letters, positions, or digits with no requirement of transforming the information (Lezak, 1983; Rosen & Engle, 1997). Validity of a WMC measurement using simple span tasks is controversial as, some studies suggest that simple span tasks may be more associated with short-term memory than WMC (Unsworth & Engle, 2007). Contrarily, complex span tasks (CSTs; Daneman & Carpenter, 1980; Turner & Engle, 1989) interleave a processing task (e.g., operation span [OSpan]—solving simple equations; symmetry span [SymSpan]—judging image symmetries; rotation span [RotSpan]—judging rotated letters) with a short list of to-be-remembered items (e.g., OSpan, letters; SymSpan, square positions; RotSpan, arrows; Fig 3). This paradigm allows for the assessment of a dynamic working memory process, which involves both processing and storage capacity (Turner & Engle, 1989).

In experimental psychology, CSTs are the most widely accepted instruments to measure WMC, and their use is supported by standardized administration and scoring procedures (Conway, Kane, & Bunting, 2005; Redick et al., 2012). It is important to note that, although complex span tasks are called WMC measures, performance is also influenced by attention-control processes and other executive control components (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Kane, Conway, Hambrick, & Engle, 2007).

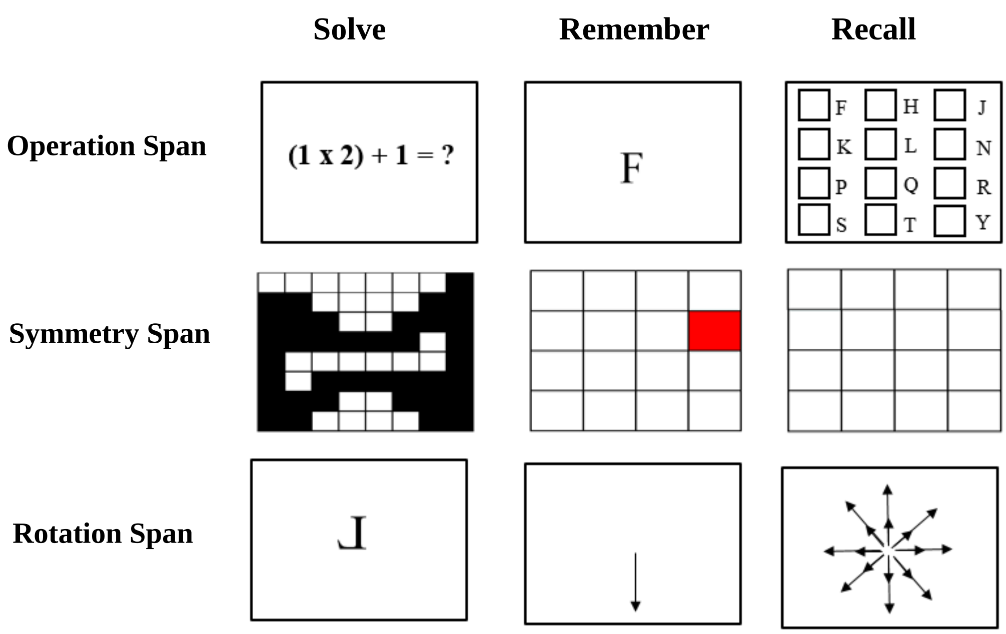

Fig. 3. llustration of the Complex Span Task used in the study

For Spanish-speaking populations, some psychometric test batteries include simple span tasks (such as verbal span and the letter-number sequencing) and normative data for this population are included in some manuals such as the WAIS-III and the WMS-III (Wechsler, 1987,1997, 2004a, 2004b). However, these tools are not complex span measures. To our knowledge, only an automated group-administrable OSpan version that is based on a Dutch OSpan task by De Neys, D'Ydewalle, Schaeken, and Vos (2002) was developed and validated in Spanish-speaking samples (Pardo-Vázquez & Fernández-Rey, 2008). Importantly, no single task can measure WMC capacity. To obtain an accurate measure of WMC it is highly recommended to use more than one WMC indicator (Conway et al 2005; Foster et al., 2015) as scores on any single indicator would be driven by the ability of interest (WMC) and other systematic and random influences such as the nature of the storage component itself (Conway et al., 2005; Foster et al., 2015). Nonetheless, this recommendation entails an extended length of time for both researchers and participants. Long and tedious experimental sessions can lead to decreases in participant motivation and a reduction of attention resources that negatively influence CST performance (Heitz, Schrock, Payne, & Engle, 2008). To manage this issue, recent studies have developed shorter versions of the CSTs, allowing the reduction of test administration time without affecting the accuracy measurement of the construct (Foster et al., 2015; Gonthier, Thomassin, & Roulin, 2016; Oswald, McAbee, Redick, & Hambrick, 2015). Most available CSTs—both long and short versions—have been developed and validated for English- and French-speaking populations, but not Spanish (Conway et al., 2005; Foster et al., 2015; Gonthier et al., 2016; Oswald et al., 2015; Redick et al., 2012). Thus, Spanish-speaking population is limited in using CSTs to measure WMC.

3. Academic achievement

Academic success is a key determinant in college students' future prospects as better academic achievement can facilitate more opportunities in terms of employment (French, Homer, Popovici,

& Robins, 2015). Furthermore, as is has been previously outlined, children and adolesecents' academic achievement is related to WMC (St Clair-Thompson & Gatercole, 2006).

WMC measures have been mainly used in laboratory-based settings, which may be considered isolated from real world situations. Thus, WMC measures as well as other traditional neuropsychological assessments can raise questions in terms of ecological validity. In this context, the academic achievement, is another pivotal variable of the present thesis which accounts for applied aspects of cognition in a more ecologically valid context.

Summary of key issues. Section B

- Cognitive control involves three core components: inhibition, cognitive flexibility and working memory.
- Working memory refers to a complex system that allows to hold and manipulate information in mind to access goal-relevant information and support complex cognition.
- WMC has many implications for school and vocational success as well as for everyday functioning and it is highly related to fluid intelligence.
- Emerging adulthood (18-25 years) is a life period replete of developmental challenges. Cognitive control abilities in general and working memory in particular, become crucial in this stage of life.
- A wide variety of cognitive tasks are used to measure WMC. CSTs are the most widely accepted instruments to measure WMC in experimental psychology.
- Complex Span Task paradigm allows for the assessment of a dynamic working memory (WM) process, which involves both processing and storage capacity.
- Most available CSTs—both long and short versions—have been developed and validated for English- and French-speaking populations, but not Spanish.
- As WMC measures may lack of ecological validity, the academic achievement is another pivotal variable of the present thesis.

SECTION C. IMPACT OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIORS ON COGNITION AND BRAIN HEALTH

Introduction

The study of health-related behaviors –specifically PA and cardiorespiratory fitness (CRF)– and brain health has mainly been focused on developmental or aging populations. One reason for this preferential focus of research is that children and older adults are in a stage of life where brain and cognition shows high inter-individual variability compared to young and middle-aged adulthood. Thus, researchers argued that it is during these critical periods when PA benefits can have its strongest effects (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011b). Contrarily, there is a dearth of evidence in young adults (see section D).

The aim of this section is to provide a brief state of the art regarding how PA and SB patterns, which are the cornerstones of the present thesis, can influence cognitive outcomes and markers of brain health (i.e. brain structure and function) in children and older populations.

