Effect of age, vascular parameters, physical activity, and cardiorespiratory fitness on executive performances : role of cerebral oxygenation

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THESE

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EFFET DE L'AGE, DU PROFIL TENSIONNEL, ET DES NIVEAUX D'ACTIVITE PHYSIQUE ET DE CONDITION PHYSIQUE SUR LES PERFORMANCES EXECUTIVES : ROLE DE L'OXYGENATION CEREBRALE

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Resume

De nombreuses études ont montré que l'activité physique régulière et le niveau de condition physique étaient associés à la performance cognitive et plus particulièrement aux fonctions exécutives. Parmi les nombreux mécanismes physiologiques qui sous-tendent cette association, l'oxygénation du cortex préfrontal semble avoir un rôle majeur. Il est bien établi que l'impact spécifique de l'oxygénation préfrontale sur le lien entre l'activité physique et la cognition est influencé par certains facteurs comme le sexe, l'âge, et la santé cardio-vasculaire.

Par conséquent, l'objectif de cette thèse était d'étudier l'impact de l'activité physique et du niveau de condition physique sur les fonctions exécutives au cours du vieillissement chez des hommes sains. L'influence de l'oxygénation du cortex préfrontal et de la santé cardiovasculaire sur la relation « niveau de condition physique – fonctions exécutives » a également été étudiée. A partir de la littérature existante, nous avons formulé l'hypothèse que l'activité physique et le profil cardiorespiratoire auraient des effets bénéfiques sur les fonctions exécutives chez les hommes jeunes et plus âgés, et que pour ces deux populations, l'oxygénation du cortex préfrontal et la santé cardiovasculaire seraient impliquées dans cette relation. Une revue de littérature et quatre études transversales ont été réalisées pour vérifier ces hypothèses.

Notre revue de littérature a indiqué que :

- Chez les personnes âgées, un niveau de condition physique plus élevé est associé à de meilleures performances dans certains tests de fonction exécutive. Même si le nombre limité d'études disponibles ne permet pas de tirer des conclusions définitives.
- Un niveau de condition physique plus élevé chez les personnes âgées est associée à une moindre rigidité artérielle, à une réactivité vasculaire plus élevée, et à une plus grande amplitude de l'oxygénation cérébrale au cours de l'exercice ou d'une tâche cognitive.
- Un plus grand volume de matière grise et une plus grande d'intégrité de la substance blanche sont liés àu profil cardiorespiratoire, mais moins systématiquement associés à l'activité physique.
- Au moins de 12 semaines d'un programme d'exercice aérobie sont nécessaires pour obtenir un effet significatif sur les fonctions cognitives

Nos études expérimentales nous ont permis de conclure que :

Chez les jeunes hommes:

- Les individus actifs obtenaient de meilleures performances dans les tâches exécutives que les inactifs et avaient un changement important dans l'oxygénation du cortex préfrontal lors des conditions les plus complexes de la tâche de Stroop.
- Un niveau de condition physique plus élevé était liée à une meilleure performance en double tâche et une plus grande oxygénation des deux côtés du cortex préfrontal.

Chez les hommes âgés:

- Le niveau de condition physique n'est pas lié aux performances de Stroop ni à l'oxygénation du cortex préfrontal.
- Un niveau de condition physique plus élevé est lié à une meilleure performance et une plus grande oxygénation de cortex préfrontal droit au cours d'une tâche de Stroop dans le groupe de 61+ ans mais pas dans le groupe de 55-60 ans, ce qui suggère l'importance de la classification de groupe d'âge pour évaluer l'effet du niveau de condition physique sur les fonctions exécutives chez les hommes âgés.
- Les hommes âgés ont des relations plus fortes entre plusieurs paramètres cardiovasculaires et la performance des taches de Stroop que les jeunes hommes.

Ce projet de recherche montre que l'activité physique et le niveau de condition physique ont des effets positifs sur les fonctions exécutives chez les jeunes hommes et âgés, en particulier dans la tâche la plus complexes. L'oxygénation du cortex préfrontal et la santé cardiovasculaire modulent la relation entre l'activité physique et la cognition. Nous concluons que d'être physiquement actif ou d'avoir un meilleur niveau de condition physique donne des effets avantageux pour la santé vasculaire, l'oxygénation du cortex préfrontal, et les fonctions exécutives non seulement chez les hommes âgés, mais aussi chez les jeunes hommes.

Mots-clés: activité physique, niveau de condition physique, cortex préfrontal, oxygénation cérébrale, spectroscopie infrarouge, pression artérielle, vasculaire, tâche de Stroop, double-tâche, tâche de n-back, jeunes hommes, hommes âgés, athlète master

Abstract

Many studies have reported that regular physical activity and cardiorespiratory fitness were associated with cognitive performance and more selectively with executive functions. Among numerous physiological mechanisms that may underlie the association between them, prefrontal cortex oxygenation seems to play a major role. However, the specific impact of prefrontal oxygenation on the link between physical activity and cognition is influenced by several factors, such as gender, age, or cardiovascular health. Therefore, the aim of this thesis was to investigate the impact of physical activity and cardiorespiratory fitness on executive functions across the adults' age span in healthy males, as well as the influence of prefrontal cortex oxygenation and cardiovascular health. To obtain those objectives, we conducted a review of the effect of physical activity on the brain in older adults and four cross-sectional studies.

From our review, we highlighted that:

- In older adults, higher fitness level is associated with better performance in several executive function tests. Even though the limited number of studies available makes it difficult to draw definitive conclusions.
- Better cardiovascular fitness in older adults is associated with improve arterial stiffness, higher vascular reactivity, and greater amplitude of cerebral oxygenation during exercise or cognitive tasks.
- Greater gray matter volume and white matter integrity were related to the cardiorespiratory fitness but less consistently related to physical activity.
- At least 12 weeks of an aerobic exercise program are required to give advantageous effects to the brain

And our experimental works show that:

In young males :

- The active individuals performed better in executive tasks than their inactive counterparts and had a larger change in prefrontal cortex oxygenation during the most complex conditions of Stroop task.
- High cardiorespiratory fitness was related to a better performance in dual-task and greater oxygenation on both sides of the prefrontal cortex.

In older males :

- Cardiorespiratory fitness is not related to Stroop task performance nor prefrontal cortex oxygenation in overall older males.
- Higher cardiorespiratory fitness was related to a better performance and greater right prefrontal cortex oxygenation during a Stroop task in 61+ years old group but not in 55-

60 years old group, suggesting the importance of age-group classification to evaluate the effect of cardiorespiratory fitness on executive function in older male subjects.

- Older males have stronger relationships between several vascular parameters and Stroop task performance than young males

This work shows the relationship between physical activity and cardiorespiratory fitness on executive functions in young and older males. The potential neurophysiological mechanisms that underlie that relationship, especially prefrontal oxygenation and vascular health, are presented.

Keywords: physical activity, cardiorespiratory fitness, prefrontal cortex, cerebral oxygenation, functional near-infrared spectroscopy, blood pressure, vascular, Stroop task, dual-task, n-back task, young males, older males, master athlete

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List of publication

List of publications on this thesis :

1. **Roman Goenarjo**, Laurent Bosquet, Sarah Fraser, Anaick Perrochon, Nicolas Berryman, Valentine Metier, Olivier Dupuy. *Prefrontal oxygenation reserve: The relationship between physical activity level and the cognitive load during a Stroop task in healthy young males*. In revision process in Frontiers in Behavioral Neuroscience.
2. **Roman Goenarjo**, Olivier Dupuy, Sarah Fraser, Anaick Perrochon, Nicolas Berryman, Laurent Bosquet. *Cardiorespiratory fitness, blood pressure, and cerebral oxygenation during a dual-task in healthy young males*. Published in Behavioral Brain Research. DOI: 10.1016/j.bbr.2019.112422.
3. Olivier Dupuy, **Roman Goenarjo,** Sarah Anne Fraser, Louis Bherer, Laurent Bosquet. (2019) *Master athlete and cognitive performance: What are the potential explanatory neurophysiological mechanism?* Published in Movement and Sports Sciences. DOI: 10.1051/sm/2019023.
4. **Roman Goenarjo**, Olivier Dupuy, Sarah Fraser, Anaick Perrochon, Nicolas Berryman, Laurent Bosquet. *The relationship between cardiorespiratory fitness and prefrontal oxygenation during a Stroop task in healthy older males*. In preparation to be submitted.
5. **Roman Goenarjo**, Olivier Dupuy, Sarah Fraser, Anaick Perrochon, Nicolas Berryman, Laurent Bosquet. *The correlation between vascular parameters and Stroop task performance in young and older males.* In preparation to be submitted.

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- Poster communications :
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- Oral communications :
    1. **Roman Goenarjo**, Olivier Dupuy, Sarah Fraser, Anaick Perrochon, Nicolas Berryman, Laurent Bosquet. (Mars 2018). *Interactions of blood pressure regulation, brain oxygenation, and executive functions during dual task walking in young and older men*. Was presented in le séminaire thématique de l'école doctorale Biosante, Université de Poitiers, Poitiers, France.

2. **Roman Goenarjo** (Juin 2018). *Interactions cœur-cerveau: de la rigidité artérielle, de la sensibilité baroréflexe et de l'oxygénation cérébrale sur les fonctions exécutives pendant une double tâche.* Was presented in the competition of "Ma These en 180 secondes (MT180)" in the 10th Joint Working Group Indonesia-France Cooperation 2018, Poitiers, France.
3. **Roman Goenarjo**, Olivier Dupuy, Anaick Perrochon, Nicolas Berryman, Sarah Fraser, Laurent Bosquet. (Juillet 2018). *The effect of aerobic fitness and blood pressure on brain activation during a dual task in healthy young adults*. Was presented in the 23ème annual congress of European Congress of Sport Science (ECSS), Dublin, Ireland.
4. **Roman Goenarjo**, Olivier Dupuy, Anaick Perrochon, Nicolas Berryman, Sarah Fraser, Laurent Bosquet. (Juillet 2019). *Prefrontal oxygenation reserve: link between physical activity level and executive functioning during computerized stroop task in healthy young males*. Was presented in the 23ème annual congress of European Congress of Sport Science (ECSS), Prague, Czech République and was participated in the competition of Young Investigator Award (YIA) ECSS 2019.

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INTRODUCTION

Executive function refers to a collection of cognitive abilities such as planning, set maintenance, impulse control, working memory, and attentional control" (Roberts and Pennington 1996). In general, executive function refers to an ability to maintain an appropriate problem-solving set for the accomplishment of a future goal (Yogev-Seligmann, Hausdorff, and Giladi 2008; Welsh and Pennington 1988). Executive function is essential for the quality of life, as executive functions are associated with the mental and physical aspects of health, also success in school and life. As human goes older, executive function is one of the main contributors to cognitive decline (Glisky 2006). Interestingly, when older adults receive supporting stimuli, executive function performance is better (Kirova, Bays, and Lagalwar 2015). Those facts reflect that executive function is a malleable cognitive function and could be influenced by various factors.

Aging is a factor that influences the executive functions. Several hypotheses, such as the hemispheric asymmetry reduction in older age model (HAROLD), the compensation-related utilization of neural circuits hypothesis (CRUNCH), and the astrocyte-neuron lactate shuttle (ANLS) model put forward a physiological basis of the effect of aging in the brain as a functional unit (Cabeza 2002; Reuter-Lorenz and Cappell 2008; Pierre J. Magistretti and Allaman 2015). Hypothetically, this relationship is mediated by the cerebrovascular system (Pierre J. Magistretti and Allaman 2015). The age-related change and dysfunction in the cerebrovascular system differentiate the executive function performances in young and older adults.

On the other side, physical activity has been known to give benefit to the cognitive function and to resist the deteriorating effect of aging (Mandolesi et al. 2018). More specifically, physical activity has been reported to improve executive function performance and cerebrovascular control. However, cardiovascular control is regulated differently in young and older adults (Uchino, Birmingham, and Berg 2010; Strait and Lakatta 2012). The benefit of physical activity, as well as the effect of aging on executive function, may be mediated differently between young and older adults (Strait and Lakatta 2012). The variety of methods that are used in the topic regarding the measure of physical activity and executive function give the challenge to draw a conclusion between results obtained. Standardization of the methods of research in this topic remains an issue that needs to be considered. Therefore, a comprehensive study that integrates components on the axis of the cardio-neurovascular-cognition in young and older subjects is required to give a better illustration of the relationship between physical activity and executive function performance.

We hope that we could shed some light on the effect of age and physical activity on executive function in males with this thesis. Therefore, we have two objectives: (1) To understand the impact of age and physical activity on cerebral oxygenation and executive function in males. (2)

To observe the influence of age on the correlation between vascular health and executive function. To obtain those objectives, five studies were conducted in this thesis project.

The first objective is defined by four studies, a literature review study and three experimental studies. The review study will summarize the effect of physical activity on brain structure, brain function, and executive function performance in older adults. Therefore, we could grasp the general view of the effect of physical activity on the brain. Hence, three cross-sectional studies will be directed to observe the impact of aging and the effect of physical activity on the brain with an emphasis on cerebral oxygenation and executive functions. Last, a study to identify the relation of vascular health variables to executive function will be conducted to fulfill the second objective. We will compare several vascular parameters and executive function performance on young and older male groups to observe the correlation between parameters and performances and also whether these groups modified the relationship in a different manner.

"On Wednesday, 13 September 1848, a railway foreman named Phineas Gage had a work accident in which an explosion launched a tamping iron out of the borehole and through the left side of his skull (Haas 2001). *It entered from under his left cheekbone, exiting through the top of his head, destroyed some of his brain* (Baars and Gage 2010). *Amazingly, Phineas Gage is still alive after that accident, he even could walk, speak, and had normal awareness* (Haas 2001; Baars and Gage 2010). *However, He had changed from a capable foreman with a well-balanced mind and shrewd business sense to a fitful, irrelevant, grossly profane, impatient, capricious, and vacillating individual* (Haas 2001). *He was also incapable to proceed with any plans. He was "no longer Gage" according to his friends* (Haas 2001). *After his dead, the skull and the tamping iron were donated to the Warren Museum at Harvard University School of Medicine* (Haas 2001). *Computer reconstruction on the skull found that the areas of the damaged brain corresponded to the frontal lobe* (Baars and Gage 2010). *This series of events have inspired research in the field of cognitive neuroscience about the relationship between frontal lobe and executive function."*

LITERATURE REVIEW

1 Executive Function

This section discusses the definition and components of executive function, brain organization of executive function, and the physiological basis of executive functioning in the brain. It presents the implications of executive impairment in various aspects. This chapter also explains the recent brain organization of executive function.

1.1 Executive Function

Executive function is one of the cognitive domains according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) along with complex attention, learning and memory, language, perceptual-motor function, and social cognition (Sachdev et al. 2014). It was Pribram in 1973, one of the first to use the term "executive" to describe the function of the frontal cortex (Pribram 1973). After that, Lezak (1982) defines executive function as a mental capacity necessary for setting goals, planning how to achieve them, and accomplishing these plans effectively (Lezak 1982). Then, Welsh and Pennington (1988) added inhibition as a part of executive function and describe it as "the ability to maintain set for future-oriented and goal-directed activity" (Welsh and Pennington 1988). This description includes the capacity to inhibit or defer a response, to plan strategically future actions, and to maintain a mental representation of the desired goal (Welsh and Pennington 1988). Then in 1996, Roberts and Pennington tried to cluster the components of executive function as they stated: "Executive function refers to a collection of related but somewhat distinct abilities such as planning, set maintenance, impulse control, working memory, and attentional control" (Roberts and Pennington 1996). In general, executive function refers to an ability to maintain an appropriate problem-solving set for the accomplishment of a future goal (Yogev-Seligmann, Hausdorff, and Giladi 2008; Welsh and Pennington 1988).

Modification of information by executive function is essential for the quality of life. With EF, skills such as reasoning, planning, and problem-solving are developed to overcome problems. Indeed, EFs are relevance to the mental and physical aspects of health, also success in school and life (see Table 1).

1.2 Components of Executive Function

There are three core of executive function (Diamond 2013; Miyake et al. 2000; Miyake and Friedman 2012): inhibition [inhibitory control, including self-control (behavioral inhibition) and interference control (selective attention and cognitive inhibition)], working memory, and cognitive flexibility (also called set-shifting, mental flexibility, or mental set shifting and closely linked to creativity). From these, the more complex executive functions are built, such as reasoning, problem-solving, and planning (Collins and Koechlin 2012).

1.2.1 Inhibitory Control

Inhibitory control is described as control of attention, behavior, thoughts, and emotions to outweigh an internal drift or external lure, and instead, do what is more appropriate or needed (Diamond 2013). Inhibitory control enables us to focus attention on a stimulus and suppressing attention to other stimuli. Besides known as selective or focused attention, this has been called attentional control or attentional inhibition, endogenous, top-down, active, goal-driven, voluntary, volitional, or executive attention (Theeuwes 2010). Self-control is an aspect of inhibitory control of behavior and emotion. This aspect is about resisting temptations and not acting impulsively (Diamond 2013). Stroop test is the most frequently used test in the research measuring inhibitory control. (Faria, Alves, and Charchat-Fichman 2015)

Table 1. Relevancy of Executive Function to Some Aspects of Life

Aspects	Relevancy of Executive Function
Mental health	Executive functions are impaired in mental disorders, including addictions, attention deficit hyperactivity (ADHD), conduct disorder, depression, obsessive-compulsive disorder (OCD), schizophrenia (Baler and Volkow 2006; Lui and Tannock 2007; Fairchild et al. 2009; Taylor Tavares et al. 2007; Penadés et al. 2007; Barch 2005)
Healthy lifestyle	Better executive functions are associated with higher participation in regular exercise classes, less obesity, overeating, and substance abuse (Will Crescioni et al. 2011; H. V. Miller, Barnes, and Beaver 2011; Riggs et al. 2010; Hall, Elias, et al. 2008)
School readiness	Executive functions are more critical for school readiness than IQ or reading or math score (Blair and Razza 2007; Duncan et al. 2007)
School success	Executive functions predict both math and reading competence throughout the school years (Borella, Carretti, and Pelegrina 2010; Duncan et al. 2007)
Job success	Better executive functions are associated with higher productivity and lower difficulty to find and keep a job (Bailey 2007)
Marital harmony	Partners with better executive functions are less difficult to live with, more responsible, and less likely to act impulsively (Eakin et al. 2004)
Public safety	Better executive functions are associated with less reckless behavior, violence, and crime (Broidy et al. 2003; Denson et al. 2011)
Risk of fall	Better executive functions are associated with decreased risk of falls (Mirelman et al. 2012)
Quality of life	Better executive functions are associated with a better quality of life (Davis et al. 2010)

1.2.2 Working Memory

Working memory is defined as the capability to hold information in mind and to manipulate or to mentally work with it (Baddeley 1998; Smith and Jonidesl 1999). Working memory is essential for making sense of information that develops over time. Many activities require holding in mind what happened previously and relating to what comes later, such as making sense of written or spoken language, doing a calculation, reordering items, and translating instruction into action plans. Working memory is also crucial to the ability to see the connection between things (Diamond 2013). Digit Forward and Backward subtests (WAIS-R or WAIS-III) and N-back test are two frequently used tests in this component. (Faria, Alves, and Charchat-Fichman 2015)

1.2.3 Cognitive Flexibility

Cognitive flexibility is termed as the ability to switch flexibly back and forth between tasks, operations, or mental sets (Miyake et al. 2000). Cognitive flexibility is constructed on inhibitory control and working memory (Davidson et al. 2006). In cognitive flexibility, switching between tasks needs a capacity to change perspectives. To change perspectives, inhibition of the previous perspective and activation of another perspective are needed (Diamond 2013). In this logic, cognitive flexibility involves inhibitory control and working memory. Another aspect of cognitive flexibility is creative thinking or to change a way to solve a problem (Diamond 2013). Trail Making Test (TMT) form B, Wisconsin Card Sorting Test (WCST), and Stroop Test are the most frequently used tests to assess cognitive flexibility (Faria, Alves, and Charchat-Fichman 2015).

1.2.4 Resume

- Executive function is defined as the ability to maintain an appropriate problem-solving set for the accomplishment of a future goal.
- The executive function consists of three core components: inhibition, working memory, and flexibility.
- Executive function is related to various aspects of life, such as mental health, unhealthy lifestyle, school readiness and success, job success, marital harmony, public safety, risk of fall, and quality of life.

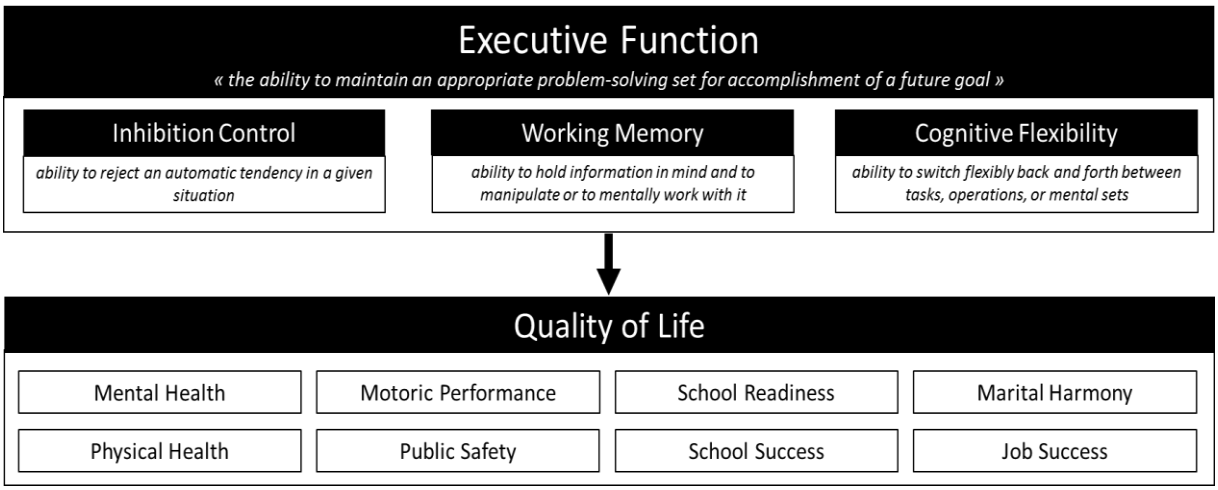


Figure 1. Resume of components of executive function and its relevance to some aspects of life

1.3 Brain Organization of Executive Function

The underlying organization of executive function has historically been attributed to the frontal lobes, Firstly based on work by Luria (1969), who reported that patients with frontal lobe damage failed to modify their behavior appropriately on various mental tasks (Munro et al. 2018).

Shallice (1982) and Goldman-Rakic (1987) declared that the prefrontal cortex has an important role in executive function (Shallice 1982; Goldman-Rakic 1987). However, Some of the investigators in this topic, such as Fletcher (1996) argued that the underlying physiological organization of executive function is complex and likely involves integrated neural networks from various brain regions (J. M. Fletcher 1996). In the following part, according to their lobes, as presented in Figure 2, brain lobes associated with tasks of executive functions in a healthy subject are described.

1.3.1 Frontal Lobe

The frontal brain lobe, in general, was implicated in all executive functions' measures across all studies. Based on tasks, specifically, the N-back working memory task indicated activation in similar areas. Specifically, results from Drobyshevsky, Baumann, and Schneider (2006) showed activation in the dorsolateral prefrontal cortex and the left precentral cortex (Drobyshevsky, Baumann, and Schneider 2006). Moreover, this study reported decreased activation in the left dorsolateral prefrontal cortex, inferior frontal cortex, and the precentral gyrus with increased age. Satterthwaite et al. (2013) reported increased activation in the dorsolateral prefrontal cortex due to an increased working memory load from the N-back task (Satterthwaite et al. 2013). Also, Ball et al. (2011) reported increased activation in the lateral prefrontal cortex, as well as the left inferior and middle frontal gyrus (Ball et al. 2011).

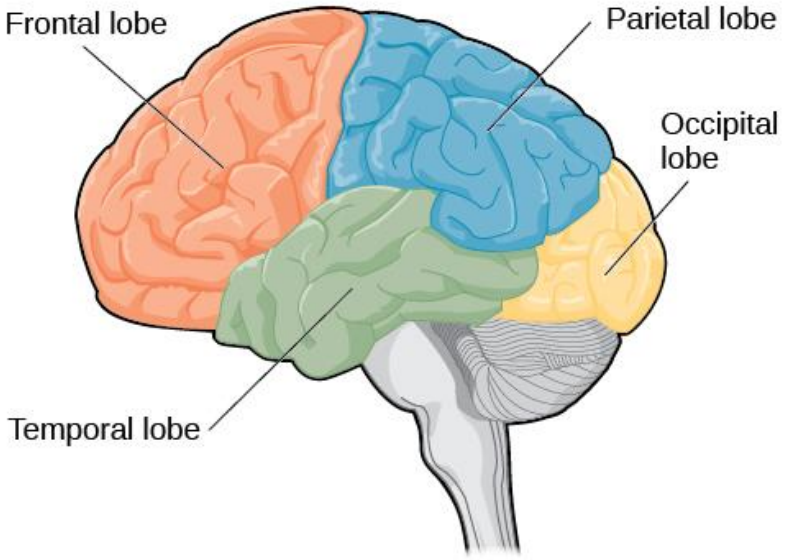


Figure 2. The lobes of the brain (Taken from (Lumen 2019b)**)**

Secondly, fMRI results while performing the go/no-go task indicated increased activation in the right middle and inferior frontal gyrus (Fuentes-Claramonte et al. 2016; Mulligan et al. 2014; Ball et al. 2011), as well as bilateral activation in the anterior prefrontal, and inferior and middle frontal lobes (Dodds, Morein-Zamir, and Robbins 2011; Mulligan et al. 2014). The frontal brain lobe increased activation was found to be associated with inhibition (Ball et al. 2011; Dodds, Morein-Zamir, and Robbins 2011; Mulligan et al. 2014).

Several fMRI studies that used the Stop-signal task (SST) reported increased activation in the frontal gyrus, and prefrontal and frontal cortices (Chikazoe et al. 2009; Jimura et al. 2014). Specifically, Ide and Li (2011) reported the adult participants of their study showed increased activation in the ventrolateral prefrontal cortex during behavior adjustment as a response to errors (J. S. Ide and Li 2011). Similarly, Hu and Li (2012) indicated activation in the right prefrontal cortex during reparatory motor inhibition (Hu and Li 2012). Also, adult participants with shorter stop-signal reaction times showed greater activity in the right orbital frontal cortex during preparatory inhibition (Hu and Li 2012). White et al. (2014) found increased right frontal pole and left middle frontal gyrus activation was correlated with quicker processing of the Go stimulus in Stop and Go trials and the right inferior frontal gyrus, the medial frontal gyrus, and basal ganglia were correlated with the stimulus processing speed during Stop-trials (White et al. 2014).

Lastly, shifting tasks were found to increase in activation within the frontal brain lobe (Munro et al. 2018). Specifically, Witt and Stevens (2012) found activity in frontal lobes during the switching of a task (Witt and Stevens 2012). Another study indicated that adults with an average IQ showed greater activation in the prefrontal lobe via fMRI than did a comparison group of high IQ individuals (Graham et al. 2010). Besides, a study with youth participants who underwent DTI imaging while completing the Stroop task found improved task switching was related to greater integrity of the precentral gyrus WM and superior corona radiate in the frontal cortex (Seghete, Herting, and Nagel 2013).

1.3.2 Parietal Lobe

The parietal brain lobe is activated during a range of executive function tasks, including the N-back task, go/no-go task, and SST (Munro et al. 2018). Regarding the N-back task, fMRI results found to significantly activate the precuneus, as well as the superior parietal cortex (Satterthwaite et al. 2013). With the go/no-go task, a study indicated that the attention-shifting requirements within this task were associated with the increased activation in the left inferior parietal cortex of the adult participants (Dodds, Morein-Zamir, and Robbins 2011). Similarly, the SST was also found increased activity in the precuneus among a group of healthy adult participants (Chikazoe et al. 2009; S. Zhang and Li 2012).

1.3.3 Temporal Lobe

In the healthy subjects, no study was found an association between executive functioning and activation in the temporal lobe. However, in subjects with ADHD or dementia, four studies indicated brain activation in the temporal lobe (Banich et al. 2009; Dibbets et al. 2010; Spinelli et al. 2011; Eslinger et al. 2011). Specifically, those studies reported activation in the temporal gyrus based on fMRI imaging, among adult, children, and adolescent participants with ADHD and in patients with dementia. The executive functions' measures consisted of the Stroop task (Eslinger et al. 2011; Banich et al. 2009), a switch task (Dibbets et al. 2010), and the go/no-go task (Spinelli et al. 2011).

1.3.4 Occipital Lobe

Same as in the temporal lobe, no study was found an association between executive functioning and activation in the occipital lobe in healthy subjects. In studies among participants with ADHD, results in the occipital brain lobe varied across three studies, with each study using a different executive function measure. Specifically, Dibbets et al. (2010) found increased activation in the lingual gyrus of the occipital lobe from administration of the switch task (Dibbets et al. 2010), while two other studies indicated reduced activation in the cortico-subcortical networks of the bilateral occipital lobe from the N-back task (Massat et al. 2012) and the right occipital cortex from the go/no-go task (Suskauer et al. 2008).

1.3.5 Resume

- The frontal lobe was reported in all studies that relate brain lobe activation with executive function tasks.
- The parietal lobe was also associated with executive functions in several studies that used go/no-go task, Stop-signal task, and N-back task.
- The temporal and occipital lobes were involved during executive function tasks in subjects with ADHD or dementia but not in healthy subjects.
- Studies of brain organization of executive function showed that the frontal lobe is the main lobe of executive functions with the involvement of the parietal lobe in several tasks. Temporal and occipital lobes seem activated only in a particular population of subjects.

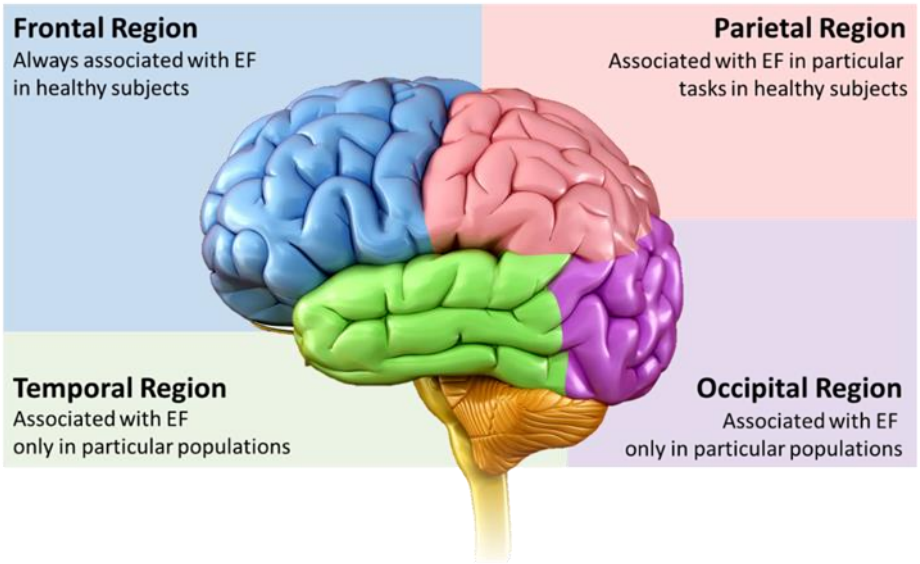


Figure 3. The Lobes of the brain and its association with executive function

1.4 Effect of Executive Function on The Health-Promoting Behaviors

In addition to being affected by physical activity level and cardiorespiratory fitness, executive function is also likely to be necessary for the initiation and maintenance of physical activity and cardiorespiratory fitness by promoting healthy behaviors. Healthy behaviors typically involve the pursuit of longer-term benefits at the expense of short-term gain (Chapman 2005). Important outcomes such as weight loss, fitness, and health are all achieved by effortfully and consistently changing behavior in the present (e.g., by doing exercise, by eating healthy foods, by resisting sedentary activities, by not smoking, or by drinking less alcohol). Therefore, it is reasonable that good EF— an ability to maintain an appropriate problem-solving set for the accomplishment of a future goal (Yogev-Seligmann, Hausdorff, and Giladi 2008; Welsh and Pennington 1988). — should improve the chances that people will be able to initiate and maintain healthy behaviors to obtain health benefits. This reciprocal relationship of executive function, healthy behaviors, health benefits (specifically on the brain and neurovascular function) outlined in figure 4.

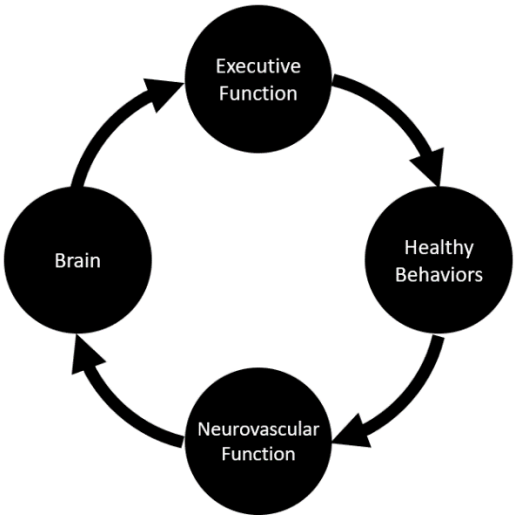


Figure 4. The reciprocal relationship between executive function, healthy behaviors, and health benefits

A cohort study from Peeters et al. (2015) followed up over two years, 534 young adults who yet to drink alcohol. Executive function performance at the beginning of the study significantly predicts when they begin drinking alcohol and whether or not they experience an over-drinking (Peeters et al. 2015). The same study also reported that in the next 6-month period, Executive function also significantly predicts an increase in alcohol consumption (Peeters et al. 2015). Studies of transcranial magnetic stimulation (TMS), a technique where the activity in specific areas of the cortex can be reduced using external electromagnetic pulses, further revealed the role of executive function on health behaviors. Lowe et al. (2014) used TMS focused at the left dorsolateral prefrontal cortex (DLPFC) to decrease its activation temporarily [338]. They reported that the subjects had a decrease in performance on executive function tests and an increase of self-reported snack food cravings and consumption after left DLPFC stimulation (Lowe, Hall, and Staines 2014). The result is in line with fMRI studies, which report that left DLPFC activation is associated with the self-control of cravings for unhealthy foods and cigarettes (Hare, Camerer, and Rangel 2009; Kober et al. 2010).

Executive function is essential for healthy behaviors. With executive function, skills such as reasoning, planning, and problem-solving are developed to initiate and maintain healthy behaviors. Indeed, executive functions are related to participation and maintenance of a wide range of health behaviors (see Table 2).