1. Physical activity, sedentary behavior, and cognitive outcomes

1.1 Studies in children

1.1.1 Academic achievement

To date, research examining the relationship of PA on academic achievement outcomes has predominantly focused on school-aged children (Castelli et al., 2014). This formative research is valuable for developing PA interventions before, during, or after school time as well as informing policy makers about potential programs that can be effective in improving academic outcomes. However, scarce research has focused on understanding how PA influences academic outcomes in young university adults despite the fact that they are required to excel in academic performance (see section D).

Evidence regarding the link between PA and academic achievement emerged several decades ago (Ismail, 1967). In the past few years several systematic reviews addressing these relationships have been published (e.g. Donnelly et al., 2016; Howie & Pate, 2012). Some reviews concluded that time spent in PA does not detract from educational outcomes, and it may even be associated with improved academic achievement (e.g. Sullivan, Kuzel, Vaandering, & Chen, 2017); however, the evidence is remains inconsistent. For example, in 2008, the Centers for Disease Control and Prevention (2010) reviewed 50 studies examining relationships between PA (including school-based PA, classroom PA, extracurricular PA) and academic performance (measures of academic achievement, academic behavior, cognitive skills and attitudes). Although findings were positively interpreted and the report concluded that "physical education and PA may help advance academic performance for many students and should not hinder academic progress"; more than half of all examined associations were positive (50.5%), while 48% were not significant and 1.5% were negative (Centers for Disease Control and Prevention, 2010). A recent systematic review provides new insights into this area suggesting that while physically active lessons generally improved academic achievement, increases in activity during physical education had a null effect on academic achievement (Donnelly et al., 2016). However, systematic reviews examining PA and academics have noted methodological concerns including weak study designs, small samples and inconsistent exposures and outcomes (Centers for Disease Control and Prevention, 2010; Howie & Pate, 2012; Donnelly et al., 2016; Singh, Uijtdewilligen, Twisk, Mechelen, & Chinapaw, 2012). As an example, the review by Singh et al. (2012) included 10 observational/longitudinal studies, and four intervention studies, with only two of them considered to have high methodological quality. Future studies using more rigorous methodological approaches are needed to provide stronger evidence regarding the link between PA and academics in children.

Relative to SB, some reviews examined the impact of sedentary behaviors on a wide range of different cognitive outcomes including the academic achievement (Carson et al., 2016; Tremblay, LeBlanc, Kho, Saunders, Larouche, Colley, Goldfield, & Gorber, 2011). These reviews conclude that higher durations of self-reported reading and homework were associated with higher academic achievement (Carson et al., 2016) while watching TV for more than 2 hours per day was negatively associated with academic achievement (Tremblay et al., 2011). However, these conclusions should be interpreted cautiously as reviews were based on weak to moderate quality evidence and most of studies measured screen-based SB and have not considered a wider range of sedentary activities (Carson et al., 2015; Carson et al., 2016).

More recently, few studies have objectively measured SB or used a combination of both objective and subjective measures (Esteban-Cornejo et al., 2015; Haapala et al., 2017; Lopes, Santos, Mota, Pereira, & Lopes, 2017; Syväoja et al., 2014). Similar to previous conclusions of review studies, cross-sectional evidence of self-reported SB indicates that higher durations of time spent in doing homework/reading were associated with higher academic achievement (Esteban-Cornejo et al., 2015) while specific domains of self-reported SB during leisure-time (e.g. watching TV, Internet surfing, sitting doing nothing) were negatively associated with academic performance (Esteban-Cornejo et al., 2015, Syväoja et al., 2013). On the other hand, evidence employing objective measures (accelerometry) found that total/leisure-sitting time was not associated with indices of academic achievement (Syväoja et al., 2013; Lopes, Santos, Mota, Pereira, & Lopes, 2017; Esteban-Cornejo et al., 2015).

To the best of our knowledge, only one study provides initial evidence about the potential interactions between SB and PA relative to academic achievement in children (Haapala et al., 2017). Lower levels of MVPA and higher levels of sitting time (measured using a combined heart rate and movement sensor) and particularly their combination were related to poorer reading skills in boys. In girls, higher levels of sitting time had a small association with better arithmetic skills (Haapala et al., 2017).

1.1.2 Cognition

Apart from measures of academic performance, researchers also measured select aspects of cognition using a wide variety of tests. To date, several reviews and meta-analysis that examined the relationships between PA/fitness and cognition in children have been published (e.g. Donnelly et al., 2016; Howie & Pate, 2012; Keeley & Fox, 2009; Sibley & Etnier, 2003; Tomporowski, Davis, Miller, & Naglieri, 2008).

In 2003, Sibley & Etnier conducted a meta-analysis and concluded that PA participation was related to cognitive performance with an overall effect size of 0.32. PA was related to all cognitive categories examined (i.e. perceptual skills, developmental level/academic readiness, intelligent quotient, achievement, math test, verbal test and other) except for memory. However, the meta-analysis included both acute and regular exercise training studies, and the number of memory outcomes was limited at that time. In addition, the authors warned the questionable methodological rigor of most of studies (Sibley & Etnier, 2003).

Thirteen years later, among other aims, Donnelly et al. (2016), conducted a systematic review examining the influence of PA/fitness on children's cognitive performance. Correlational evidence showed that higher level of fitness/PA was positively related to a wide variety of cognitive measures (e.g. attention, cognitive control, processing speed) after adjusting for different confounders (SES, body mas index, grade, IQ). The review found that the few existing longitudinal and prospective studies (N=4) supported cross-sectional studies indicating that higher fitness was associated with better cognitive performance. Although characteristics of the PA interventions (N=10) were heterogeneous (e.g. aerobic, skill-based games), PA interventions have a positive effect on cognition, and more specifically in cognitive control-dependent tasks (Donnelly et al., 2016). Another recent meta-analysis in children and adolescents examined the effect PA interventions on cognition (Vazou, Pesce, Lakes, & Smiley-Oyen, 2016). The authors categorized three types of PA (aerobic, motor skill, cognitively engaging) and four comparison groups (no treatment, academic, traditional physical education and aerobic). They found that overall PA interventions had a small to moderate effect on cognition (0.46) (Vazou, Pesce, Lakes, & Smiley-Oyen, 2016). PA interventions had no effect on cognition compared to traditional PE (0.09) or aerobic group (0.80), but importantly, PA interventions had moderate positive effects compared to no treatment (0.86) or academic content (0.57) (Vazou et al., 2016).

Specifically, for working memory processes, the impact of PA is controversial. Scudder et al. (2014) found that fitness levels were related to better WMC (measured using the n-back task paradigm) in children. Similarly, a randomized controlled trial (RCT) study showed improvements in WMC (measured using a modified Sternberg task) for the PA group but not for the waitlist control group (Kamijo et al., 2011). Conversely, other studies found that objectively measured MVPA was not related to spatial working memory (measured using a Corsi block task and a visual memory span task) in adolescents (Syväoja, Tammelin, Ahonen, Kankaanpää, & Kantomaa, 2014; Van der Niet et al., 2014).

Overall, the evidence suggests that PA has a positive influence on cognition. However, more research is needed to further elucidate which components of cognition can benefit the most by PA, which are the mechanisms responsible for PA benefits, and how to better characterize PA to obtain such benefits in terms of type, amount, frequency and timing (Donnelly et al., 2016; Howie & Pate, 2012; Keeley & Fox, 2009; Sibley & Etnier, 2003; Tomporowski, Davis, Miller, & Naglieri, 2008).