Table 2. Relation of Health Behaviors with Executive Function

Aspects	Relation with Executive Function
Alcohol consumption	Individuals with better executive functions having less alcohol temptation and less likely to drink to excess or develop problems with alcohol (Hofmann et al. 2012; Fernie et al. 2013)
Food consumptions	Individuals with better executive functions are more likely to stick to their stated dietary intentions, less likely to consume fatty foods, have less unintentional chocolate consumption (Allan, Johnston, and Campbell 2011; Allan, McMinn, and Daly 2016; Hall 2012)
Medication	more likely to correctly adhere to medication regimes (Stilley et al. 2010; Panos et al. 2014)
Physical activity	Better executive functions predict the realization of physical activity intentions, participation in regular exercise classes, related to a closer correspondence between intended and actual physical activity, and associated with physical activity behaviors (Hall, Fong, et al. 2008; Hall, Elias, et al. 2008; McAuley et al. 2011; Sheeran 2002)
Smoking	Smokers with greater brain activation in the right inferior frontal gyrus, pre-supplementary motor area, and basal ganglia during a response inhibition task are less likely to smoke in response to cravings than others; and better executive function smokers are more likely to quit smoking, successfully (Brega et al. 2008; Nestor et al. 2011).
Weight loss program	Dieters with better response inhibition are more likely to resist temptation successfully and to lose weight than the ones with weak response inhibition (Hofmann et al. 2014)
Attachment to general health behaviors	Executive functions moderate the strength of the association between intentions and health behaviors (Hall, Fong, et al. 2008)

1.4.1 Resume

- In addition to being affected by physical activity level and cardiorespiratory fitness, executive function is also likely to be necessary for the initiation and maintenance of physical activity and cardiorespiratory fitness by promoting healthy behaviors.
- Executive functions are related to participation and maintenance of a wide range of health behaviors
- The link of executive function, healthy behaviors, and health benefits is likely a reciprocal relationship.

1.5 Summary of Section

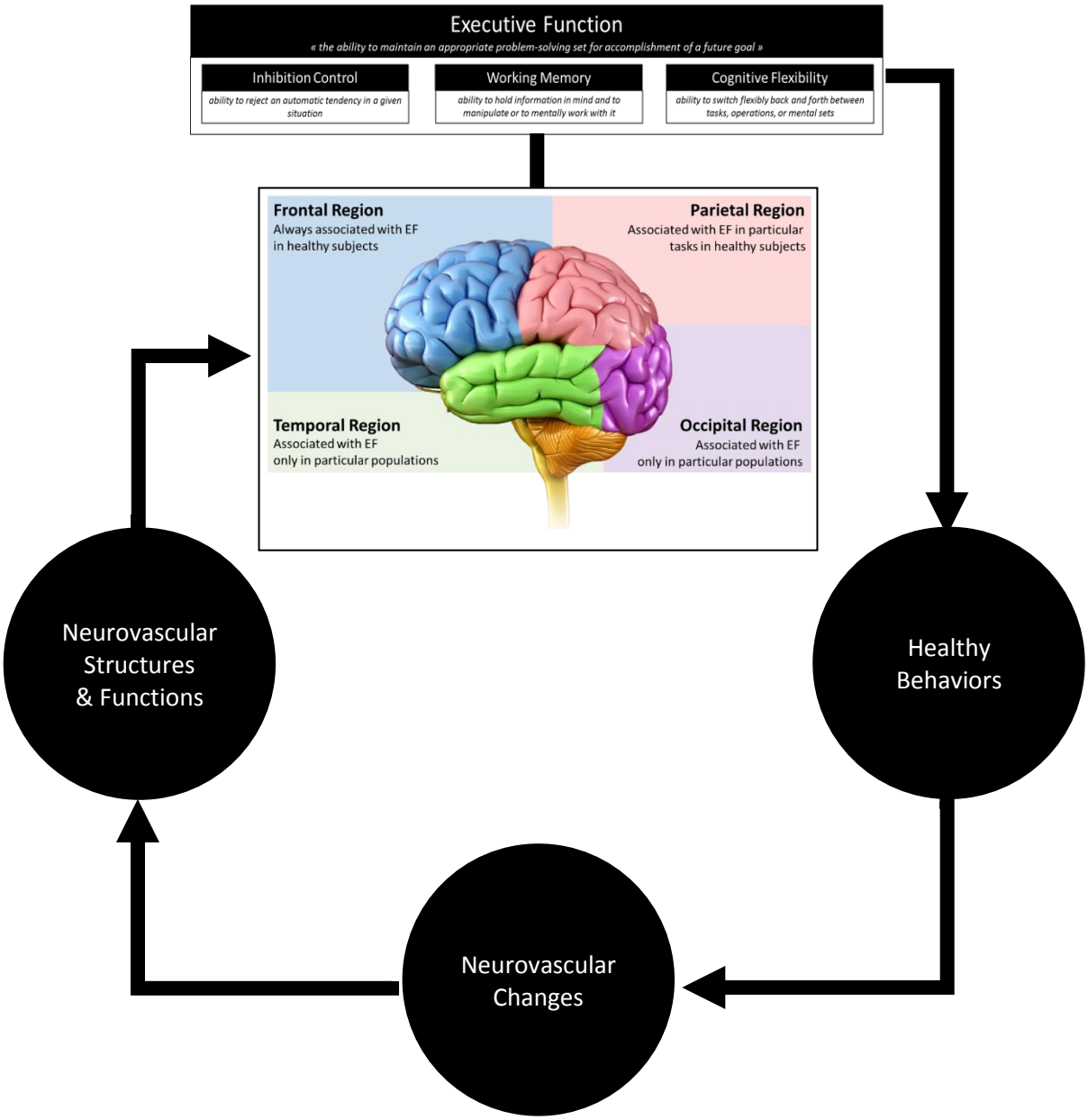


Figure 5. Schematic integration of components and brain organization of executive function in their relationship with healthy behaviors and neurovascular components

Having its first annual meeting in 1971, cognitive neuroscience, a relatively new multi-disciplinary science that is concerned with the biological processes and aspects that underlie cognition, began to be known publicly ("Cognitive Neuroscience" 2019; Baars and Gage 2010). *At that time, research in the field of cognitive neuroscience was constrained by the unavailability of conducting empirical study at physiological level* (Posner and DiGirolamo 2000). *The discoveries and developments of various brain imaging tools, such as EEG, fMRI, and fNIRS, helped to unveil mysteries of human brain and opened various opportunities for cognitive neuroscientists to investigate and determine brain-cognition mechanisms, from the development of the brain to the aging process of the brain, including the understanding of executive function and its underlying physiological processes*

2 Physiological Basis of Brain Function

This section discusses the primary cells that made the brain (neuron and glia), how brain cells activated, and how the energy generated during the activation. The last part of this chapter discussed neurovascular coupling and the role of cerebral blood flow (CBF) on neurovascular coupling.

2.1 Brain Cells and Their Functions

The central nervous system (CNS) includes the brain and spinal cord. It consists of two basic types of cells: neurons and glia. Neurons are the primary cells for the cognitive processes in the brain as they transmit signals between them, and glia provides a supporting system to the function of neurons. Neurons and glia are illustrated in Figure 6.

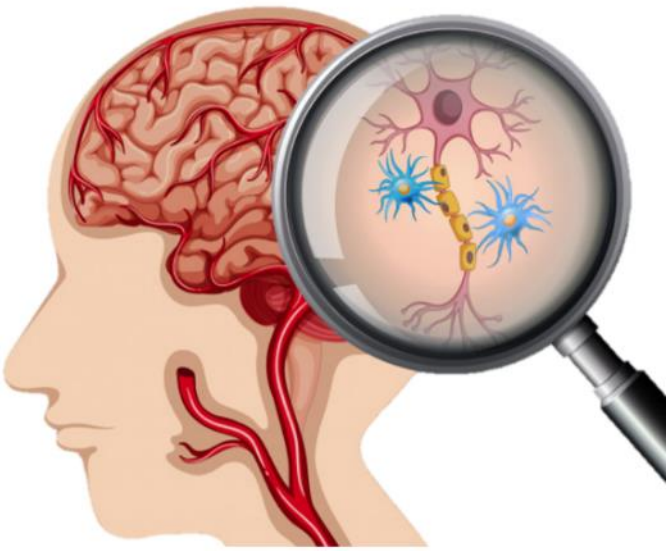


Figure 6. Cartoon illustration of neuron and glia in the brain (modified from (Freepik 2019; Designua 2019)**)**

2.1.1 Neurons

Neurons are information messengers that control various behaviors from basic reflexes to more complicated behaviors like executive functioning. This function based on the ability of neurons to communicate with cells or other neurons. Neurons use electrical impulses and chemical signals to transmit information to the target cells (L. R. Squire et al. 2012).

Similar to other cells, each neuron has a cell body that comprises a nucleus, mitochondria, Golgi apparatus, smooth and rough endoplasmic reticulum, and other cellular structures (L. R. Squire

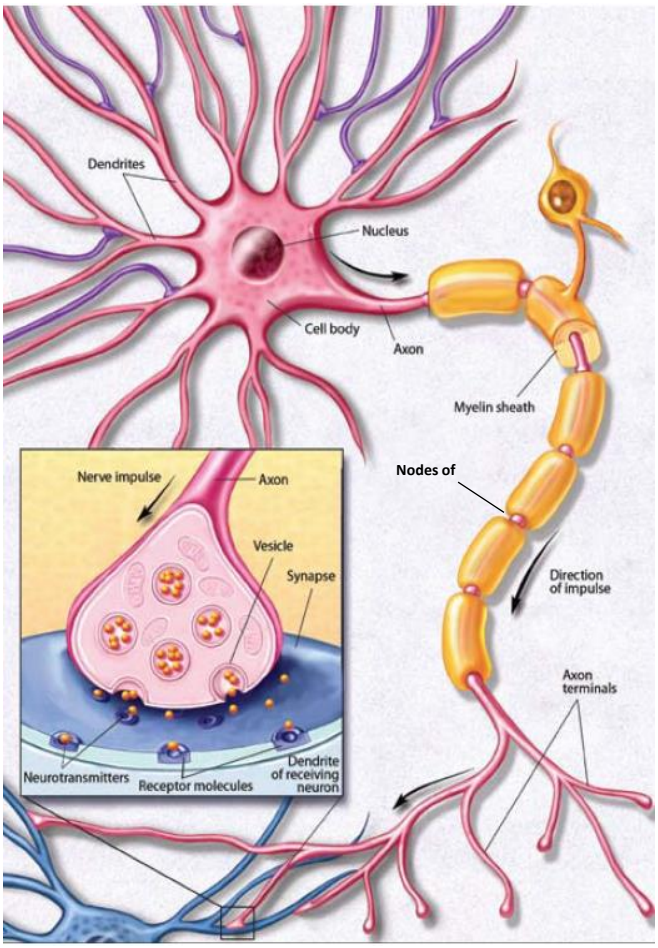


Figure 7. Cartoon illustration of a neuron within the nervous system. Inset, bottom left corner: illustration of a synapse, a specialized junction where the end of axon terminal of one neuron contacts with the dendrite of another neuron or other structures (Modified from [M. Miller, Kibiuk, and Stuart 2008]).

et al. 2012). Neurons also have dendrites for receiving the electrical signals that start neuronal communication. Dendrites are structures that extend away from the cell body to collect messages from other neurons at specialized junctions called synapses (L. R. Squire et al. 2012). Some neurons have multiple dendrites, while other neurons do not have any dendrites (L. R. Squire et al. 2012). Dendritic spines are small protrusions that increase surface area for possible synaptic connections (L. R. Squire et al. 2012).

After a signal is received by the dendrite, it will travel to the cell body. The cell body has a specialized structure, the axon hillock, that integrates signals from multiple dendrites and serves as a connector between the cell body and an axon (Costanzo 2014; Bloom 2012). An axon is a structure that propagates the integrated signal from the axon hillock to specialized endings of the axon called axon terminal (L. R. Squire et al. 2012). These terminals form synapse on other neurons, muscles, or other target organs. Chemicals released from axon terminals to the synapse allow signals to be communicated. Neurons mostly have one or two axons, but some neurons do not have any axons (Costanzo 2014). Axons are covered with myelin, a lipid substance that minimizes the dissipation of the traveling electrical signal along the axons, increasing the velocity of signal conduction (Costanzo 2014). Along the axon, there are gaps in between the myelin sheaths (L. R. Squire et al. 2012; Costanzo 2014). These gaps are called nodes of Ranvier, sites where ions diffuse along the axon (L. R. Squire et al. 2012). The myelin is not part of the neuron. Myelin is produced by glial cells, which will be explained in the following section (Bloom 2012). All of those neurons' structures are illustrated in Figure 7 (M. Miller, Kibiuk, and Stuart 2008).

2.1.2 Glia

While glia is often thought of as the supporting cast of the nervous system, the number of glial cells in the brain 1.4 times the number of neurons (Hilgetag and Barbas 2009). Glial cells have a

vital role in supporting the function of neurons. Glial cells buffer ions and chemicals that could harm neurons, provide myelin sheaths around axons, and guide developing neurons to their destinations (Bloom 2012; Costanzo 2014; L. R. Squire et al. 2012). Scientists have discovered that glial cells also play a role in responding to nerve activity and modulating communication between nerve cells (Bloom 2012).

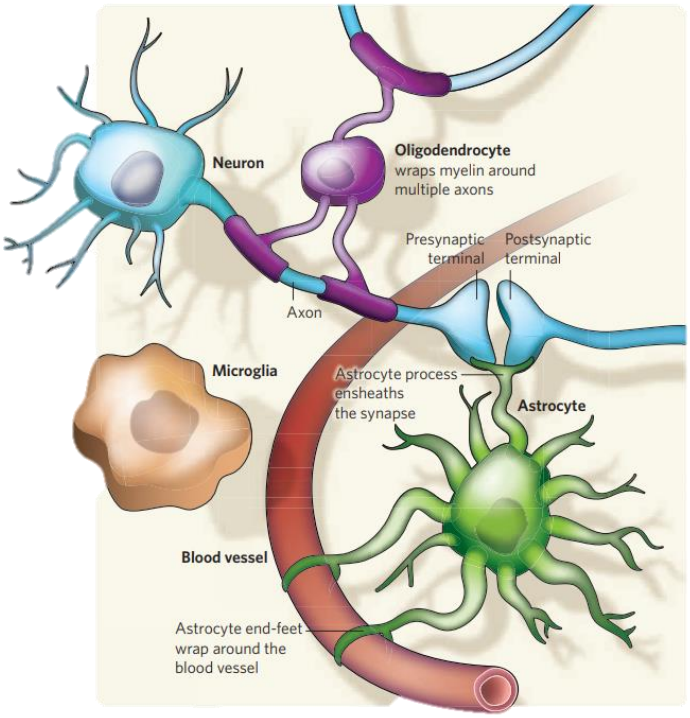


Figure 8. Cartoon illustration of glial cells within the neurovascular system (Taken from [Allen and Barres 2009]).

There are several different types of glia, three of which are shown in Figure 8 (Allen and Barres 2009). They provide structural support for synapses, control the concentrations of ions and chemicals in the extracellular fluid, and deliver nutrients and other substances to neurons (Bloom 2012). Astrocytes connect both capillaries and neurons in the CNS to synchronize neurotransmission and metabolism of neurons (Bloom 2012; Allen and Barres 2009). Astrocytes also form the blood-brain barrier to blocks the entrance of toxic substances into the brain (Bloom 2012; Costanzo 2014; Allen and Barres 2009). Astrocytes regulate nerve activity, transmit calcium waves between astrocytes, and modulate the activity of surrounding synapses (Bloom 2012). Microglia scavenge dead cells and protect the brain from invading microorganisms (Bloom 2012). Last, oligodendrocytes produce myelin sheaths around axons in the CNS to speed up the conduction velocity of the action potential (Bloom 2012; L. R. Squire et al. 2012; Allen and Barres 2009). One oligodendrocyte can produce myelin for multiple neurons, but also one axon can be myelinated by several oligodendrocytes (Bloom 2012).

2.1.3 Resume

- Neurons are the main cells in the brain for cognitive function by stimulating electrical impulses and secreting chemical signals to relay information between them.
- Glia is the supporting cells of nervous systems by buffer harmful ions and chemicals and modulates oxygen and nutritional supply to neurons.
- Several types of glia cells: Astrocyte, microglia, and oligodendrocyte.

2.2 Brain Activation

Brain activation is related to the function of the brain to generate electrical potentials and release chemical signals (Roland 1994). All functions performed by the brain, from a simple motor reflex to more advanced functions like making a memory or a decision, need neurons to communicate with other neurons. While humans use words and body language, neurons use electrical and chemical signals to communicate (L. R. Squire et al. 2012). Neurons usually receive and integrate signals from multiple other neurons before they send signals to other neurons. For the nervous system to be well-functioning, neurons must be able to receive and send signals. These actions can occur because neuron has a charged cellular membrane (an electrical potential difference between the inside and outside of the membrane), and it can change in response to neurotransmitter released from other neurons (Costanzo 2014). To understand how neurons communicate, it is important to know the resting membrane potential and how an action potential is generated.

2.2.1 Neuronal Charged Membranes

The lipid bilayer that constructs the membrane of a neuron is impermeable to charged ions (Costanzo 2014; L. R. Squire et al. 2012). Charged Ions must pass through ion channels located in the membrane to enter or exit the neuron. Ion channels have different configurations: closed, open, and inactive, as illustrated in Figure 9 (Lumen 2019a). To allow charged ions to pass inside or outside of the cell, some ion channels need to be activated (L. R. Squire et al. 2012). These types of ion channels are sensitive to the environment changes and can change their configuration accordingly (L. R. Squire et al. 2012). These Ion channels that change their configuration in response to voltage changes are called voltage-gated channels (Costanzo 2014). Voltage-gated channels regulate the relative concentrations of ions between the inside and outside the cell. The difference in total electrical charge between the inside and outside of the cell is called the membrane potential (Costanzo 2014).