Compared to the available evidence for the positive association between PA and cognitive abilities, little is known about the impact of sedentary behaviors on the central nervous system and how these behaviors, independently or not, affect cognition. The cross-sectional study by

Syväoja and colleagues (2014) found that a higher amount of self-reported video game play and computer use was associated with weaker performance in measures of cognitive functions (working memory, shifting and flexibility of attention) while total screen time was not associated with any measures of cognitive functions. In addition, high levels of total objective sitting time (measured via accelerometry) was associated with better sustained attention (Syväoja et al., 2014). Another prospective study found that self-reported time doing homework and total objectively measure sedentary time (measured via accelerometry) at age 7 years were positively associated with cognition (measured using the British Ability Scales) at age 11 years (Aggio, Smith, Fisher, & Hamer, 2016).

Yet, the scarce number of studies do not allow for the appraisal of the relation of SB and cognitive outcomes in children. There is no doubt that sedentary behaviors have emerged as a new research thread and more studies will continue to develop in the near future (Hillman, Erickson, & Hatfield, 2017).

1.2 Studies in older adults

Healthy aging involves a gradual decline of cognitive abilities (e.g. processing speed, conceptual reasoning), as well as changes in brain structure and function (Harada, Natelson Love, & Triebel, 2013). Conversely, dementia is a term linked to pathological aging (Diagnostic and Statistical Manual of Mental Disorders, DSM-V, 2013). In consonance with the framework of the present thesis which is focused on healthy population, the relation of PA/CRF to cognition, brain structure and brain function, (see part 2.2) will be reviewed in healthy older people free of neurocognitive impairment.

1.2.1. Cognition

Studies examining the influence of PA on cognition in older adulthood appeared prior to studies in younger age groups. Cross-sectional, longitudinal and intervention evidence examining PA effects on cognition was synthetized in recently published systematic reviews and meta-analyses (e.g. Carvalho, Rea, Parimon, & Cusack, 2014; Colcombe & Kramer, 2003; Hall, Smith, & Keele, 2001; Smith et al., 2010). In 2003, Colcombe & Kramer, analyzed 18 randomized PA trials and found that moderate-intensity aerobic exercise increased cognitive performance (Effect Size =0.47) independently of the cognitive task assessed, training parameters or participants' characteristics. Yet, the largest effect size was found for indices of cognitive control (ES=0.68). Colcome's review, as well as others (Hall et al., 2001; Smith et al., 2010) support the "selective improvement" hypothesis, which states that aerobic exercise selectively improves performance on tasks that tap executive-control processes relative to other aspects of cognition (Kramer et al., 1999).

Other meta-analysis conducted on RCT confirmed that aerobic exercise training was associated with enhanced cognitive performance (Smith et al., 2010; Northey, Cherbuin, Pumpa, Smee, & Rattray, 2017), yet, less consistent effects were found for working memory processes (Smith et al., 2010). Estimates from the effect sizes of cognitive improvements vary considerably between meta-analytic studies. For example, Smith et al., 2010, showed improvements in attention and processing speed, executive function, and declarative memory, with effect sizes between 0.123-0.158, while the most recent meta-analysis indicated that aerobic exercise improved cognition in people over 50 years old with an effect size of 0.24 (Northey et al., 2017). Most recently, a meta-analysis by Northey et al., 2017 concluded that, similar to current exercise guidelines, exercise interventions that included physical exercise (both aerobic and resistance exercise) for at least 45min at moderate to vigorous intensity as many days of the week, improved cognitive performance (Northey et al., 2017). Put simply, it seems that any exercise is better than none and more is better than less.

Contrarily, other systematic reviews and meta-analysis do not support such effects (Angevaren, Aufdemkampe, Verhaar, Aleman, & Vanhees, 2008; Etnier, Nowell, Landers, & Sibley, 2006; Young, Angevaren, Rusted, & Tabet, 2015). This lack of parallelism between studies could be due to several factors such as the lack of monitorization of attendance in PA interventions, lack of inclusion of moderator effects in meta-analytical studies, heterogeneity of cognitive measures used across studies, characteristics of exercise interventions (type of exercise, duration, intensity) and lack of base-line assessments in RCT.

Similar to childhood studies, scarce evidence has examined the effect of SB on cognitive outcomes in older people. A recent systematic review (Falck, Davis, & Liu-Ambrose, 2017) exposed some preliminary findings into this area, suggesting that greater amounts of sedentary behaviors are associated with cognitive decline and may contribute to all-cause dementia risk in adult population. Yet, the limited number of studies (N=8) and the heterogeneity of SB measures and cognitive tasks used across the studies made it difficult to draw robust conclusions. The examination of sedentary behaviors and their relation to the central nervous system across the lifespan are currently considered a call for new research directions (Hillman et al., 2017).

2. Physical activity, sedentary behavior and indices of brain health. Changes in brain structure and function

2.1 Studies in children

Recently, research efforts have been aimed at determining the underlying mechanisms responsible for PA benefits on cognition through the study of changes in brain structure and function.

2.1.1 Brain structure

To date, evidence on PA and brain structure in childhood is in its initial stages. The few existing cross-sectional studies indicate that there is a relationship between CRF and grey matter volume in specific regions of the basal ganglia (i.e. striatum and pallidus) (Chaddock, Erickson, Prakash, VanPatter, et al., 2010a) and the hippocampus (Chaddock, Erickson, Prakash, Kim, et al., 2010b). These structures support executive functions and certain types of memory (i.e. relational memory). Importantly, higher grey matter volumes in these brain regions were linked to better performance on executive functions and relational memory tasks (Chaddock, Erickson, Prakash, Kim, et al., 2010b; Chaddock, Erickson, Prakash, VanPatter, et al., 2010a). Additionally, a longitudinal study revealed that higher-fit children showed higher basal ganglia volumes (dorsal striatum and globus pallidus), which also predicted cognitive performance (inhibition task) one year later (Chaddock, et al., 2012). Apart from changes in the volume of specific brain regions, another recent study in Spanish children found that physical fitness was related to the shape of specific subcortical brain areas. That is, physical fitness −including CRF, muscular strength and speed agility− was associated with expansions and contractions of specific regions of subcortical brain areas (i.e. nucleus accumbens, amygdala, striatum, pallidum, hippocampus, and thalamus). Specifically CRF was mainly related to subcortical expansions (Ortega et al., 2017). However, the lack of behavioral measures does not allow for the extension of how these morphological indicators relate to cognitive performance.

Further, evidence shows that changes in white matter integrity may be related to better executive function in children (Chaddock-Heyman, Erickson, Voss, Powers, et al., 2013a). Cross-sectional data indicated that higher fit children had greater white matter integrity than lower fit children in several white matter tracts (i.e. sections of the corpus callosum, corona radiata, and superior longitudinal fasciculus; Chaddock-Heyman et al., 2014). In addition, a small RCT found that children who received a PA intervention had greater integrity in white matter tracts that are part of the neural network supporting executive functions (Schaeffer et al., 2014). Furthermore, increased integrity of white matter tracts was evidenced in those with higher intervention attendance (Krafft et al., 2014).