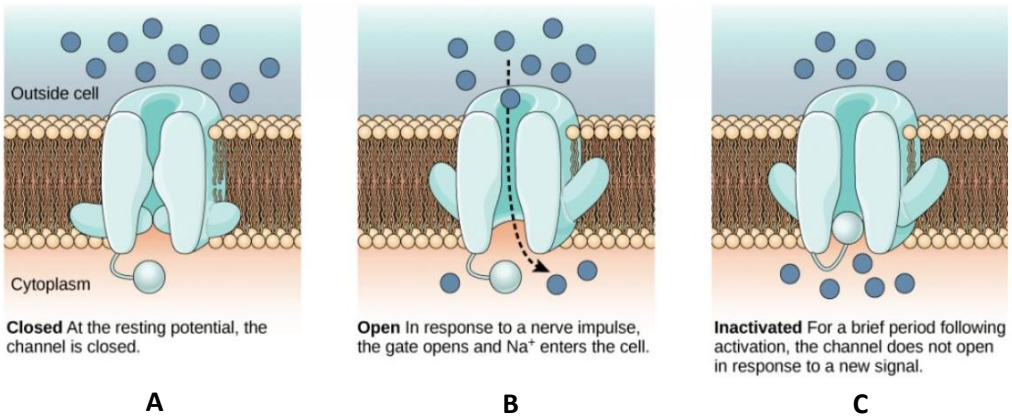


Figure 9. A sequence of action of a voltage-gated ion channel. A. Closed, B. Open, C. Inactivated (modified from (Lumen 2019a)**)**

2.2.2 Resting Membrane Potential

Neurons at rest have a negative charge: generally, the inside of a cell is 70 millivolts more negative than the outside (Costanzo 2014). This state is called the resting membrane potential; it is caused by differences in the concentrations of ions inside and outside the cell at rest (Costanzo 2014; L. R. Squire et al. 2012). If the membrane were evenly permeable to all ions, the system would reach equilibrium. However, because ions cannot cross the cell membrane freely, there are different concentrations of ions inside and outside the cell, as presented in Table 2 (Costanzo 2014; Bloom 2012).

Table 3. Extracellular and Intracellular ion concentrations during resting membrane potential (modified from (Costanzo 2014)**)**

Substance	Extracellular Fluid (mEq/L)	Intracellular Fluid (mEq/L)
Na^+	140	14
K^+	4	120
Ca^{2+}	2.5	$1x10^{-4}$
Cl^-	105	10
HCO_3^-	24	10

Na^+, sodium ions; K^+, potassium ions; Ca^{2+}, calcium ions; Cl^-, chloride ions; HCO_3^-, bicarbonate ions; mEq/L, milliequivalents per litre

The difference in the quantity of positively charged potassium ions (K+) between the inside and outside of the cell determines the resting membrane potential (Costanzo 2014; L. R. Squire et al. 2012). The negative charge when the cell at rest is generated by the cell membrane greater permeable to K+ movement than the sodium ion (Na+) movement (Costanzo 2014; L. R. Squire et al. 2012). In neurons, K+ is maintained at high concentrations within the cell, while Na+ is maintained at high concentrations outside of the cell (Costanzo 2014; L. R. Squire et al. 2012). The cell possesses K+ and Na+ leakage channels that allow the two cations to diffuse down their concentration gradient. However, the neurons have far more K+ leakage channels than Na+ leakage channels (L. R. Squire et al. 2012). Therefore, K+ diffuses out of the cell at a much faster rate than leaks in of Na+. Because more K+ are leaving the cell than Na+ are entering, negative charge is generated inside the cell. Once established, the actions of the Na+/K+ ATPase pump help to preserve the resting potential. The action of Na+/K+ ATPase is an energy-consuming event for bringing two K+ ions into the cell while removing three Na+ ions, one molecule of adenosine triphosphate (ATP) is consumed (Costanzo 2014; L. R. Squire et al. 2012). These interactions of events displayed in Figure 10 (Lumen 2019a).

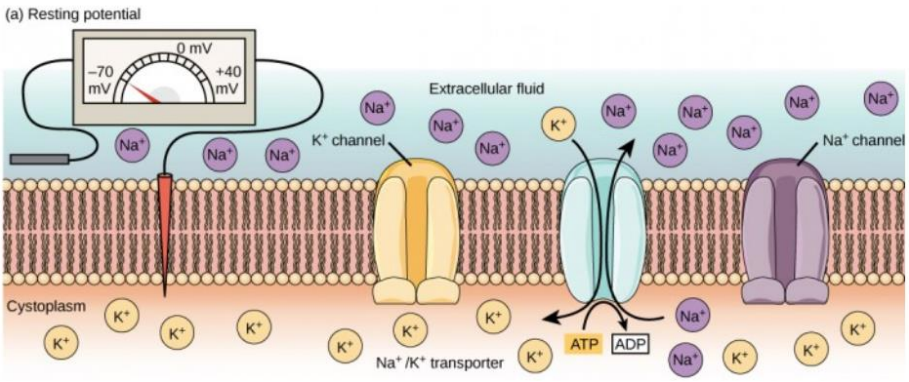


Figure 10. Interaction of ions, channels, and Na^+/K^+ ATPase during resting membrane potential in a neuron (Taken from (Lumen 2019a)**)**

2.2.3 Action Potential

A neuron receives stimuli from other neurons and sends the signal to another neuron. Transmission of a signal between neurons is carried by a chemical called neurotransmitters (Bloom 2012; L. R. Squire et al. 2012; Costanzo 2014). Transmission of a signal along the neuron is carried by a sudden change of the resting membrane potential called an action potential (Costanzo 2014; Bloom 2012; L. R. Squire et al. 2012). Neurotransmitters bind to receptors on dendrites then opened ion channels (Bloom 2012; L. R. Squire et al. 2012; Costanzo 2014). At excitatory synapses, this opening of the ion channels allows sodium ions to enter the neuron and depolarize the membrane. Depolarization marked by a decrease in the voltage difference between the inside and outside of the neuron (L. R. Squire et al. 2012). If the depolarization of the target neuron reaches its threshold potential (-55 mV) (L. R. Squire et al. 2012), Na+ channels in the axon hillock open, permitting positive ions to enter the cell (Lumen 2019a). After the sodium channels open, the neuron will completely depolarize to a membrane potential of about +40 mV (Costanzo 2014; L. R. Squire et al. 2012). Action potentials are an "all or none" event, that once the threshold potential is reached, the neuron always completely depolarizes (Costanzo 2014; Bloom 2012; L. R. Squire et al. 2012).

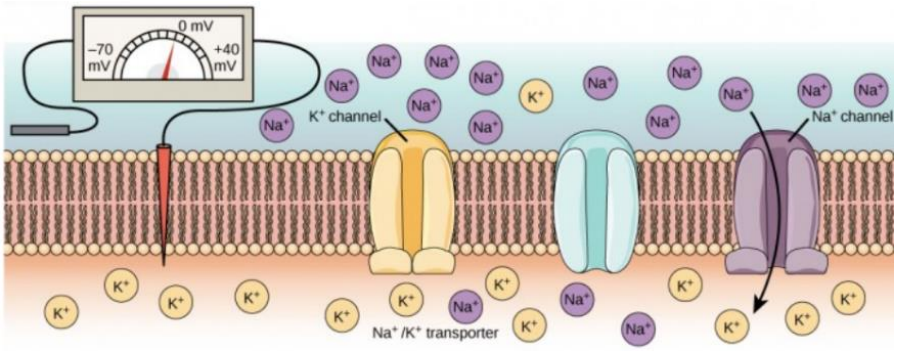


Figure 11. Events involving ions, channels, and Na^+/K^+ ATPase that lead to depolarization (Taken from (Lumen 2019a)**)**

Once depolarization is complete, the cell must reset the membrane voltage back to the resting potential. To return to the resting potential, the sodium (Na+) channels will close and cannot be opened (Costanzo 2014; L. R. Squire et al. 2012). Concurrently, voltage-gated potassium (K+) channels start to open and allow K+ to leave the cell (Costanzo 2014; L. R. Squire et al. 2012).

As K+ leaves the cell, the membrane potential starts to decrease and will become negative. The diffusion of K+ to the outside of the cell continues until it hyperpolarizes the membrane cell. At this point, the Na+ channels already return to their resting state and able to open again if the membrane potential exceeds their threshold potential (Costanzo 2014). Eventually, the extra K+ diffuses out of the cell through the K+ leakage channels, changing the cell from its hyperpolarized state to the resting membrane potential (Costanzo 2014; L. R. Squire et al. 2012).

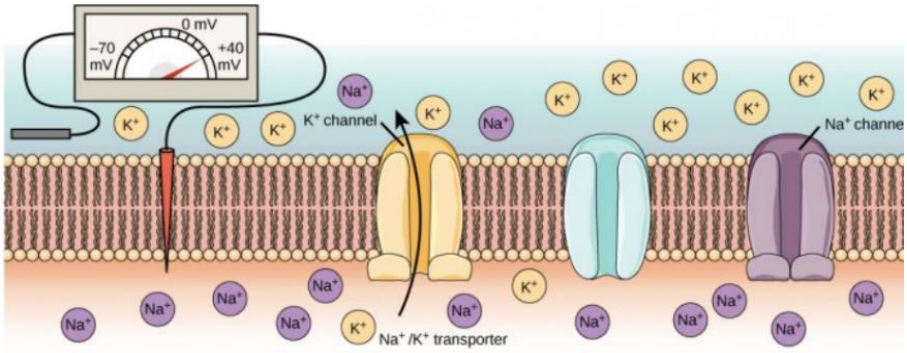


Figure 12. Events involving ions, channels, and Na^+/K^+ ATPase that lead to hyperpolarization (Taken from (Lumen 2019a)**)**

2.2.4 Resume

- Brain activation is related to the basic function of the brain to transmit information between neurons by generating electrical potentials and releasing chemical signals, which consists of preserving resting membrane potential and forming action potential.
- The numbers of potassium ions (K+) and sodium ion (Na+) across the cell membrane determine the resting membrane potential.
- The movements of potassium ions (K+) and sodium ion (Na+) across the cell membrane through its channels or pumps generate an action potential.
- The formation of an action potential can be separated into five steps:
  - Depolarization of target cell by stimuli from a sensory cell or another neuron.
  - Opening of all the Na+ channels, If the threshold of excitation is reached.
  - Opening of K+ channels at the peak action potential. K+ begins to leave the cell, and at the same time, Na+ channels close.
  - Hyperpolarization of the membrane as K+ ions continue to leave the cell. The hyperpolarized membrane is a refractory period and then cannot fire another action potential.
  - Closing of the K+ channels close and restoration to the resting potential by the Na+/K+ ATPase.

2.3 Energy Demands for Brain Activation

Although the human brain is 2% of the body's weight, it accounts for 20% of relative oxygen consumption (Attwell et al. 2010) Compare to other organs, the brain is one of the greatest users of oxygen in humans (Table 3) (Dienel 2018). The fact that the brain has a minimal oxygen reserve and neuron cannot store glycogen, making the sustainability of energy in the brain has

important implications. Deficits in the brain's energy supply make it susceptible to decrease cognitive performance to brain damage during anoxia or ischemia, and knowing the demands made by different neural mechanisms may help understand the importance of the brain's energy metabolism to maintain brain functions.

Table 4. Relative oxygen consumption in adult human organs (Modified from (Dienel 2018)**)**

Organ	% Body Mass	% Oxygen Utilization (%O_2use)	%O_2use/%Body Mass
Liver	2	17	8.5
Gastrointestinal tract	2	10	5
Kidney	0.5	6	12
Heart	0.4	11	27.5
Brain (adult)	2	20	10
Brain (5-years-old)	6	50	8.3

% body mass, percentage of organ mass per total body mass; %O_2use, percentage of organ oxygen use per total oxygen use; %O_2use/%body mass, (percentage of organ oxygen use per total oxygen use) per (percentage of organ mass per total body mass)

Based on the energy-requiring processes in neurons, the estimation of the relative demands of energy compared to the total energy is presented in Table 4. Conceptually, energy demands on neurons distinguish between the energy used for basic vegetative (non-signaling) processes and the energy used for specialized physiological signaling processes (Figure 13) (Engl and Attwell 2015; Ames 2000). Specialized physiological signaling processes seem to consume the majority of energy metabolism in CNS as glucose utilization by brain regions increased several times in response to physiological stimulation that affects physiological activity (Hibbard et al., n.d.). Inhibition of sodium-potassium pumps (Na+/K+ ATPase) with its specific inhibitors resulted in a reduction of energy usage around 50% of total energy consumption in the brain (Astrup 1982).

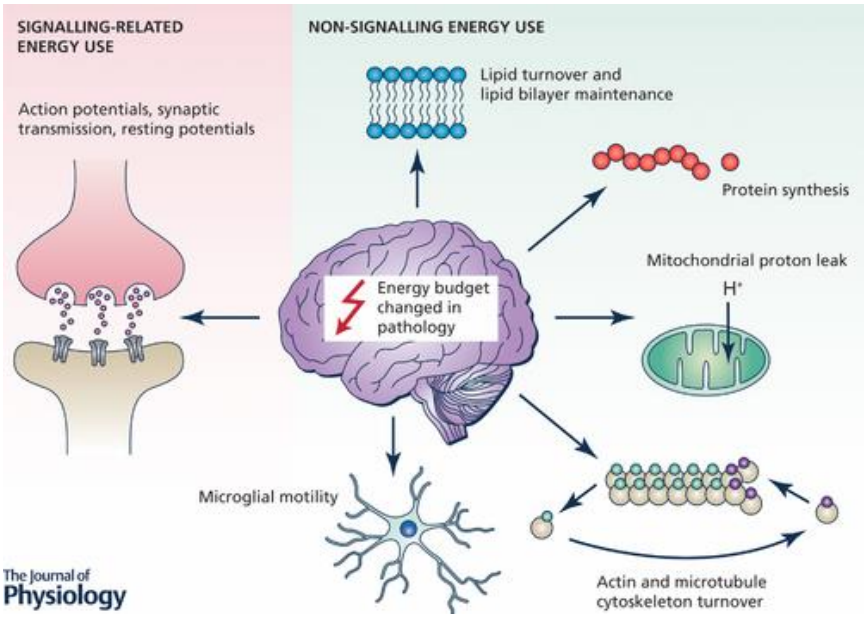


Figure 13. Distribution of energy use in the brain; specified into the basic non-signaling processes and the specialized physiological signaling processes (Engl and Attwell 2015)

That fact, making Na+ transport as the costliest processes between all specialized physiological processes in neurons. Other processes in specialized physiological processes are Ca2+ transport, neurotransmitters processing, intracellular signaling, axonal transport, dendritic transport, and cytoskeletal reshaping (Ames 2000).

In non-signaling processes, various values exist on the energetic cost of actin treadmilling, with estimates ranging from<1% up to 25% of total neuronal energy use (Engl and Attwell 2015; Ames 2000). Lipid metabolism and mitochondrial proton leak are the most energetically expensive processes, whereas protein synthesis and microglial motility have been estimated to account for tiny portions of the brain's energy consumption (Engl and Attwell 2015). The estimation of the proportion of energy use in neurons is presented in Table 4 (Engl and Attwell 2015; Ames 2000).

Table 5. Percentage of Energy Consumption in Neurons (modified from (Engl and Attwell 2015) **and** (Ames 2000)**)**

Neurons Processes		Energy Consumption	
Signaling-related processes			~60%
a.	Gated Na^+ influx through plasma membranes	~30%	
b.	Ca^{2+} influx from organelles and ECF	~5%	
c.	Processing of neurotransmitters	~5%	
d.	Intracellular signaling systems	~10%	
e.	Axonal and dendritic transport	~10%	
Non-signaling processes			~40%
a.	Lipid turnover and lipid bilayer maintenance	~10%	
b.	Protein synthesis	~1%	
c.	Mitochondrial proton leak	~10%	
d.	Actin and microtubule cytoskeleton turnover	~1-25%	
e.	Microglial motility	undecided	

2.3.1 Resume

- Brain, as an organ, use energy more than other human organs.
- Most of the energy is used in specialized physiological processes to support the signaling-related processes (~60%), and the rest is used to non-signaling processes (~40%)
- The signaling-related energy use consists of gated-Na+ influx through plasma membranes, Ca2+ influx from organelles and ECF, processing of neurotransmitters, Intracellular signaling systems, and axonal and dendritic transport.
- The non-signaling-related energy use refer to lipid turnover and lipid bilayer maintenance, protein synthesis, mitochondrial proton leak, actin and microtubule cytoskeleton turnover, and microglial motility.

2.4 Brain Metabolism

As already described in the previous section that brain activation is an energy-demanding process. Brain metabolism as a way of the brain to generate energy has an essential role not only to the survival of the brain cell itself but also to the optimization of brain functions. Studies conducted by Kety and Sokoloff over 60 years ago showed that glucose is the main substrate for brain metabolism in humans, where it is almost fully oxidized (Pierre J. Magistretti and Allaman 2015). Technological advances in the last decades have afforded new insights into neuroenergetics at the regional, cellular, and molecular levels (Pierre J. Magistretti and Allaman 2015).