Aside from PA effects on brain structure and its relation to cognition, biological markers of school achievement have been explored. Two recent studies revealed that higher CRF is related to decreased grey matter thickness and greater grey matter volumes in selective areas (frontal cortex, superior temporal areas, and lateral occipital cortex), which were also correlated with indices of academic performance (Chaddock-Heyman et al., 2015; Esteban-Cornejo et al., 2017). To the best of our knowledge, no studies have examined the associations between SB patterns and changes in brain structure.

2.1.2 Brain function

The study of the relationship between PA/CRF and brain function has been mostly studied assessing non-invasive neuroelectrical activity and more concretely, event related potentials (ERP) (Hillman, Kamijo, & Pontifex, 2012). ERP, are identified from time-locked electroencephalographic activity and afford the measurement of neuroelectric responses to external stimuli that reflect higher-order cognitive processes (Fabiani, Gratton, & Federmeier, 2009). Among others, the P3 component (amplitude and latency) has been extensively used to characterize changes in brain function and cognition in relation to PA/CRF (see Hillman, Kamijo, & Pontifex, 2012 for a review). Consistent cross-sectional evidence indicates that CRF and PA are related to better brain function during diverse types of cognitive tasks (see Donnelly et al., 2016 for review). However, as confirmed by intervention studies, benefits of PA on brain function (coupled with better behavioral performance) are larger for tasks requiring greater amounts of cognitive control (i.e. working memory, inhibition, cognitive flexibility) (Hillman et al., 2014; Kamijo et al., 2011).

Functional magnetic resonance imaging (fMRI) studies have extended findings on PA/CRF related changes in brain function. fMRI allows for non-invasive imaging the blow flood associated with neuronal activity. Researchers use the “BOLD signal” (Blood-oxygen-level-dependent), which is a proxy measure for the location of brain activity (in terms of hemodynamics) as a function of distinct cognitive processes (see Voss et al., 2015 for a detailed explanation). Although studies using fMRI are scarce, results from cross-sectional and intervention studies indicate that PA/CRF may lead to more efficient activation of brain regions underlying executive control processes in normal and overweight children (Chaddock-Heyman, Erickson, Voss, Knecht, et al., 2013b; Chaddock, Erickson, et al., 2012; Davis et al., 2011; Voss et al., 2011a). However, more research is needed to further understand the effects of PA/CRF on patterns of brain activation. To the best of our knowledge, no studies have examined the associations between SB patterns and brain function parameters.

2.2 Studies in older adults

2.2.1 Brain structure

A growing body of cross-sectional evidence demonstrates that higher fitness levels are consistently associated with greater grey matter volume in prefrontal cortex, temporal lobes, and subcortical structures including the hippocampus, and larger grey matter volumes in the caudate nucleus (see Erickson, Leckie, & Weinstein, 2014; and Prakash, Voss, Erickson, & Kramer, 2015 for review). The most significant age-related decreases in grey matter volume occur in these brain areas; thus, fitness levels seem to benefit those brain areas that are most susceptible to decline with age (Prakash, Voss, Erickson, & Kramer, 2015). Importantly, higher grey matter volume in these brain regions were linked to better performance in behavioral measures of executive functions and memory (Erickson, Leckie, & Weinstein, 2014; Prakash, Voss, Erickson, & Kramer, 2015).

Despite the relative paucity of intervention studies, they provide promising results regarding PA-related increases in grey matter volume. For instance, Colcombe et al. (2006), evidenced that an exercise intervention increased grey matter volumes in frontal, temporal, and cingulate areas while the stretching and toning control group showed a slight decline in volume in the same brain regions. Erickson et al. (2011), extended these findings specifically for the hippocampus. One year of aerobic exercise increased hippocampal volume by 2% while the control (i.e. stretching) group showed a 1.4% decrease in this brain region (Erickson et al., 2011). Importantly, changes in hippocampal volume for the aerobic exercise group were correlated with improvements on a spatial memory tasks.

White matter integrity is also susceptible to benefits of PA. Several cross-sectional studies found that higher CRF and PA levels were linked to greater white matter integrity (tracks connecting frontal, temporal and subcortical areas) (Burzynska et al., 2014; Johnson, Kim, Clasey, Bailey, & Gold, 2012; Best et al., 2017). In addition, Voss et al. (2013), conducted a one-year exercise intervention and identified that neither WM integrity or behavioral measures of cognitive control and short-term memory significantly differed from the walking group when compared to the control group (stretching exercise). However, an increase in aerobic fitness in the intervention group showed significant positive changes in white matter integrity (i.e. in frontal and temporal lobes) as well as better short-term memory performance. Finally, longitudinal studies indicated that being exercise active predicts greater memory-related microstructural integrity over time (Tian et al., 2014).

PA may also be associated to brain vasculature processes in late adulthood. Bullitt et al. (2009) reported initial evidence showing that self-reported aerobically active subjects (N=14) exhibited lower vessel tortuosity values and increased number of small vessels compared with less active subjects. To the best of our knowledge, only the study by Burzynska and colleagues (2014) examined the associations between SB and changes in brain structure. Accelerometer-based SB was associated with lower integrity of parahippocampal white matter (Burzynska et al., 2014).

2.2.2 Brain function

Cross-sectional evidence indicates that higher CRF is associated with better brain function as measured via neuroelectric and vascular function. In line with childhood studies, neuroelectric evidence (i.e. P3) suggest that higher PA is associated with greater allocation of attentional resources associated with stimulus processing, faster cognitive processing speed and reduced activity related to the monitoring of error responses (see Gajewski & Falkenstein, 2016; Hillman, Kamijo, & Pontifex, 2012 for review). Regarding vascular function, cross-sectional data indicated that higher fit women had lower resting mean arterial pressure and higher cerebrovascular conductance compared to their inactive counterparts, which was a predictor of higher cognition (Brown et al., 2010).

In intervention studies, effects of PA on brain function have also been examined via fMRI. An aerobic training intervention study (6 months three times x week) showed changes in brain activation from pre- to post-test for the intervention group relative to a control group (Colcombe et al., 2004). That is, the intervention group had greater task-related increases in brain activity (frontal and parietal lobes) and less activation in anterior cingulate cortex (a brain area involved in conflict and error monitoring) along with improvements in cognitive control task performance (Colcombe et al., 2004). Further, other research has demonstrated that under no cognitive demand (resting), aerobic training can improve the brain's resting functional efficiency in higher-level cognitive networks (Voss et al., 2010). This study showed that both aerobic (walking) and nonaerobic (stretching and toning exercises) training for 12 months resulted in greater functional connectivity in the default mode network and in frontal and temporal cortices (Voss et al., 2010).

Further research is needed to better understand how PA/CRF affects cognition and markers of brain health in terms of dose-response evaluations, which types of exercise can maximize brain health, moderators or mediators that can be involved in these effects – genes, social factors – (e.g. Barha, Galea, Nagamatsu, Erickson, & Liu-Ambrose, 2017) and how these findings can translate to everyday life contexts. Yet, there is convincing evidence that PA supports healthy aging and acts on those brain regions implicated in age-related cognitive decline. To further illustrate this point, meta-analyses of longitudinal observational studies have confirmed that self-reported engagement in PA is associated with reduced risk (high level of self-reported PA, -38%; low to moderate level of PA, -35%) of experiencing cognitive decline over several years (Sofi et al., 2011). These, as well as other studies, make a convincing argument that PA and higher CRF in late adulthood have a profound effect on maintaining cognitive health, improving function, producing anatomical changes and reducing the risk of developing cognitive impairment. To the best of our knowledge, no studies have examined the associations between SB patterns and function brain outcomes.

Summary of key issues. Section C

- The study of PA/CRF, cognition and brain health has mainly focused on developmental or aging populations and less evidence exists in young adults
- PA does not detract from children's educational outcomes. However, scant research has comprehensively assessed the relation of SB on academic outcomes.
- PA has a positive influence on cognition in children and older populations. Furthermore, aerobic exercise selectively improves performance on tasks that tap executive control processes.
- Specific to working memory processes, the impact of PA is controversial in both children and older adults.
- Despite the majority of research is cross-sectional, the evidence indicates that PA/CRF benefits brain structure and function in children.
- There is convincing evidence that PA supports healthy aging promoting positive functional and anatomical brain changes.
- Little is known about the impact of sedentary behaviors on the central nervous system and how these behaviors independently or interactively with other behaviors affect cognition, brain structure and function across the lifespan.
- The examination of sedentary behaviors and their relation to the central nervous system across the lifespan are currently considered a call for new research directions.

SECTION D. LITERATURE REVIEW: IMPACT OF PHYSICAL ACTIVITY AND SEDENTARY BEAVIOR PATTERNS ON COGNITION AND BRAIN HEALTH IN YOUNG ADULTS

Introduction

This section will present a review of the literature that examined PA and SB in relation academic achievement, cognition and brain health (brain structure and function) in the young adult population.

1. Literature review procedure

Although a comprehensive and exhaustive literature review was conducted, this search did not follow a full systematic review protocol. The search was conducted in the databases Web of Science and PubMed up to May 2017. A key word search was performed using the terms (physical activity OR aerobic fitness OR exercise) AND (sedentary behavior OR sitting time OR screen time) AND (cognitive function OR cognition* OR executive function* OR cognitive control OR brain function OR cognitive performance OR academic achievement) AND (young adults OR youth) AND (NOT acute). Studies on non-healthy young adults or studies examining the effect of an acute bout of exercise were excluded from the literature review. Comparative studies that included young and older adults were included but only results for the younger cohorts are reported.

A total of 48 studies were identified. For each study, details on source (authors, year and country), study design, population, study aim, PA and SB measures, outcome variables and measurement tools, findings and conclusions were extracted. This information is summarized in Table 3 (Appendix I).

2. Results

Overall, forty studies were cross-sectional (83.3%), four were interventional (8.3%) and four were longitudinal (8.3%). The sample mean age on the global studies was 22.06 years old, most studies included females and males altogether (n=40), only females (n=2) or only males (n=6). A total of thirty-one studies were conducted exclusively in a sample of college students, four studies included college students and population based samples, while the remaining thirteen were conducted in population-based samples.

In cross-sectional and longitudinal studies (n=44), PA measures were assessed for CRF only (n=21), a combination of self-reported measures of PA, CRF and/or accelerometry (n=7), or assessing PA levels only (n=16). In those assessing levels of PA, four studies used accelerometry, eleven studies used self-reported measures while one study used self-reported measures to assess the sweat index. Overall, five studies used non-validated questionnaires to assess levels of PA and three other studies used questionnaires designed to assess levels of PA that were only validated for older populations. SB was measured in three observational studies employing either accelerometry (n=1) or self-reported measures focused on TV viewing time (validated and non-validated questionnaires). Intervention studies (n=4) were designed to increase PA employing structured-exercise programs that ranged from three to six weeks of aerobic exercise, three to five days per week.

Regarding outcomes variables, studies used behavioral indices of cognition (n=26), academic performance (n=1), indices of cognition and academic performance (n=1), measures of brain structure (n=1), behavioral indices of cognition accompanied by measures of brain structure (n=5), brain function (n=13), or behavioral measures accompanied by eye movement recordings (n=1).

Results and conclusions of overall studies can be found comprehensively summarized in Table 3 (Apendix I).

2.1 Physical activity, sedentary behavior and cognitive outcomes

2.1.1 Academic achievement

To the best of our knowledge, the influence of PA/CRF on academic achievement in college students was measured in two cross-sectional studies, and of them, one included only females (Wald et al., 2014; Scott et al., 2014). Both studies indicated that higher CRF and self-reported PA (meeting PA guidelines) were positively associated with academic performance (grade point average). In addition, Scott et al. (2017) provided further evidence suggesting that working memory performance mediated the association between CRF and womens' academic performance. No longitudinal or intervention studies have examined PA effects on academic outcomes. Similarly, no studies assessed relationships between SB and academic outcomes in this population.

2.1.2 Cognition

Except for a few cases (Boucard et al., 2012; Scisco, Leynes, & Kang, 2008; Wilckens, Erickson, & Wheeler, 2017; Hayes, Forman, & Verfaellie, 2016), observational studies tend to support a positive relationship between PA/CRF and tasks that measure distinct aspects of cognition (i.e. cognitive control, memory, sustained attention, motor function).

Observational studies assessing SB found that high levels of TV time during young to mid-adulthood were associated with poorer executive function and slower processing speed (Hoang et al., 2016); however no relationship was observed for episodic or verbal memory (Heisz, Vandermorris, Wu, McIntosh, & Ryan, 2014; Hoang et al., 2016). In addition, a longitudinal study suggested that the relationship of SB and executive function may be bi-directional as young adults with greater executive function had less follow-up SB (Loprinzi & Nooe, 2016a).

Although scarce, intervention studies support PA-related benefits on cognition (Griffin et al., 2011; Hansen, Johnsen, Sollers, Stenvik, & Thayer, 2004; Stroth, Hille, Spitzer, & Reinhardt, 2009; Thomas et al., 2016). In addition, these studies reported that after at least 5 weeks of training, performance increased on hippocampal-dependent task, measures of executive function and visuospatial memory, but not for concentration or verbal memory (Griffin et al., 2011; Hansen et al., 2004; Stroth, Hille, et al., 2009a; Thomas et al., 2016). No interventional studies have measured SB.

2.2 Physical activity, sedentary behavior and indices of brain health. Changes in brain structure and function

Although the number of studies is scarce, the reviewed cross-sectional evidence also supports a positive association between PA/CRF and brain structure (i.e. volume integrity, white matter, cortical thickness, grey matter density) as well as brain function (i.e. neuroelectric indices of brain function and blood flow). No cross-sectional studies were found assessing patterns of SB and changes in brain structure or brain function. In addition, no longitudinal or intervention studies were found examining PA or SB effects on brain structure or function.

The reviewed cross-sectional evidence exposed some potential mediators in this relationship (i.e. sleep, CRF, environmental neurotoxicants, iron status, brain derived neurotrophic factor (BDNF); Boucard et al., 2012; Griffin et al., 2011; Oulhote, Debes, Vestergaard, Weihe, & Grandjean, 2017; Whiteman et al., 2014; Whiteman, Young, Budson, Stern, & Schon, 2016; Wilckens et al., 2017), however more studies are needed to determine moderators or mediators that may be involved in these effects. Further prospective and RCT studies in young adults are needed to provide empirical support for the PA-related benefits hypothesis in academic achievement, cognition and indices of brain health. Finally, to the best of our knowledge, only three studies have taken into consideration SB, and thus, future research should examine the impact of SB on markers of brain health and cognition.