2.4.1 Model of Glucose Metabolism

The brain is the main consumer of glucose in humans. It consumes approximately 20% of all glucose-derived energy production or 5.6 mg glucose per 100 g human brain tissue per minute (Mergenthaler et al. 2013). Glucose metabolism is a primary source of energy for the brain to maintain its functions (Pierre J. Magistretti and Allaman 2015). As a reminder, glucose metabolism starts when glucose from capillaries enters cells through glucose transporter-1 (GLUT1) and is phosphorylated by hexokinase (HK) to produce glucose-6-phosphate (glucose-6P) (cartoon-illustrated in Figure 14) (Mergenthaler et al. 2013). Glucose-6P can be processed through four main metabolic pathways (Pierre J. Magistretti and Allaman 2015): glycolysis, pentose phosphate, glycogen or through oxidative phosphorylation

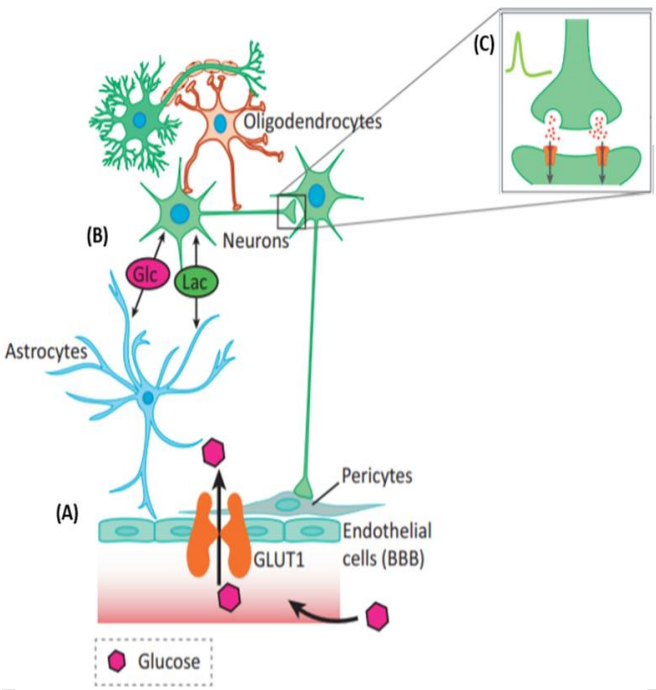


Figure 14. Transport and metabolism of glucose into the neurons. GLUT1: glucose transporter-1; BBB: blood-brain barrier; Glc: glucose; Lac: lactate; Modified from (Mergenthaler et al. 2013).

First, glucose can be metabolized through glycolysis, using two molecules of pyruvate and producing ATP and NADH. Pyruvate enters mitochondria to be metabolized through the tricarboxylic acid cycle and oxidative phosphorylation, producing ATP and CO_2 while consuming oxygen. Under hypoxic conditions, pyruvate will be processed into lactate by lactate dehydrogenase. Then lactate will be released in the extracellular space through monocarboxylate transporters (MCTs). Glycolysis produces smaller amounts of energy in the form of ATP (2 ATPs) compared to the complete oxidation of glucose in the mitochondria (30–36 ATPs). Secondly, glucose can be metabolized through the pentose phosphate pathway (PPP), leading to the production of NADPH. The PPP and glycolysis are connected at the level of

glyceraldehyde-3-phosphate (GA3P) and fructose-6-phosphate (fructose-6P). NADPH produced in the PPP is important to protect against oxidative stress by the metabolism of glutathione (GSH). GSH is an electron donor in numerous reactions, including the neutralization of reactive oxygen species (ROS). The result of neutralization of ROS, oxidized glutathione (GSSG), will be recycled back to GSH by glutathione reductase using NADPH as an electron donor.

Thirdly, especially in astrocytes, glucose-6P can also be stored as glycogen. The storage of glycogen in astrocyte is regulated by the action of glycogen synthase (GYS) (Falkowska et al. 2015). Last, oxidative phosphorylation is a process that refers to the metabolism of pyruvate or another oxidative substrate through the mitochondrial tricarboxylic acid cycle (TCA) cycle. This process leads to ATP resynthesizes through the action of the electron transport chain (ETC) and ATP synthase (Yellen 2018). All four metabolic pathways of glucose in the brain are described in Figure 15.

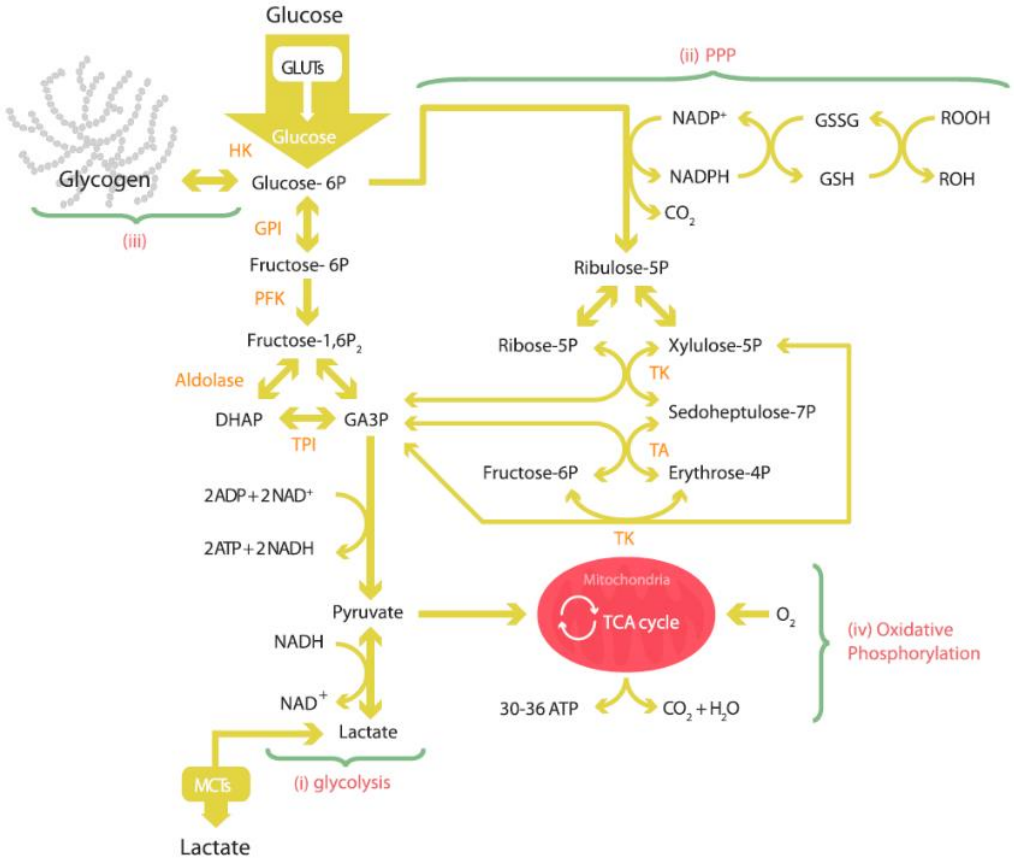


Figure 15. Schematic representation of four glucose metabolism pathways in the brain (Taken from (Pierre J. Magistretti and Allaman 2015)**)** Abbreviation: i, glycolysis pathway; ii, pentose phosphate pathway; iii, glycogen pathway; iv, oxidative phosphorylation process; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CO_2, carbon dioxide; DHAP, dihydroxyacetone phosphate; erythrose-4P, erythrose-4-phosphate; fructose-1,6-P2, fructose-1,6-bisphosphate; fructose-6P, fructose-6-phosphate; GA3P, glyceraldehyde-3-phosphate; glucose-6P, glucose-6-phosphate; GLUTs, glucose transporters; GPI, glucose-6-phosphate isomerase; GSH, glutathione; GSSG, oxidized glutathione; H_2O, dihydrogen monoxide (water); HK, hexokinase; MCTS, monocarboxylate transporters; NAD^+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (reduced form); $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); O_2, dioxygen; PFK, phosphofructokinase; PPP, pentose phosphate pathway; ribulose-5P, ribulose-5-phosphate; ribose-5P, ribose-5-phosphate; ROH, alcohol; ROOH, peroxide; sedoheptulose-7P, sedoheptulose-7-phosphate; TA, transaldolase; TCA cycle, tricarboxylic acid cycle; TK, transketolase; TPI, triose phosphate isomerase; xylulose-5P, xylulose-5-phosphate.

2.4.2 The Cellular Specificity of Energy Metabolism in Neuron and Astrocyte

In general, energy metabolism processes in the brain are carried out by two cells: neuron and astrocyte. Neuron and astrocyte have different enzymatic expressions and activities that will specify their energy metabolism pathway (described in Figure 16).

2.4.2.1 Astrocyte

Astrocytes are the only brain cells that can store glycogen (Pierre J. Magistretti and Allaman 2015). Therefore, there are multiple entry points to metabolism processes in astrocytes, such as extracellular glucose uptake or glycogen breakdown. The 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (Pfkfb3), an enzyme that modulates glycolysis in cells, is fully active in astrocytes, thus allowing upregulation of glycolysis (Pierre J. Magistretti and Allaman 2015). This process will increase the concentration of pyruvate as the end product of glycolysis. However, the process of pyruvate to enter the TCA cycle is controlled by the activity of the enzyme pyruvate dehydrogenase (PDH) (Pierre J. Magistretti and Allaman 2015).

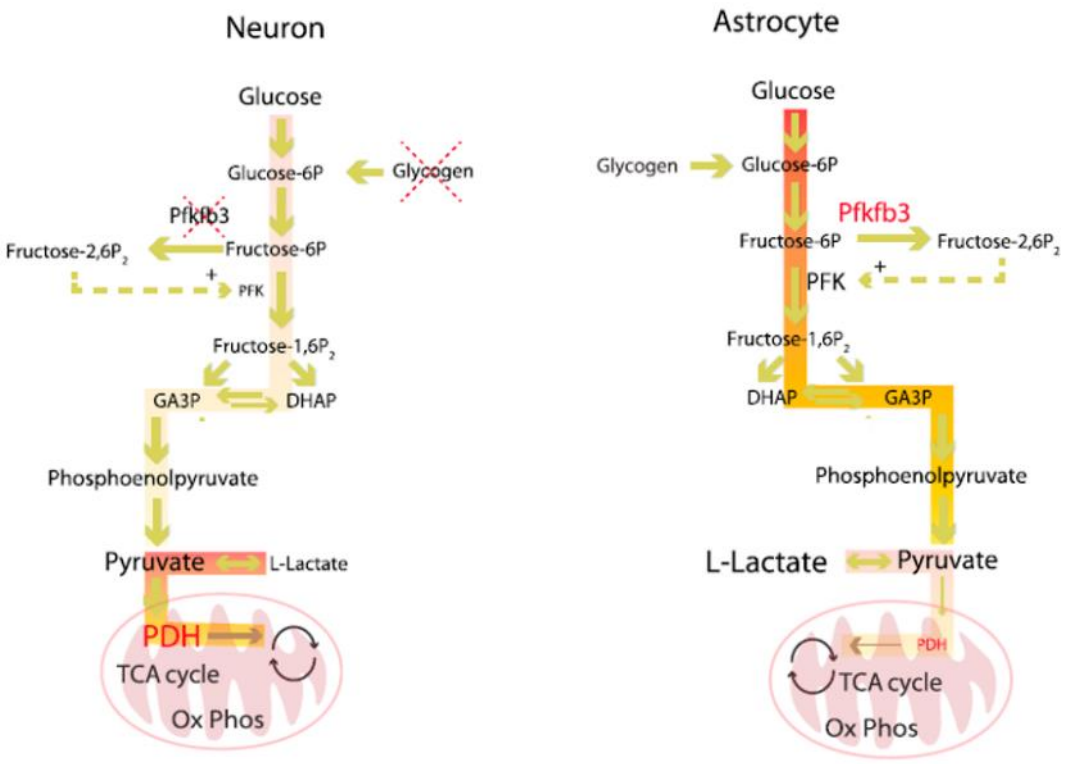


Figure 16 Comparative energy metabolism pathways of glucose between astrocyte and neuron (Modified from (Pierre J. Magistretti and Allaman 2015)**)** Abbreviation: DHAP, dihydroxyacetone-phosphate; fructose-1,6-P2, fructose-1,6-bisphosphate; fructose-2,6-P2, fructose-2,6-bisphosphate; fructose-6P, fructose-6-phosphate; GA3P, glyceraldehyde-3-phosphate; glucose-6P, glucose-6-phosphate; Ox Phos, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; Pfkfb3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; TCA cycle, tricarboxylic acid cycle.

The activity of PDH is regulated by phosphorylation at several phosphorylation sites; PDH activity is decreased when phosphorylated. Halim and collaborators reported that the

phosphorylation of PDH under basal conditions is in high degrees in astrocytes (Halim et al. 2010). This situation favors the production of lactate as the output of glycolysis in astrocytes. On the contrary, dephosphorylation of PDH by dichloroacetate results in an increase in oxidative use of glucose by astrocytes and a decrease in lactate production by these cells (Itoh et al. 2003) (Itoh et al., 2003). In conclusion, these expression and activity profiles result in active glycolysis, limited processes in the TCA cycle, and the production of L-lactate in astrocytes.

2.4.2.2 Neurons

One of the main characteristics of energy metabolism in neurons is no glycogen is stored within (Pierre J. Magistretti and Allaman 2015), because of that, metabolic processes in neurons are reliant on external supplies of lactate and glucose. L-lactate, as a main product of glycolysis, is taken up by neurons via monocarboxylate transporters (MCTs) (Pellerin and Magistretti 1994). An increased concentration of L-lactate will trigger lactate dehydrogenase to convert L-lactate into pyruvate. Then, pyruvate is used as an energy substrate through the TCA cycle. Again, as in astrocytes, PDH regulates the entry of pyruvate into the TCA cycle, but the difference is that neurons have a low degree of phosphorylation of PDH, effect in a high mitochondrial oxidative activity. Aside from L-lactate, neurons can also take up glucose via the neuronal glucose transporter-3 (GLUT3). Pfkfb3, the modulator of glycolysis, is constantly subject to proteasomal degradation that decreases its activity in neurons (Bolaños, Almeida, and Moncada 2010; Herrero-Mendez et al. 2009). Reduction of expression and activity of Pfkfb3 reduces the activity of phosphofructokinase (PFK), which will downregulate glycolysis (Pierre J. Magistretti and Allaman 2015). Therefore, glucose is mainly processed through the oxidative branch of the pentose phosphate pathway. This pathway is the main producer of NADPH, which is used to regenerate reduced glutathione to neutralize reactive oxygen species (ROS) produced by the marked oxidative activity of neurons (Pierre J. Magistretti and Allaman 2015). In summary, these expression and activity profiles in neurons result in high mitochondrial oxidative activity to produce ATP and predominantly production of NADPH to neutralize oxidative stress from its high oxidative activity.

2.4.2.3 Resume

- Brain metabolism generate energy for the integration and functions of brain cells.
- Brain cells generate energy through four metabolic pathways: glycolysis, pentose phosphate, glycogen or through oxidative phosphorylation.
- Astrocytes
  - Have the capability to store glycogen.
  - Glycolytic aerobic as the main metabolism process.
  - The high degree of phosphorylated PDH limits processes in TCA cycle and favor production of lactate.
- Neurons
  - Not have the capability to store glycogen, totally dependent on the extracellular supply of glucose or lactate.
  - Use lactate as an energy substrate through the TCA cycle.
  - The low degree of phosphorylated PDH underlies high mitochondrial oxidative activity.
  - Glucose was taken as a substrate not to generate energy but to be processed through the pentose phosphate pathway to produce NADPH to neutralize oxidative stress.

2.4.3 Neurometabolic Coupling between Astrocytes and Neurons

Further histological studies using light and electron microscopes have shown some particular structures that help astrocytes sense synaptic activity and integrate it with the delivery of energy substrates coming from the capillaries. Indeed, astrocytes have multiple processes with a size of 80–100 mm in diameter (Bushong et al. 2002; Sofroniew and Vinters 2010). One of these processes, the end-foot, touches against the capillary wall, whereas several others touch synaptic contacts. The astrocytic endfeet covers the entire outer surface of intraparenchymal capillaries (Kacem et al. 1998), leaving only clefts of 20 nm between the endfeet (Mathiisen et al. 2010).

On the synaptic side, astrocytic lamellar processes covered synaptic elements. Such cover of synapses by the astrocytic process is dynamic and presents activity-dependent characteristics, known as the astrocyte-neuron lactate shuttle (ANLS), that illustrates the coupling between neuronal activity and vascular activity (Pellerin and Magistretti 1994). The schematic representation of the ANLS is described in Figure 17.