3. Summary of gaps in the current evidence-based literature

- The literature review in section D identified a dearth of evidence examining PA-benefits on academic achievement in college students. Furthermore, the influence of sedentary behavior patterns on academic outcomes in this population remains poorly understood as the literature review did not identify any study.
- Regarding cognitive outcomes, few studies have assessed sedentary behavior parameters but no study have examined the impact of sedentary behavior patterns in a comprehensive manner.
- Lastly, the literature review identified that there is an evidence gap, as there is no evidence examining the potential interactions between sedentary behaviour and physical activity relative to academic achievement and cognitive outcomes. This issue is important as most individuals engage in both physical activity (PA) and SBs throughout the day.

RATIONALE AND THESIS AIMS

Rationale and thesis aims

The main goal of this thesis was to examine the associations between PA, SB and cognitive outcomes. Two main cognitive outcomes were assessed in the present thesis: WMC and academic achievement. While WMC provides valuable information obtained from laboratory-based settings and has a key role in cognitive control processes, academic achievement possesses ecological validity and provides an applied measure of certain aspects of cognition. Furthermore, in an effort to deeply examine associations between PA, SB and cognitive outcomes, both self-reported (questionnaires) and objective (activPAL™) measurements of these health-related behaviors were used. To reflect the natural co-dependency of PA and SB, a combined adjustment approach was used between these variables in order to examine whether associations between WMC and academic achievement with SB were independent of PA.

The research described in the present thesis has been conducted in a young adult population (college students) to gain a better understanding of the roles that PA and SB play on cognitive performance and brain health during a period of the lifespan characterized by optimal cognitive functioning. There are several reasons to focus on this group. First, some cognitive components begin to decline in young adulthood (Finch, 2009; Salthouse, 2009); thus, it is important to determine the protective role of PA or harmful effects of SB prior to the onset of cognitive decline. Second, young adults, and more specifically, college students spend considerable time in a setting that promotes SB and it has been suggested that environments which require prolonged periods of physical inactivity may contribute to establishing long-term SB patterns that persist throughout adulthood. Third, it is important to examine how healthy lifestyles can maximize learning, academic outcomes and cognitive control capabilities as they are essential in this age-group (see section B. Background).

In this context, the PhD thesis contains the following three specific research aims, which are addressed in three interrelated scientific papers published or under review in internationally peer-reviewed journals:

1. To provide a time-effective standardized method for assessing WMC in Peninsular Spanish-speaking populations (Study 1).
2. To examine combined associations between context-specific SB and PA intensities with WMC and academic achievement in a sample of university students (Study 2).
3. To study the combined relationships between PA and SB patterns examined in detail (including total time spent sitting/lying, total time spent standing, the number of breaks in sedentary time, and sedentary bout duration) with academic achievement and WMC. For the sake of simplicity, only results on academic achievement have been reported in Study 3. However, results on WMC can be found in a complimentary analysis (see results, discussion and Table 4 in Appendix II).

An overall view of each study is presented below, and a table summarizing variables and instruments used across studies can be found in the Appendix III (Table 5):

- **STUDY 1.** This study provided a time-effective standardized method for assessing working memory capacity in Peninsular Spanish-speaking populations. Specifically, the study validated an English shortened version of the complex span tasks into Spanish (Castilian) in a sample of 325 university students of the UVic-UCC. The sample was progressively recruited from April 2015 to March 2016 and all participants provided written informed consent prior to participation. This study was a preceding and fundamental step for tackling the following research questions.

- **STUDY 2.** This study examined the combined associations between self-reported, context-specific SB and PA intensities with WMC and academic achievement in a sample of university students (n=371) from UVic-UCC. The sample was progressively recruited from March 2015 to February 2016 and all participants provided written informed consent prior to participation.

- **STUDY 3.** This study investigated the combined relationships between objectively-measured SB patterns (total time spent sitting/lying, total time spent standing, the number of breaks in sedentary time, and sedentary bout duration) and PA with academic achievement in a subsample of university students from Study 2 (n= 132). The overall study was initiated in March 2015, while activPAL measures were obtained from October 2015 to March 2016. All participants provided written informed consent prior to participation.

STUDY 1

Published in Psychological Assessment Journal on 13th April 2017

Felez-Nobrega, M., Foster, J. L., Puig-Ribera, A., Draheim, C., & Hillman, C. H. (2017). Measuring Working Memory in the Spanish Population: Validation of a Multiple Shortened Complex Span Task. *Psychological Assessment*. (In press)

STUDY 2

Published in European Journal of Public Health on 18th March 2017

Felez-Nobrega, M., Hillman, C. H., Cirera, E., & Puig-Ribera, A. (2017). The association of context-specific sitting time and physical activity intensity to working memory capacity and academic achievement in young adults. *European Journal of Public Health, 9*, 755–62.

STUDY 3

Manuscript under review at Journal of Sports Sciences

Felez-Nobrega, M., Hillman, C. H., Dowd, K. P., Cirera, E., & Puig-Ribera, A. ActivPAL^{TM} determined sedentary behaviour, physical activity and academic achievement in college students.

GENERAL DISCUSSION

General discussion

1. Main findings

This PhD thesis has provided a broader range of evidence examining, for the first-time, combined relationships between PA and SB patterns with academic achievement and WMC. As most individuals engage in both PA and SB throughout the day, a combined adjustment approach between SB and PA allowed to reflect the natural co-occurrence of both behaviors. Furthermore, we provided initial evidence analyzing not only total SB levels but also key dimensions of sedentary patterns (i.e. sedentary breaks and sedentary bouts) and its relation to such cognitive outcomes. Lastly, unlike other studies that have measured SB via accelerometers designed to capture movement, SB patterns were objectively-measured using the activPAL activity monitor (PAL Technologies Ltd., Glasgow, UK), which is considered the goal standard measure of static behaviors.

In this context, the present PhD thesis is based on three original research papers/manuscripts that addressed important research questions and make an original contribution to the field. Study 1 was a preceding step necessary for conducting the subsequent studies and provided evidence that the Spanish version of a shortened complex span task has satisfying psychometric properties for assessing WMC in a sample of Spanish-speaking university students. This evidence is particularly important given the scarcity of available and validated measures of WMC for Spanish-speaking population. Study 2 and 3 examined associations of SB and PA intensities with WMC and academic achievement in a sample of university students employing self-reported (study 2) and objective measures (study 3). Key findings from studies 2 and 3 are summarized in Table 6 (Appendix IV). Briefly, regarding SB, research findings indicated that total sedentary time (self-reported or objectively measured) was not related to WMC or academic achievement. Yet, Study 2 highlighted the value of capturing domain-specific sedentary time information as findings indicated that time spent in specific leisure domains of sitting time may detract from academic performance and WMC, independent of PA intensity and duration. On the other hand, Study 3 highlighted the importance of examining not only overall levels of sitting time but the manner in which sitting/lying time was accumulated. Specifically, the findings from Study 3 indicated that independently of PA, the amount of time spent in sedentary bouts of 10-20min during weekdays was positively related to academic achievement while sedentary bouts of 20-30min during weekend days were negatively related to WMC (findings derived from the complimentary analysis). For PA intensities, Study 2 revealed that performing more than 3h/week of self-reported MPA was related to increases in WMC, but it was not associated with academic performance. LIPA or VPA were not associated with academic achievement or WMC. Objective measurements in Study 3 (and complimentary analysis) indicated that any of the PA intensities (LIPA and MVPA) were related to either academic achievement or WMC.