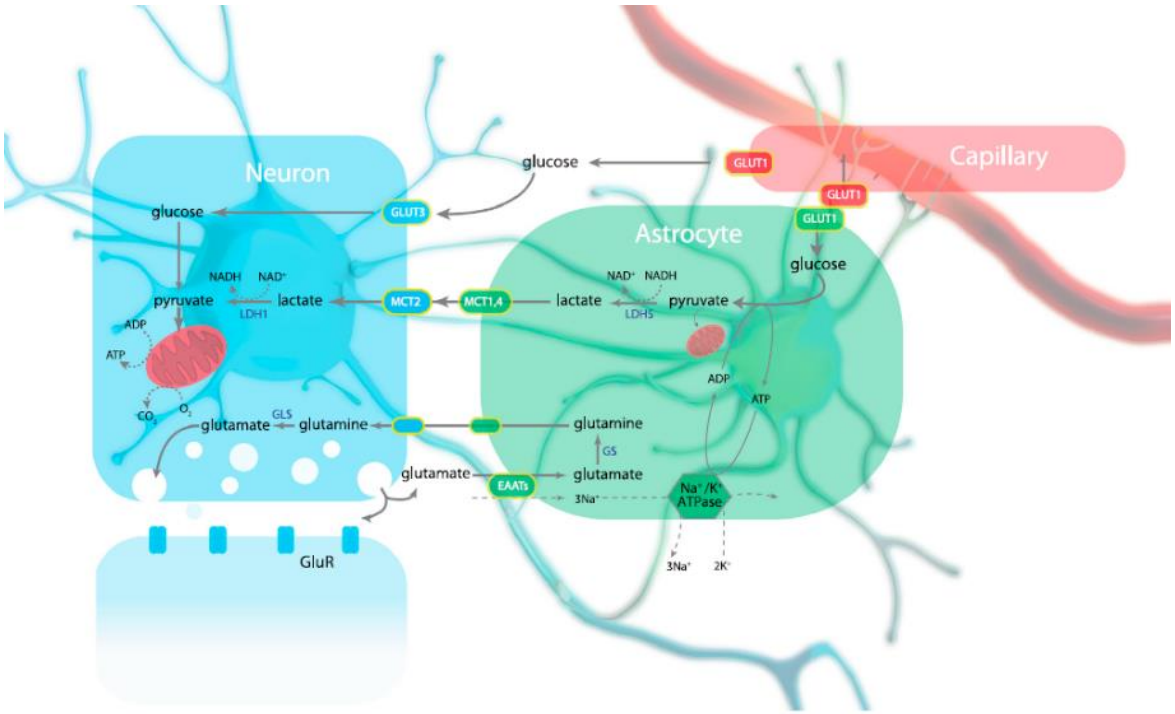


Figure 17. Schematic illustration of the Astrocyte-neuron lactate shuttle (ANLS) model (Taken from (Pierre J. Magistretti and Allaman 2015)**).** Abbreviation: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CO_2, carbon dioxide; EAATs, excitatory amino acid transporters; GluR, glutamatergic receptor; GLUT1, glucose transporters-1; GLUT3, glucose transporters-3; GLS, glutaminase; GS, glutamine synthetase; K^+, potassium ions; LDH1, lactate dehydrogenase-1; LDH3, lactate dehydrogenase-1; MCT1,4, monocarboxylate transporter-1 & 4; MCT2, monocarboxylate transporter-2; Na^+, sodium ions, NAD+, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (reduced form); Na^+/K^+ATPase, sodium-potassium adenosine triphosphatase; O_2, dioxygen.

In the model of ANLS, glutamate stimulates glucose uptake and lactate production in astrocytes (Pellerin and Magistretti 1994). This glutamate-stimulated aerobic glycolysis is triggered by the uptake of glutamate in the membrane of astrocytes. Glutamate uptake is co-transported with sodium with compensation of three sodium ions for each glutamate molecule, resulting in the change of the sodium gradient. The change of sodium gradient activates the sodium-potassium ATPase (Na+/K+ ATPase) at the expense of one ATP per turn to pump out three sodium ions. Glutamate is converted into glutamine by glutamine synthase at the cost of another ATP. This glutamate-glutamine cycle allows glutamate to be recycled to the extracellular fluid to replenish the glutamate concentration (Stobart and Anderson 2013; McKenna 2007), whereas the remaining glutamate enters the TCA cycle in astrocytes after conversion to a-ketoglutarate (McKenna 2007; Stobart and Anderson 2013). Glutamate uptake and recycling are energy-consuming processes, resulting in a decrease in ATP content in astrocytes (P. J. Magistretti and Chatton 2005). This decrease in ATP promotes glucose uptake and metabolism by disinhibiting key enzymes of glycolysis, such as hexokinase and phosphofructokinase. As noted earlier, the glucose taken up via this mechanism is processed glycolytically to yield lactate. Through specific monocarboxylate transporters (MCTs) (Halestrap 2015; Pierre and Pellerin 2005), MCT1 (also present in other glial cells and endothelial cells) and MCT4 (specific for astrocytes), lactate is released, to be taken up by MCT2 (selective for neurons) into neurons and, after conversion to pyruvate, is processed oxidatively in mitochondria to produce 14–17 ATPs per lactate molecule.

2.4.4 Role of Oxygen in Neurovascular Signaling

Variations in O_2 concentration in brain tissue alter neurovascular coupling in the way it alters the levels of lactate and adenosine that modulate the pathways by which these messengers regulate vascular tone.

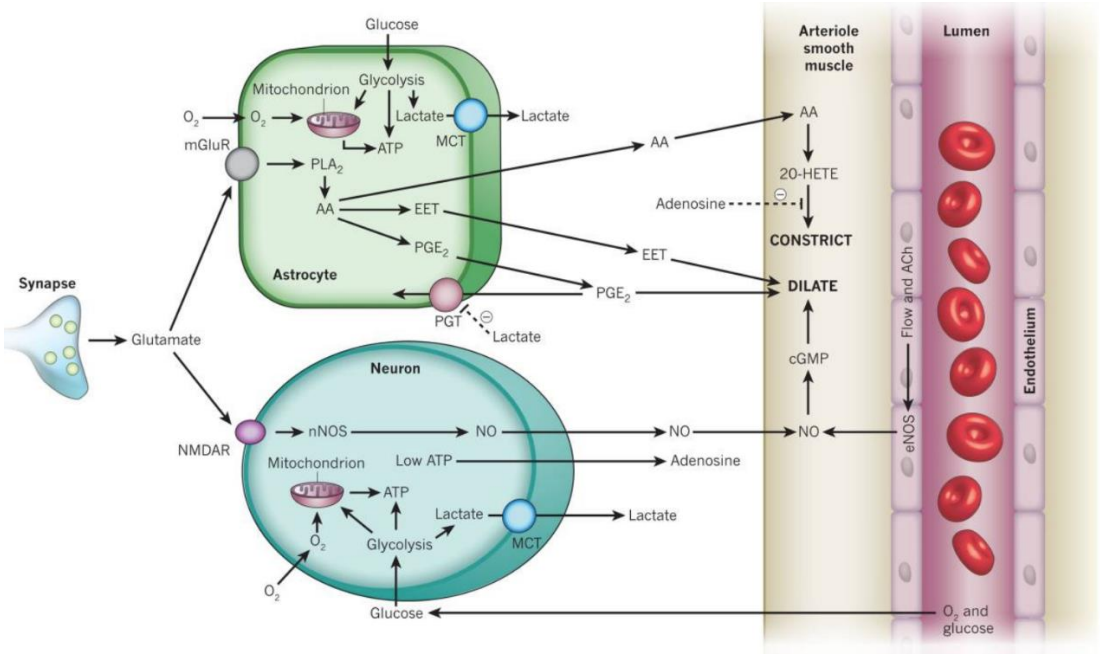


Figure 18. Neurovascular signaling responses at a decreased concentration of oxygen (Taken from (Attwell et al. 2010)**).** Abbreviation: 20-HETE, 20-hydroxyeicosatetraenoic acid; AA, arachidonic acid; ACh, acetylcholine; ATP, adenosine triphosphate; cGMP, cyclic guanosine monophosphate; EET, epoxyeicosatrienoic acid; eNOS, endothelial nitric oxide synthase; MCT, monocarboxylate transporter; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptors; NO, nitrogen monoxide; nNOS, neuronal nitric oxide synthase; O_2, dioxygen; PGE2, prostaglandin-E2; PGT, prostaglandin transporter; PLA2, phospholipase A2.

As O_2 concentrations decrease, the lack of energy for ATP synthesis causes an increase in the level of extracellular adenosine, which binds to adenosine A2A receptors on vascular smooth muscle cells to weaken vessel constriction. Also, a decrease in the rate of oxidative phosphorylation relative to the rate of glycolysis results in lactate production. Monocarboxylate transporters release the lactate into the extracellular space, where it reduces the clearance of extracellular PGE2 by the prostaglandin transporter. Thus, when PGE2 is released from astrocytes, extracellular PGE2 increases to a greater degree, resulting in larger arteriole dilations (molecular sequences are illustrated in Figure 18) (Gordon et al. 2008). This effect of lactate may partly explain why, in humans and rats in vivo, cerebral blood flow is regulated by the lactate/pyruvate concentration ratio and thus by the NADH/NAD+ ratio (Ido et al. 2001). Interestingly, lactate is released into the extracellular space during synaptic activity (Caesar et al. 2008), which should promote vasodilation.

Despite our understanding of how O_2 levels regulate astrocyte-mediated neurovascular coupling in brain slices (Gordon et al. 2008), imposing artificially high O_2 concentrations in vivo does not lead to smaller vasodilations or the emergence of vasoconstrictions (Lindauer 2010). This could reflect a potentiation of NO-mediated signaling from neurons to arterioles (relative to that occurring in brain slices superfused with 95% O_2) by the high O_2 level produced by hyperbaric

O_2 (as NOS activity is potentiated by the higher O_2 concentrations) (Lindauer 2010), which outweighs the effect of O_2 on astrocyte-Mediated Signaling.

2.4.5 Integration of Neurovascular Coupling during Neuronal Activity

Neurovascular imaging techniques such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS), rely on cerebral blood flow and cerebral oxygenation as indirect measures of cerebral activity. The vascular oxygen content results from the balance between consumption by the cells (cerebral metabolic rate of oxygen ($CMRO_2$)) and intake from the cerebral blood flow (CBF) (Valabrègue et al. 2003). Therefore, a better understanding of the physiological mechanisms that induce oxygen variations will help the interpretation of neuroimaging data.

The physiological mechanisms underlying one of the components of the fMRI signal, namely the BOLD signal, are highly relevant to neurovascular-related neuronal activity. Observation made in the late 1980s by Fox (Fox et al. 1988) and more recently with higher-resolution technologies by Lin et al. (2010) (A. L. Lin et al. 2010) have established that during activation a certain degree of metabolic disproportion occurs, that local increases in CBF and glucose utilization (CMRGlu) are not matched by equal increases in oxygen consumption ($CMRO_2$) (Buxton 2010; A. L. Lin et al. 2010). While both astrocytes and neurons take glucose from extracellular during metabolism, the cellular specificity of metabolism between them, which uses more glycolysis and oxidative pathway, is the possible explanation of this rate disproportion (Pierre J. Magistretti and Allaman 2015). This occurrence predicts that in the activated region, the capillaries on the venous side should be enriched in oxyhemoglobin (HbO_2), as the excess oxygen carried by the increased blood flow is not being consumed (Pierre J. Magistretti and Allaman 2015). Oxygen excess, in turn, results in decreased relative levels of deoxyhemoglobin (HHb) and produces a signal specific for the activated region (Figure 19) (Ferrari and Quaresima 2012).

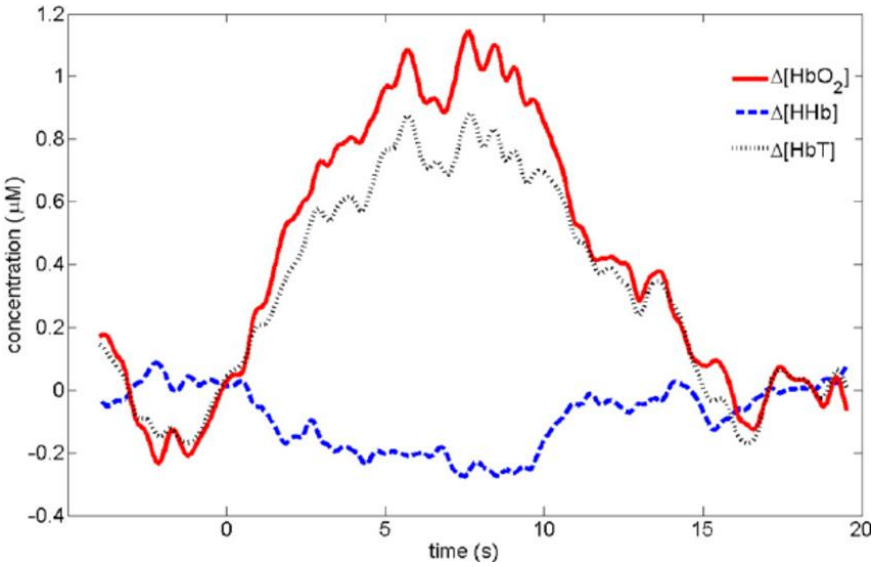


Figure 19. Hemodynamics response curves, showing changes in HbO_2, HHb, tHb concentration during brain activation (Taken from (Correia et al. 2012)**)**

As previously discussed, the glutamate-stimulated aerobic glycolysis, as formulated by the ANLS mechanism, provides a metabolic process with cellular markers presented in the BOLD signal (Pellerin and Magistretti 1994). Glucose is processed through aerobic glycolysis in astrocytes, implying that pyruvate formed through the glycolytic pathway is converted to lactate rather than entering the TCA cycle and the following oxygen-consuming process of oxidative phosphorylation (Pellerin and Magistretti 1994). The occurrence of this glycolytic step in astrocytes also implies that during the activation, oxygen consumption will not increase, following observed increases in oxyhemoglobin in the activated region. Given the oxidative nature of neurons, the released lactate will be oxidized, resulting in a delayed increase in oxygen consumption (Pellerin and Magistretti 1994).

Integration of neurovascular coupling during neuronal activity combines cellular events, metabolic indices, and neuroimaging resolutions to explain the physiological mechanism of brain activation. As proposed by Magistretti and Allaman (2015), brain activation starts with glutamate released by synaptic activity that produces excitatory postsynaptic potentials (EPSPs) in target neurons (Figure 20, inset 1) and is taken up by astrocytes (Figure 20, inset 1) (Pierre J. Magistretti and Allaman 2015). The immediate energy needs of activated neurons are met by oxidation of lactate present in the extracellular space, resulting in a transient decrease in lactate levels and oxygen concentration (Figure 20, inset 2) (Pierre J. Magistretti and Allaman 2015). The decreased HbO_2 levels produce the initial dip of the BOLD signal (Figure 20, inset 4) (Pierre J. Magistretti and Allaman 2015). The occurrence of a delayed transient aerobic glycolysis in astrocytes resulting in increased glucose uptake and lactate production. These conditions provide a temporal window during which oxygen is not consumed commensurately with glucose metabolism (Figure 20, inset 3), providing a transient relative decrease in HHb due to the increased HbO_2 concentration that results in a positive BOLD signal (Figure 20, inset 4) (Pierre J. Magistretti and Allaman 2015).

Figure 20. Multiscale integration of neurovascular coupling and brain activation (Taken from (Pierre J. Magistretti and Allaman 2015)**)** Abbreviation: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CBF, cerebral blood flow; CMRGlu, cerebral metabolic rate of glucose; $CMRO_2$, cerebral metabolic rate of oxygen; CO_2, carbon dioxide; EPSP: excitatory postsynaptic potential, Glut, glutamate; K^+, potassium ions; Lac, lactate; Na^+, sodium ions; O_2, dioxygen; OEF, oxygen extraction fraction; Ox phos, oxidative phosphorylation; TCA cycle, tricarboxylic acid cycle.

2.4.6 Resume

- Neurometabolic coupling represents a link between synaptic activity and energy delivery.
- According to the astrocyte-neuron lactate shuttle (ANLS) model, astrocyte and neuron have a major role in the neurometabolic coupling in the brain.
- Changes in O_2 concentration in brain tissue alter the neurovascular coupling
- Decreased of O_2 concentrations promote vasodilation.
- Increased of O_2 concentrations in vivo does not lead to vasoconstriction.
- Neurovascular imaging techniques such as functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) help to a better understanding of the physiological mechanism of neurovascular coupling.
- Integration of neurovascular coupling during neuronal activity comprised several events such as the glutamate released by synaptic activity produces excitatory postsynaptic potentials (EPSP), the oxidation of lactate from extracellular space, the initial decrease of deoxyhemoglobin levels, the delayed transient aerobic glycolysis in astrocytes, and the transient relative decrease in deoxyhemoglobin.

2.5 Cerebral Blood Flow (CBF)

As already explained in the previous sections, the brain always requires a continuous supply of glucose and oxygen from the cerebral circulation to maintain brain function because its energy reserve is relatively small. On the contrary, although the skull assures protection to the brain, it also limits the brain's tolerance to increase blood volume and pressure. Accordingly, precise control of blood delivery to the brain is crucial. The following factors have been recognized to regulate CBF, alone and synergistically (as reviewed in (Meng et al. 2015)), arterial blood gases, neural metabolism (or neurovascular coupling), blood pressure (or cerebral autoregulation), and finally autonomic nervous activity.

2.5.1 Effect of CBF on Executive Function

It remains difficult to identify the direct effect of change in CBF on cognitive function because studies on healthy individuals have not isolated changes in CBF. During dynamic exercise at mild to moderate intensity, increases in cerebral metabolism or cerebral neural activity are paralleled by transient increases in CBF (Ogoh and Ainslie 2009), (K. Sato et al. 2011). Indeed, cognitive function improves during a single bout of moderate exercise (McMorris et al. 2011). In contrast, during prolonged exercise, CBF gradually decreases to the resting values, and this is associated with hyperventilation (Ogoh et al. 2005). Ogoh et al. (2017), for the first time, examined the effect of an isolated change in CBF on cognitive function in humans (Ogoh 2017). Thus, in this study, Ogoh et al. reported that the cognitive function had been found to improve during prolonged exercise despite a decrease in CBF (Ogoh et al. 2014). Also, unexpectedly, an isolated change (hypercapnia-induced increase) in CBF by manipulating cerebral perfusion did not affect cognitive function at rest or during exercise (Ogoh 2017). These findings suggest that exercise-induced improvement in cognitive function is not simply due to a change in global CBF. Thus, these findings suggest that another factor modified by exercise, rather than a change in CBF, affects cognitive function. However, the mechanism of exercise-induced improvement in cognitive function remains an ongoing debate.