2. Physical activity, academic achievement and working memory capacity in young adults

2.1 Physical activity and academic achievement

Findings from the present thesis indicate that PA (subjectively or objectively measured) was not associated with better academic achievement. Healthy young adults are presumed to be at their cognitive peak and some studies have speculated that there may be little room for PA-related improvements in this population. Nonetheless, our findings do not support a ceiling effects argument, as other explanations may be better candidates to explain the lack of association. First, the homogeneity in academic achievement scores obtained in our studies (SD=0.7) might have disguised significant associations. Second, the method for measuring academic achievement in this population may not provide an accurate measure of college students' overall cognitive performance as several factors can influence grade point average (e.g., difficulty of the content, subjectivity of evaluation processes, etc.). Third, as it has been outlined along the background section, regular PA may result in specific rather than global effects on cognition and brain health. Thus, academic achievement obtained via grade point average may capture a broad and general measure of cognitive performance. However, it should be noted that grade point average was included as a fundamental outcome of the study because it possesses ecological validity compared to standardized tests of cognition. Lastly, some studies across different population groups suggested that CRF but not PA can benefit academic achievement and other brain outcomes (e.g. functional integrity, indices of executive control) (Oliveira et al., 2017; Pindus et al., 2016; Stroth, Kubesch, et al., 2009b; Voss et al., 2016). Thus, when examining relationships of health behaviors and cognition, distinctions between PA and CRF may be important.

2.2 Physical activity and working memory capacity

This PhD thesis identified positive associations between high levels of self-reported MPA and WMC, which were later dismissed when objective measures of PA were introduced. Several cross-sectional studies have also examined the association between PA/CRF and working memory in young adults, however the evidence is inconsistent. Several hypotheses could explain the inconsistency of such associations. First, similar to associations of PA and academic achievement, the ceiling effect argument has been used to justify the lack of association in the young adult population (e.g. Pontifex et al., 2014). Second, methodological concerns for measuring WMC across studies should be highlighted. For example, assessments of WMC with the Sternberg task have found no significant associations between behavioral measures of WMC and PA or CRF in young adults (Kamijo, O'Leary, Pontifex, Themanson, & Hillman, 2010a; Wilckens et al., 2017). However, it has been suggested that this task may capture short-term memory processes rather than WMC *per se* (Unsworth & Engle, 2007). Other studies in young adults employed n-back tasks to measure WMC, finding no influences of PA (Wilckens et al., 2017). n-back tasks have been subjected to few behavioral tests of construct validity and this paradigm may be useful for experimental research but may not capture individual differences in working memory (Jaeggi, Buschkuehl, Perrig, & Meier, 2010). Lastly, complex span paradigms have been used to explore relationships between WMC and PA in young adults. Lambourne (2006), used the Reading Span and found that self-reported PA was related to better performance on this task. Although complex span tasks are the most widely accepted instruments to measure WMC, one single indicator (e.g. Operation Span, Reading Span, Symmetry Span, etc.) cannot accurately measure WMC (Conway et al., 2005; Felez-Nobrega, Foster, Puig-Ribera, Draheim, & Hillman, 2017b; Foster et al., 2015). These examples illustrate that the methodology used to measure working memory may be critical to understanding the influence of PA.

Third, the association of PA and WMC may vary depending on the use of objective or subjective PA measures. This is well illustrated by our own results as high levels of self-reported MPA were positively associated with increases in WMC, but no such beneficial association was observed for objective measures of PA (MVPA). Examples of different results based on PA measurements tools have been previously reported in the literature. For instance, Syväoja et al. (2014) found that children's objectively measured MVPA was related to reaction time while self-reported MVPA was not. A possible explanation for the divergent findings between measures may be that subjective and objective measures may not capture the same information. For instance, in self-reported measures, participants categorize time spent in MPA and VPA based on subjective perceptions that are influenced by participants' physical fitness (Bouchard, Shephard & Stephens, 1994). Alternatively, objective measures of PA cannot accurately capture upper body activities or activities that involve cyclic movements (e.g., bicycling), which indicates that objective assessments may underestimate specific types of PA (Warren et al., 2010). Importantly, our study indicated that both assessments made similar estimates of MVPA. While objective measures estimated 5,9hours/week of MVPA (Study 3), self-reported MVPA (MPA+VPA) indicated a total of 6hours/week (Study 2). These data indicate that diverging results may not be fully explained by issues in MVPA estimations. However, another hypothesis that could explain the lack of agreement between objective and subjective measures in our studies is that self-reported measures captured MPA and VPA, while previously validated count-to-activity thresholds allowed objective measures to capture MVPA. Thus, in Study 3 where objective measures of MVPA were obtained, the effect of MPA (if any) could have been weakened by VPA.

3. Sedentary behavior, academic achievement and working memory capacity in young adults

For decades, physicians, public health scientist and neuroscientist have been focused on understanding the need for increasing MVPA to maintain and improve physical and brain health (Hillman, Erickson & Kramer, 2008). The unique focus on this important, but limited, element of the overall PA spectrum does not address the consequences of engaging in a wide range of sedentary behaviors that occupy most adults' waking hours (Katzmarzyk, 2010). The importance of assessing not only MVPA but also LIPA (non-exercise PA) and SB has been recognized several years ago in physical health research, but the examination of SB levels and patterns and they relation to cognition and brain health is still an emerging area in the neuroscience and PA field.

Thus, results obtained regarding SB patterns cannot be compared with previous literature because most research to date has not comprehensively examined this behavior. That is, some studies have used the term "sedentary" when they are actually referring to "inactivity" (not meeting PA guidelines), most studies have only assessed levels but not patterns of SB which includes breaks and bouts, some studies in childhood population have used accelerometer-based devices which capture no-movement behaviors instead of SB.

4. The complexity of health-related behaviors

PA and SB are related behaviors characterized by complex relationships. According to the present results, PA and SB are two factors that independently contributed to cognitive performance. Study 2 suggested that PA intensities do not counteract the negative associations of SB and WMC, as results were mutually adjusted for SB and PA intensities. Study 3 indicated that breaking sedentary time was related (positively and negatively) to academic achievement and WMC and results remained significant in active and inactive participants. On the other hand, other studies have suggested that the relation of PA, SB and cognition may be bi-directional. That is, PA and SB may potentially influence brain outcomes but at the same time cognitive aspects (e.g. higher cognitive control) can regulate the selection and engagement in healthier lives (Loprinzi, Herod, Cardinal, & Noakes, 2013; Loprinzi & Nooe, 2016).

Complex relationships between PA, SB and health are also being explored using isotemporal substitution analyses. This analytical technique, which accounts for the fact that a day has 24 hours, estimates the effect of replacing one behavior with another for the same amount of time (Mekary, Willett, Hu, & Ding, 2009). Despite the fact that isotemporal analysis have been frequently used in studies examining relationship between PA, SB and physical health outcomes (García-Hermoso, Saavedra, Ramírez-Vélez, Ekelund, & del Pozo-Cruz, 2017), studies using this paradigm for exploring relationships with cognitive outcomes are, to date, scarce (Fanning et al., 2017). Nevertheless, this statistical approach that accounts for the 24h cycle has undoubtfully set the roots for future research in the field of PA and neuroscience.