2.5.2 Main Determinants of CBF

Cerebral blood flow is controlled and influenced by several determinants, including neurovascular coupling, arterial blood pressure, CO_2 and O_2, cardiac output, and autonomic nervous system. Therefore the influence of each determinant will be described in this section and illustrated in Figure 21 (Meng et al. 2015).

2.5.2.1 Cardiac Output

Approximately 15% of cardiac output (CO) is delivered continuously to the brain to meet the metabolic demand of neuronal activity. Therefore, alterations in CO may influence CBF (Meng et al. 2015). In healthy adults, the elevation of CO via albumin infusion and reduction of CO using lower body negative pressure demonstrated a linear correlation between changes in CO and CBF at rest and during exercise, independent of changes in carbon dioxide partial pressure

in arterial blood ($PaCO_2$) or BP (Ogoh et al. 2005). In contrast, patients with heart failure reported a non-linear correlation between acute changes in CO and CBF when changing position from supine to sitting (Fraser et al. 2015). Furthermore, heart failure patients with lower CO showed smaller CBF than normal control subjects, but heart transplantation restored their CBF to a similar level observed in the control subjects (Gruhn et al. 2001).

2.5.2.2 Arterial Blood Pressure

Another important regulator of CBF is mean arterial pressure (MAP). In 1959, a review study by Lassen suggested that CBF remained stable across a wide range of blood pressures (MAP ~ 60–150 mmHg) (Lassen 1959). This result implied that the cerebrovascular system had the ability to modulate its resistance in response to a change in blood pressure, a phenomenon called cerebral autoregulation (CA), preventing both brain ischemia and over perfusion. Although Lassen's work remains widely cited, its findings are being increasingly challenged, as previous evidence suggests a narrower range of cerebral autoregulation (Bisson, Marc, and Brassard 2016). It also reported that pulse pressure (PP) is directly correlated with the amplitude of CBF pulsatility (Tarumi et al. 2014). In the cardiovascular system, elevated PP represents a hallmark of vascular aging and results from the stiffening of the large arteries (aorta or carotid artery) (Tarumi, Zhang, and Ln 2017).

2.5.2.3 Autonomic Nervous System

Finally, the sympathetic nervous system is another potential CBF regulator, as cerebral vessels are innervated by numerous adrenergic and cholinergic fibers (Bleys et al. 1996). Studies using ganglion blockade, found an increase in CBF (K. Ide et al. 2000; Treggiari et al. 2003), as reviewed by Willie et al. (Christopher K. Willie et al. 2014). The sympathetic nervous system also seems to have a protective role during rises in blood pressure, especially in larger cerebral arteries. Pharmacological ganglionic blockade during blood pressure elevations also results in a greater increase in CBF, suggesting impaired cerebral autoregulation (R. Zhang, Crandall, and Levine 2004; Kimmerly et al. 2003). Together, these findings illustrate the buffering role of the sympathetic nervous system against increases in perfusion pressure (Christopher K. Willie et al. 2014).

2.5.2.4 Neurovascular Coupling

Neurovascular coupling is a regulator of regional CBF, like neurons, glial cells, and microvasculature are anatomically and metabolically related, forming the neurovascular unit (C. K. Willie et al. 2011, 2012). Regional CBF is coupled to neuronal metabolism, which is varied in space and time. During neuronal activation, the synaptic release of neurotransmitters leads to an elevation of regional CBF (functional hyperemia) through vasodilation (Attwell et al. 2010). With the advent of neuroimaging technology, functional hyperemia can be assessed by the blood-oxygen-level-dependent (BOLD) signal using functional magnetic resonance imaging (MRI) (Tarumi, Zhang, and Ln 2017). In a study by Zhu et al. 2015, regional BOLD spontaneous fluctuations associated with the change of systemic arterial blood pressure and CBF measured in

the middle cerebral artery (D. C. Zhu et al. 2015). These observations propose that regional dynamic changes in CBF may be influenced by the changes in cardiovascular function.

2.5.2.5 Carbon Dioxide and Oxygen

The brain vasculature is highly sensitive to CO_2, with changes in carbon dioxide partial pressure in arterial blood ($PaCO_2$) resulting in changes in all cerebrovascular vessels (called cerebrovascular reactivity) (Pfeifer et al. 2012), although regional differences have been observed with hypocapnia (K. Sato et al. 2012; C. K. Willie et al. 2012). Increases in $PaCO_2$ (hypercapnia) result in an elevation in blood flow through smooth muscle relaxation and vessel dilatation, whereas decreased $PaCO_2$ (hypocapnia) induces a reduction in CBF through increased vascular resistance (Faraci, Heistad, and Mayhan 1987). Hypoxia also influences the cerebrovasculature [25] but only below a certain threshold (~50 mmHg) and depending on the concomitant $PaCO_2$ (as hypercapnia increases, whereas hypocapnia decreases, sensitivity to hypoxia) (Mardimae et al. 2012). Of importance, CBF response to O_2 relies on O_2 blood content rather than oxygen partial pressure in arterial blood (PaO_2), as anemia and hemodilution can increase CBF (Todd et al. 1994).

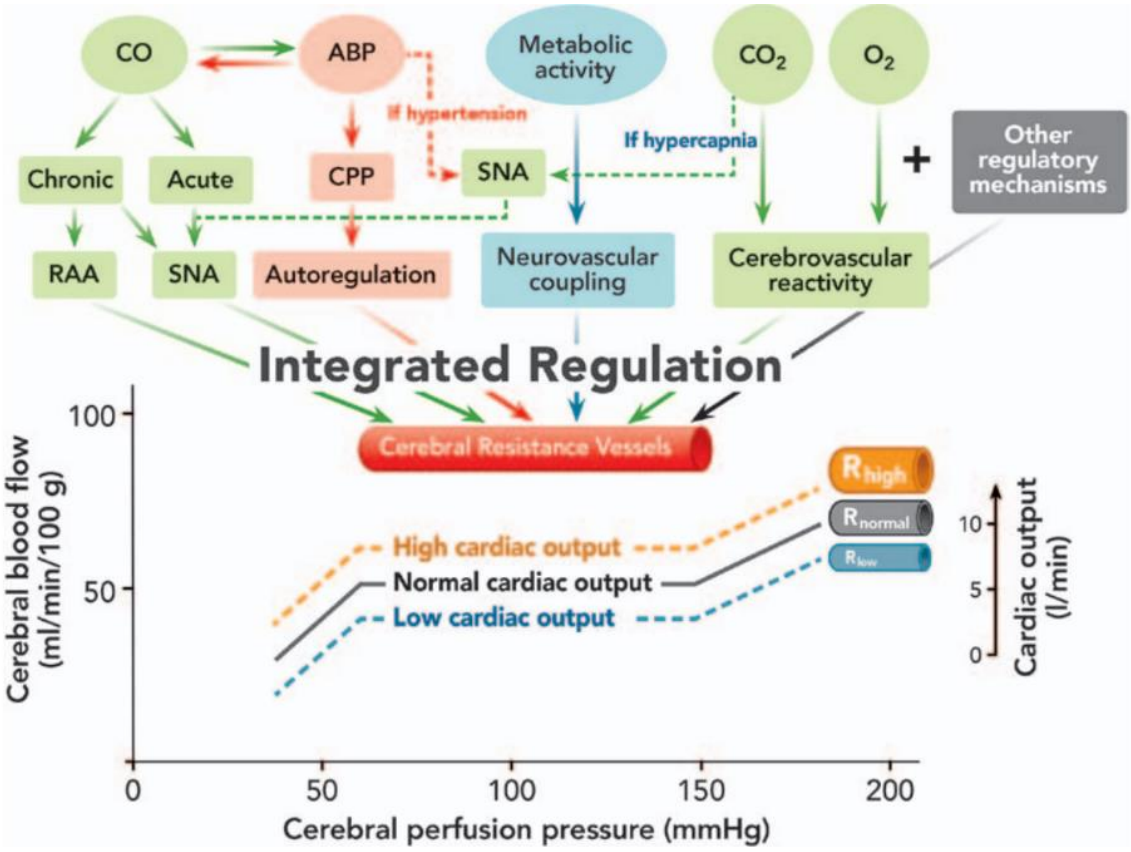


Figure 21. The conceptual framework of the integrated regulation of brain perfusion (Taken from (Meng et al. 2015)**)** Abbreviation: ABP, arterial blood pressure; CO, cardiac output; CO_2, carbon dioxide; CPP, cerebral perfusion pressure; O_2, dioxygen; RAA, renin-angiotensin-aldosterone axis; R_{high}, caliber of the cerebral resistance vessels at high cardiac output; R_{low}, caliber of the cerebral resistance vessels at low cardiac output; R_{normal}, caliber of the cerebral resistance vessels at normal cardiac output; SNA, sympathetic nervous activity.

2.5.3 Resume

- Cerebral blood flow (CBF) is an important factor for brain function and metabolism because it regulates the supply of glucose and oxygen at cerebral circulation.
- The effect of CBF on executive function is still an ongoing debate.
- Cerebral blood flow is controlled and influenced by some determinants: neurovascular coupling, arterial blood pressure, CO2 and O2, cardiac output, and autonomic nervous system.

2.6 Summary of Section

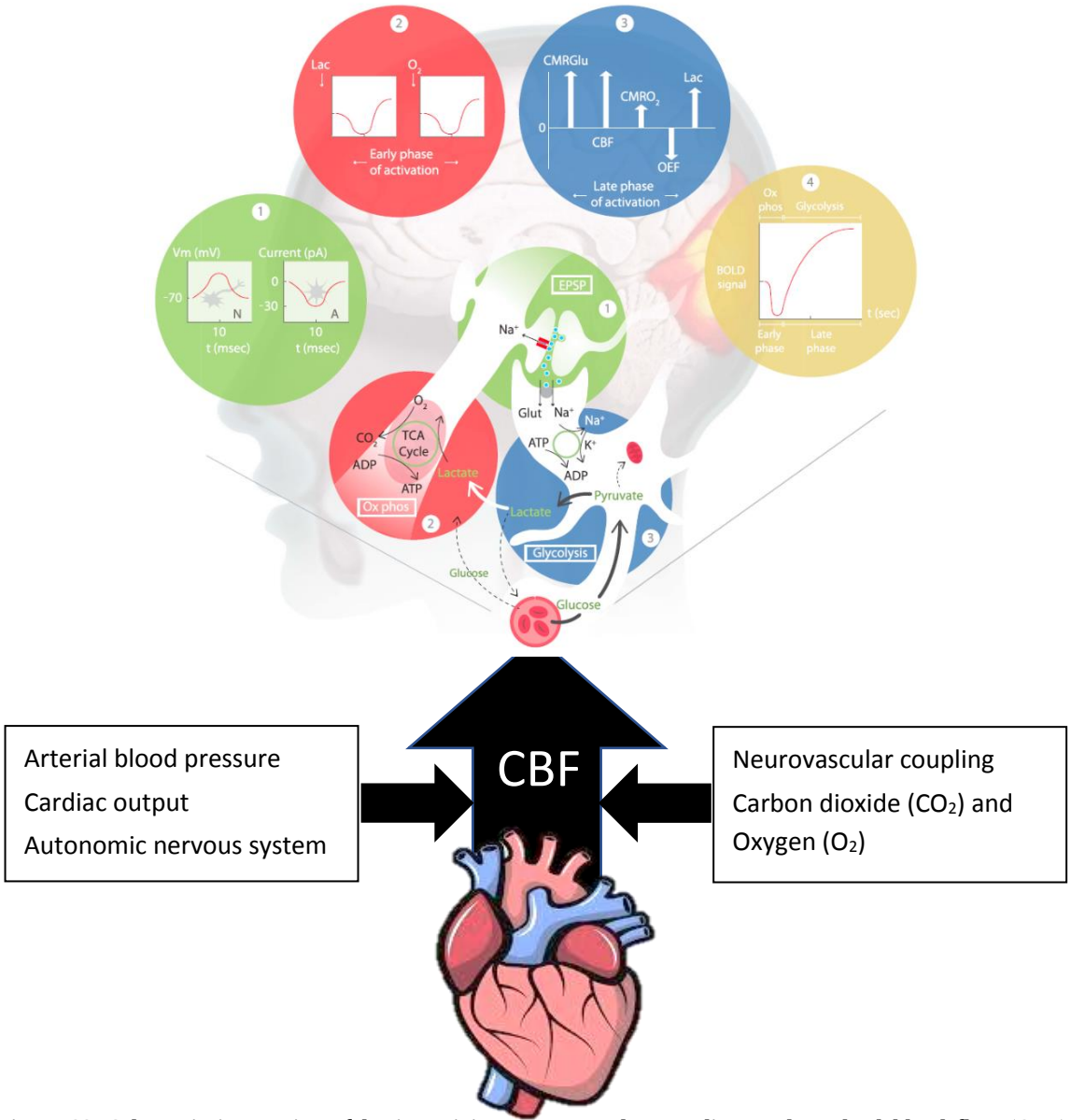


Figure 22. Schematic integration of brain activity, neurovascular coupling, and cerebral blood flow (CBF). Neurovascular coupling during brain activation is regulated by CBF. CBF itself controlled by several determinants, including arterial blood pressure, cardiac output, autonomic nervous system, neurovascular coupling, CO_2, and O_2. Abbreviation: ADP, adenosine diphosphate; ATP, adenosine triphosphate; CBF, cerebral blood flow; CMRGlu, cerebral metabolic rate of glucose; $CMRO_2$, cerebral metabolic rate of oxygen; CO_2, carbon dioxide; EPSP, excitatory postsynaptic potential; Glut, glutamate; K^+, potassium ions; Lac, lactate; Na^+, sodium ions; O_2, dioxygen; OEF, oxygen extraction fraction; Ox phos, oxidative phosphorylation; TCA cycle, tricarboxylic acid cycle.

In 1999, Roberto Cabeza, a cognitive neuroscientist, revealed that during cognitive performances, older adults tend to use both sides of prefrontal more than in younger adults (Cabeza 2002). *Bilateral prefrontal activity in older adults may reflect compensatory processes and reorganization of neurocognitive networks in the brain. On the other hand, a series of cognitive tests showed that not all components of cognition decline with aging, some are not affected, and some even better. These results change the previous paradigm where aging means a persistent decline in bodily functions due to physiological deterioration* (Rose et al. 2012). *The relationship between aging and brain, including cognition and executive function, seems to be more complex than other body organs.*

3 Aging and Executive Function

This section discusses the effect of aging on executive function. It presents the comparison of aging effect between body organs, several theories that construct cognitive aging, the implications of aging on executive function separated into three parts: aging and neuro-cardiovascular parameters, aging and brain structures-and-functions, aging and executive function.

3.4 Physiological Implication of Aging on Body Organs

Aging constitutes a decline in the functional ability of body organs or systems. It results from the interaction of processes that occur over time and genetics interacting with various disease states and the individual's lifestyle (Passarino, De Rango, and Montesanto 2016). The complex nature of aging makes the individual variation in functional changes and rates of aging (Passarino, De Rango, and Montesanto 2016).

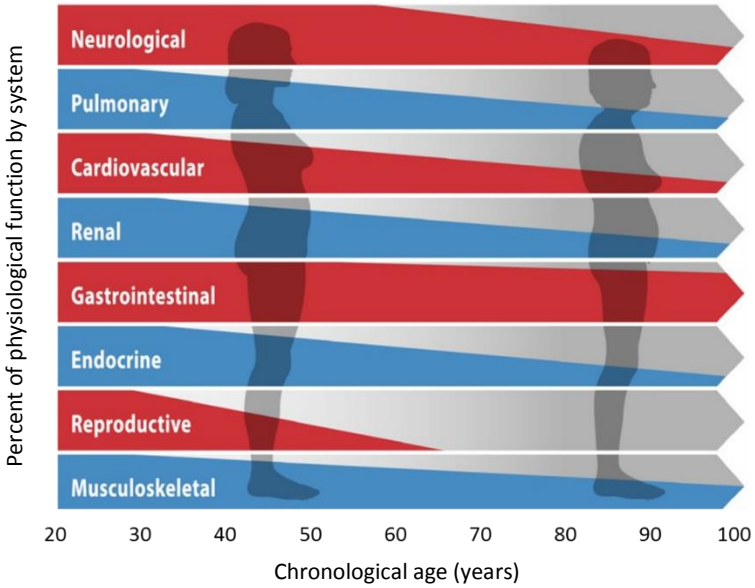


Figure 23. Changes in maximal physiological body system function as a function of age (Modified from (Khan, Singer, and Vaughan 2017)**)**

The human body function maintains significant reserve capacity (Goldspink 2005). Along with increasing age, reserve capacity is reduced, and it makes humans more vulnerable to stresses. Decrease of reserve capacity places an older individual at a higher risk of succumbing to stresses that a younger individual might overcome. While even under ideal conditions, an individual loses some of their functional reserves. Diseases and environmental factors significantly affect the rate of loss (Goldspink 2005; Passarino, De Rango, and Montesanto 2016).

Physiological aging involves a progressive impairment in maximal organ function with differential trajectories across organ systems (illustrated in figure 23) (Khan, Singer, and Vaughan 2017). Importantly, multiple factors (genetics, environmental conditions, and developmental programming) determine maximal organ function, which varies significantly between individuals (Lange et al. 2015). Aging affects organ systems and must be measured

through a variety of physiological examinations, as aging varies greatly between organ systems and individuals.