5. Known and putative mechanisms underlying physical activity, sedentary behavior and brain outcomes

To explain PA influences on cognition, several multiple level mechanisms have been suggested. Briefly, at cellular and molecular levels, evidence indicates that PA (exercise) increases the release of neurotrophins and growth factors (e.g. brain-derived-neurotrophic factor, nerve growth factor, insulin-like growth factor 1, vascular endothelial growth factor). These factors promote and support the regeneration of blood vessels, the generation of new neurons as well as their survival, they promote neuron body growth, synaptogenesis, and formation of new dendrites. Furthermore, neurotransmitters (e.g. dopamine, serotonin) and endocrinological changes (glucocorticoids) are assumed to influence the association between PA and cognition (see for review: Cotman & Berchtold, 2002; Cotman, Berchtold, & Christie, 2007; Stillman, Cohen, Lehman, & Erickson, 2016a; van Praag, 2008). Evidence supporting these mechanisms is predominantly from nonhuman animal studies. From human studies, mechanisms at systemic level, which includes brain function and structure, have been proposed to explain PA-related benefits (see section C, Background). In addition, behavioral and socioemotional mechanisms (e.g. sleep, mood) have been theoretically hypothesized as important moderators and mediator factors that can influence these relationships; however, there is still scarce evidence in this regard (Stillman et al., 2016a). Although future studies are needed to provide a better understanding of how PA engenders its benefits on the central nervous system, much less is known about how SB influences brain and cognition and which are the mechanisms that could be involved.

Initial evidence on the pathophysiology of SB has emerged from the physical health research field. Physiological studies suggest that SB affect metabolic parameters by increasing blood pressure, lipid and glucose levels (Hamilton, Hamilton, & Zderic, 2007). In brain health, emerging evidence has speculated potential pathways by which SB may impair the central nervous system. It has been suggested that SB may modulate hemodynamic responses by directly producing effects on vascular structure and function (e.g. arterial stiffness), which ultimately will impair arterial health (Grace, Climie, & Dunstan, 2017). Importantly, vascular dysfunction is associated with an increased incidence of Alzheimer disease and dementia (Barnes, 2015). Other studies have highlighted the importance of maintaining glucose levels for enhancing brain health (Geijselaers, Sep, Stehouwer, & Biessels, 2015). Hyperglycemia and hypoglycemia sustained over time may cause brain damage. Researchers have claimed that reductions in SB and LIPA replacements may contribute to enhanced brain health by maintaining glycemic control (Wheeler et al., 2017).

Strengths and limitations

This present PhD thesis, as a whole, has several strengths and limitations. First, rigorous and comprehensive methods are an important strength of this PhD thesis. WMC was measured using a validated complex span task (that included three indicators), which ensured that the tool adequately measured the construct for this population. In addition, SB and PA patterns were assessed using both subjective and objective measures. Regarding objective measurements, SB patterns were measured with what is currently considered the gold standard. Moreover, comprehensive self-reported questionnaires have been used allowing to capturing volume and patterns of such behaviors and differentiating among weekdays and weekend days. However, while self-reported measures afforded contextual information, this does not necessary reflect cognitive engagement related to the activity. This may be of special importance when examining relationships between SB and cognitive outcomes. Second, while cross-sectional designs do not afford causal conclusions, an advantage of using this design was the inclusion of a combined approach between PA and SB. Third, analyses were adjusted for gender and age, but other possible confounders may, at least in part, explain the findings. Lastly, this PhD thesis made an original contribution to the field, emphasizing the importance of linking SB and cognitive outcomes, and although little evidence is currently available to explain and discuss the findings, this study may contribute to promoting novel studies in other research areas that certainly need further investigation.

The main strengths and limitations are briefly summarized for each study in Table 7.

Table 7. Strengths and limitations of the three studies

	Strengths	*Limitations*
STUDY ONE	First study to validate a complex Span Task for Spanish-speaking population. To promote valid and standardized methods for assessing WMC, to facilitate generalization of results and intercultural study replications, these tasks are freely accessible at the Georgia Tech Attention and Working Memory Lab website (http://englelab.gatech.edu).	The range of variability in general abilities is restricted and people with low Gf and low WMC were underrepresented. These data may not generalize to Latin American Spanish speakers.
STUDY TWO	First study to examine sedentary behavior in relation to cognition in young adults. Most of cross-sectional studies assessed time allocated to PA and SB throughout the day and its relationship to cognitive outcomes in isolation, but not with a combined adjustment approach that reflects the natural co-dependency of both behaviors. Self-reported measures allow to gather domain-specific information.	Cross-sectional designs do not afford causal conclusions. Self-reported estimates have the potential to contain error. Caution is urged in generalizing these findings to other populations.
STUDY THREE	First study to objectively examine SB in relation to cognition in young adults. This study used an objective measure for SB that is currently considered the gold standard. The examination of not only SB levels but also its patterns in terms of bouts and breaks. The combined adjustment approach between PA and SB.	Cross-sectional designs do not afford causal conclusions. Caution is urged in generalizing these findings to other populations.

Implications and recommendations for future research

The findings outlined in this thesis provide valuable initial information to encourage the development of further observational research as well as intervention studies. According to the results presented, SB intervention studies should focus on either schools and university settings or in leisure-time contexts. The present findings have arisen the need to gain deeper knowledge of the effect that SB patterns have on cognitive and brain outcomes, which will have implications for public health guidelines and recommendations.

The results of this thesis have addressed existing gaps in the current scientific literature, but it is important to acknowledge that future research studies are needed. These research needs include:

- Explore whether SB impacts cognition using more comprehensive measurements of SB. That is, future research should endeavor to use activPAL™ measures to examine total sitting/lying time and patterns of SB, accompanied by activity logs to gather domain-specific and activity-related cognitive demands information.

- Explore the characteristics of sitting/lying time interruptions to improve academic achievement (e.g. frequency of breaks, interruptions of SB with LIPA or MVPA). In addition, it is important to expand these aims for other markers of brain health such as brain structure and function, as well as multiple aspects of cognition.

- Conduct experimental research in order to better characterize the impact of SB (including levels and patterns) on academic achievement and overall brain health. Furthermore, examining the role of PA in these relationships is also a fundamental research need.

- Outline evidence linking both SB and PA to cognition in other populations.

- To examine using long-term studies whether PA and SB may be critical targets for prevention of cognitive decline and promotion of a healthy cognitive aging.

- To determinate moderators and mediators that influence PA and SB effects on cognition (e.g. diet, sleep, gens, social support) since human behaviors are influenced by environmental, psychological, biological and sociocultural factors.

CONCLUSIONS

The present thesis aimed to explore the associations of PA and SB with academic achievement and WMC in a sample of college students. Several main conclusions can be drawn from the findings:

- While PA and SB are naturally co-dependent, they may have independent contributions for cognitive performance.

- Self-reported MPA, may benefit WMC in young adults; however, specific domains of leisure-time SB may have an unfavorable influence on WM processes and academic performance regardless of PA.

- Interruptions in prolonged periods of sitting time every 10-20min via short breaks may optimize cognitive operations associated with academic performance.

- Time spent in MPA, reductions in leisure-sedentary time and breaks in sitting time are important targets for intervention strategies in college students.

- The understanding of SB and its relation to cognition and brain health is emerging and merits further exploration.

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