3.5 Theories/Hypothesis of Cognitive Aging

Although there is no question that normal aging is accompanied by changes in cognitive abilities, there is still debate about what specific mechanisms, if any, underlie these changes. Several theories have suggested a single, fundamental mechanism that can account for much of the decline in cognitive function across domains. These theories range in explanation from the neurochemical (the dopamine theory of aging) to the localized (the frontal hypothesis of aging) to the process level (theories of processing speed and inhibition also the cognitive reserve hypothesis). These theories are not mutually exclusive, given that they attempt to explain different levels at which cognitive abilities can be affected. Examples of some current theories of cognitive aging are addressed in Table 6..

3.5.1 Frontal Hypothesis

The frontal aging hypothesis posits that the frontal lobes are particularly sensitive to the aging process and that declines in frontal efficiency can account for many of the cognitive deficits associated with cognitive aging (Dempster 1992; Greenwood 2000). Age-related cognitive changes in multiple domains, including executive functioning, language, and memory, can be traced to inefficiency in frontal-based processes such as strategy initiation, retrieval from long-term memory, and effortful processing. Although there is consistent evidence of declines in frontal functioning with normal aging, there is still some disagreement over whether the frontal lobes are preferentially susceptible to normal aging compared to other regions (Drag and Bieliauskas 2010). For example, Greenwood (2000) argues that the frontal lobe is not particularly unique in showing age-related changes and suggests that it may be more appropriate to view aging from a network rather than a localization approach (Greenwood 2000). Therefore, aging may not simply affect only one region but rather alter the dynamic of a more complex processing network that spans several brain regions.

Dopamine Theory

At the neurochemical level, the dopamine hypothesis of aging postulates that the cognitive deficits associated with normal aging are mediated by age-related dysregulation in the dopamine system (Bäckman et al. 2006). There is substantial evidence suggesting that normal aging is accompanied by dopamine dysregulation in multiple areas of the brain, and fluctuations in dopamine levels can significantly affect cognition (Van Dyck et al. 2002; Drag and Bieliauskas 2010), (Luciana, Collins, and Depue 1998). Several studies have demonstrated that dopamine

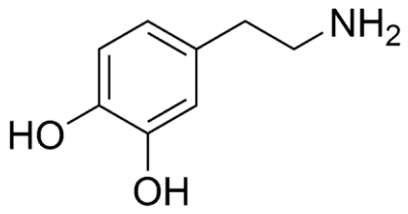


Figure 24. Chemical structure of dopamine (Taken from [Examined Existence Team 2019])

markers are a strong predictor of cognitive performance, particularly executive functioning abilities, in normal aging (Bäckman et al. 2000). The chemical structure of dopamine is shown in Figure 24. (Examined Existence Team 2019)

3.5.2 Processing Speed and Inhibition Theory

The inhibitory control hypothesis suggests that decreased efficiency in inhibitory processes can explain age-related changes in certain cognitive abilities such as working memory (Hasher and Zacks 1988; Greenwood 2000). The ability to inhibit or suppress task-irrelevant stimuli is thought to rely on the frontal lobes, and impairments in these processes can lead to deficits on interference-sensitive tasks. For example, if irrelevant information is allowed to enter working memory, there is a heightened susceptibility to distraction, especially when presented with multiple sources of information (following a conversation in a crowded room). Within the memory domain, older adults show increased susceptibility to retrieval interference compared to younger adults, particularly when facts share the same concepts and compete with each other at retrieval, termed the ‘‘fan effect’’. The fan effect, named after its conceptual likeness to a folding fan, refers to the finding that as the number of facts associated with a particular concept (the size of the fan) increases, speed, and accuracy in retrieving these facts from memory decreases (Gerard et al. 1991). Thus, as the size of the fan increases, so does the amount of interference from irrelevant information in memory. Older adults are more susceptible to the fan effect, suggesting an age-related decrease in the inhibitory mechanisms required to screen out conceptually relevant but non-target information (Radvansky, Zacks, and Hasher 1996; Gerard et al. 1991). Many complex cognitive tasks rely on inhibitory processes to suppress irrelevant information, clear away information that is no longer useful, and override the production of dominant but inappropriate responses. Inhibition is particularly important on tasks requiring an individual to sustain goal-directed activity. Such tasks include those involving problem solving, working memory, set-shifting, and selective attention.

Table 6. Description of Cognitive Aging Theories or Hypotheses

Theories/Hypotheses	Description
Frontal hypothesis	frontal lobes are sensitive to the aging process and related to cognitive deficits associated with cognitive aging
Dopamine theory	Age-related dysfunction in the dopamine system related to the cognitive deficits associated with normal aging
Processing speed and inhibition theory	Decreased efficiency in specific cognitive processes, such as processing speed and inhibitory processes underlie the age-related decrease in certain cognitive abilities
Cognitive reserve hypothesis	The volume of cerebral tissue and higher intelligence or greater educational attainment are protective factors against developing cognitive aging

3.5.3 Cognitive Reserve Hypothesis

The cognitive reserve hypothesis consists of two distinct models, which Stern (2002) refers to as passive and active models of the reserve (Stern 2002). The passive model suggests that simply having more cerebral tissue, for example, a larger brain size, is a protective factor against developing dementia. Individuals with larger brain size may cope longer with pathological changes in the brain since they can tolerate a greater amount of brain injury before passing the threshold of their functional brain impairment. The active model of reserve emphases on the association between higher intelligence or higher educational attainment and the delay in dementia onset. Individuals with higher intelligence or greater educational attainment may have more widespread and efficient neural networks, which may help them cope better with age-related changes in the brain (Stern 2002). It might be possible to accumulate more active reserve through the course of a cognitively enriched lifetime. Again, the passive (hardware) and active (software) models are not mutually exclusive; after all, neuroimaging studies have shown that brain volume and performance on IQ tests are moderately but significantly correlated. All of those theories/hypotheses of cognitive aging are summarized in table 5.

3.5.4 Resume

- Physiological aging refers to a progressive detrimental change in maximal organ function with differential trajectories across organ systems.
- Aging involves multiple factors, including genetics and environmental conditions.
- In the past decade, cognitive aging research has changed from general resource measures to more specific cognitive control or executive functions.
- Theories of cognitive aging mainly separated into four theories/hypotheses: frontal hypothesis, dopamine theory, processing speed and inhibition theory, and cognitive reserve hypothesis.

3.6 Aging and Neuro-Cardiovascular Parameters

3.6.1 Aging and Angiogenesis

Angiogenesis is a process of endothelial proliferation and differentiation to form a new blood vessel (Fam et al. 2003). One of the main substrate in angiogenesis in the brain is vascular endothelial growth factor (VEGF), an angiogenic protein (illustrated in Figure 25), is known to have neuroprotective and neurotrophic functions (T.-W. Lin, Tsai, and Kuo 2018). VEGF could be synthesized and released by peripheral vascular endothelial cells and brain cells, including astrocytes, ependymal cells, and neuronal stem cells (Nowacka and Obuchowicz 2012). The activation of

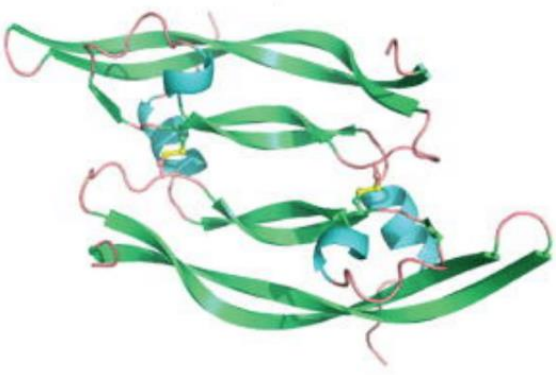


Figure 25. Cartoon representation of the x-ray structure of chemically synthesized VEGF (Mandal and Kent 2011).

the intracellular tyrosine kinase domains of the VEGF receptors initiates the activation of several downstream signaling pathways which in turn enhances the proliferation of neuron precursors (Petrova, Makinen, and Alitalo 1999; Palmer, Willhoite, and Gage 2000).

The formation of a functioning vasculature requires not only VEGF but also the interaction of endothelial cells, extracellular matrix, and surrounding cells. The main physiological stimuli for angiogenesis are tissue ischemia and hypoxia, inflammation, and shear stress (Fam et al. 2003). Several specific factors are identified to stimulate or inhibit angiogenesis, including vascular growth factors, adhesion molecules, inflammatory cytokines, and nitric oxide. Essentially, the regulation of these factors in both spatial and temporal domains is important to influence neovascularization, and different activities are required in the different phases of angiogenesis from initiation to maturation. The sequence of regulation of angiogenesis is described in Figure 26. The sequence starts with a response to stimuli such as hypoxia, VEGF induces vasculogenesis, and endothelial cell proliferation. Ang1–Tie2 interactions mediate vessel maturation and maintain vessel integrity through the recruitment of periendothelial cells. Ang2 blocks Ang1–Tie2 signaling, loosening pericytes, and again exposing the endothelium to inducers of angiogenesis such as VEGF. When induced by VEGF, endothelial cells migrate and proliferate to form new capillary sprouts and blood vessels. Ang2 expression without VEGF stimulation will lead to vessel regression and apoptosis. This sequence underlines the essential role of VEGF, endothelial cells, and surrounding cells in the angiogenesis.

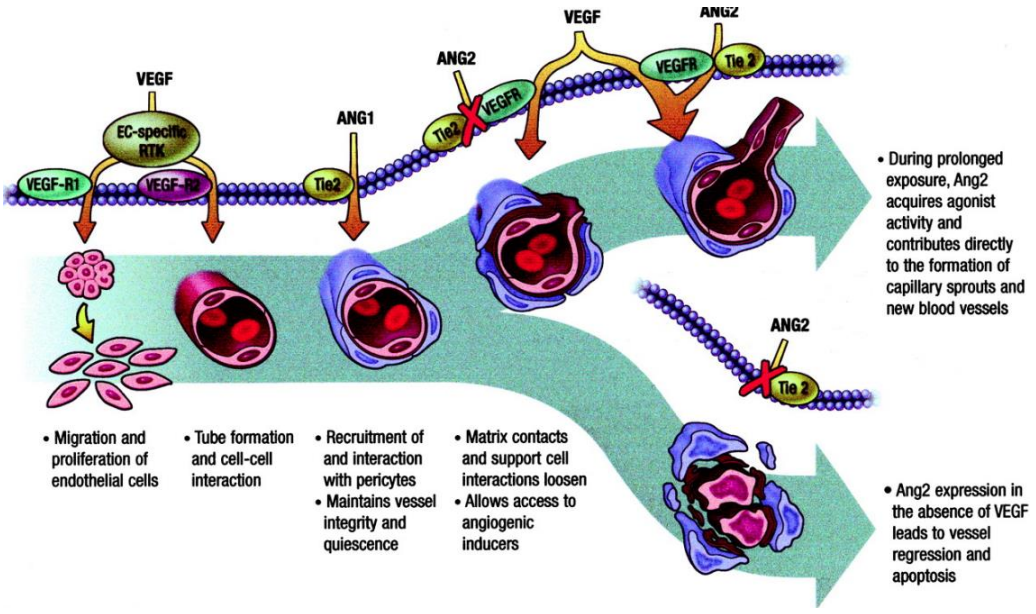


Figure 26. Regulation of angiogenesis (Taken from (Fam et al. 2003)**).** Abbreviation: ANG1, angiopoietin-1; ANG2, angiopoietin-2; Tie2, transmembrane tyrosine-protein kinase receptor for angiopoietin VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor VEGF-R2, vascular endothelial growth factor receptor 2.

In aging, increased p19(Arf) expression suppresses VEGF-A production, whereas exogenous VEGF-A downregulates p16 and p21, stimulating the proliferative capacity of endothelial cells (Watanabe et al. 1997; Kawagishi et al. 2010). Studies in animal models reported reduced VEGF production and lower expression levels of VEGF receptors in old animals (Wagatsuma 2006). Moreover, the administration of exogenous VEGF-A protein or transcriptional activation of VEGF-A restored angiogenesis in old animals (Rivard et al. 1999; Yu et al. 2006; Pola et al. 2001). In humans, the VEGF mRNA level is lower in older subjects at resting condition, after exercise (Ryan et al. 2006), and after ischemia in comparison to younger control subjects (Croley et al. 2005). At the cellular level, older subjects have reduced capillary density and reduced angiogenesis in response to ischemia (Gavin et al. 2007; Parizkova et al. 1971; Coggan et al. 1992). Aging also reduces the response to exogenous angiogenic growth factors delivered in clinical trials (Gupta, Tongers, and Losordo 2009). In general, aging decreases VEGF production that reduces capillary density and lowers the angiogenetic activity in response to hypoxia or exercise.

3.6.2 Resume

- Angiogenesis is a dynamic process of endothelial proliferation and differentiation to form a new blood vessel.
- VEGF initiates the activation of several downstream signaling pathways which in turn enhances the vasculogenesis and endothelial cell proliferation.
- Aging decreases VEGF production that reduces capillary density and lowers the angiogenetic activity in response to hypoxia or exercise.

3.6.3 Aging and Cerebral Blood Flow

Aging is the main risk factor for cognitive decline (Lipnicki et al. 2013). Given that the cerebral blood flow (CBF) or regulation of cerebral circulation is weakened in the older adults, it probable that aging-induced cognitive decline may be mediated or associated with a decrease in CBF (Lu et al. 2011). CBF regulation associated with cerebral metabolism, therefore, likely plays an important role in the preservation of cognitive function.

The CBF progressively decreases in normal aging men and women, while women tend to have greater CBF than men (Lu et al. 2011). This age-related reduction of CBF may reflect decreased cerebral metabolic rate (Marchal et al. 1992) and cerebrovascular dysfunction (Y. S. Zhu et al. 2011). Starting from 30 years old, cerebral metabolic rates for oxygen and glucose decrease by 5% per decade, and these reductions of metabolic rate are coupled to the concurrent decrease in CBF (illustrated in Figure 27) (Leenders et al. 1990; Petit-Taboué et al. 1998; Lu et al. 2011). In this case, aging may impair neuronal and glial mitochondrial metabolism. A spectroscopy study demonstrated that metabolic rates for neuronal tricarboxylic acid and glutamate-glutamine cycles are reduced in older adults (Boumezbeur et al. 2010). Aside from these aging effects, it has been

shown that women have higher levels of cerebral metabolic rate for oxygen (Lu et al. 2011) and glucose (Willis et al. 2002), which may explain why women have higher levels of CBF than men.

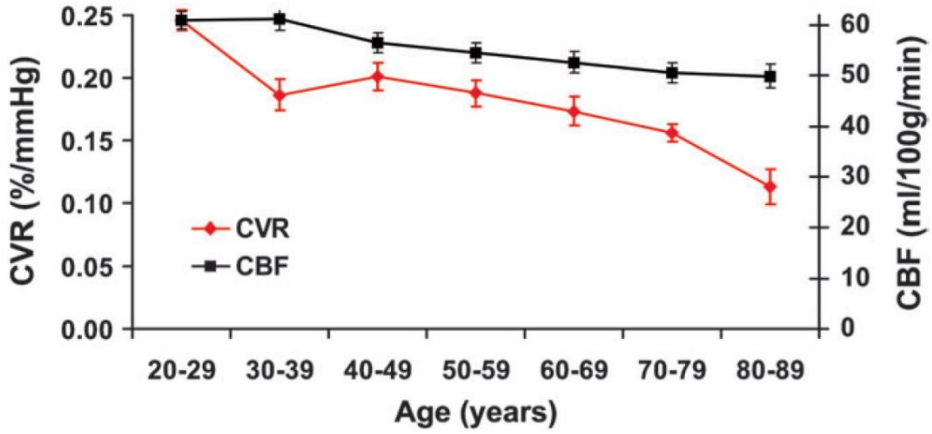


Figure 27. Decade-by-decade alterations in prefrontal CVR and CBF. Display scales for CVR and CBF are shown on the left and right axis, respectively (Taken from (Lu et al. 2011)**).**
Abbreviation: CBF, cerebral blood flow; CVR, cerebrovascular reactivity.

3.6.3.1 Aging and Blood Pressure

Aging is related to a gradual increase in mean arterial pressure (Franklin et al. 1997). The increase of arterial pressure is associated with heightened sympathetic neural activity and impaired peripheral vasodilatory function (Hart et al. 2012). Moreover, a study which measures direct intracranial pressure using an intra-parenchymal probe reported a negative correlation between age and intracranial pressure (Czosnyka et al. 2005). If this observation is generalized to healthy aging adults, age may increase cerebral perfusion pressure (CPP) due to the effects of both increased mean arterial pressure and decreased intracranial pressure. With the elevated CPP, the cerebrovascular bed may make a compensatory remodeling by increasing resistance to protect brain tissues from overperfusion.

3.6.3.2 Aging and Cardiac Output

Age-related reduction of CBF may also be related to concurrent changes in CO (Tarumi, Zhang, and Ln 2017). The widely accepted dogma suggests that ~15% of CO is distributed to the brain in healthy adults (L. R. Williams and Leggett 1989); however, it is not well understood whether this proportion can change with the alteration of CO or CBF in aging adults. Therefore, Xing et al. (2017) studied 139 healthy aging adults (20–80 years) who do not have a history of neurological, cardio- or cerebrovascular disease. CBF was measured from the bilateral internal carotid and vertebral arteries using phase-contrast MRI, while CO was measured by echocardiography. They found that advancing age is associated with the decreasing proportion of CO distributed to the brain; however, CO was maintained, and only CBF was decreased in older adults (Xing et al. 2017). These findings suggest that age-related reduction of CBF may not be attributed to the reduction of CO.

3.6.3.3 Aging and Autonomic Nervous System

The autonomic nervous system is a set of pathways of neurons that control various organs, using several chemicals and signals to maintain homeostasis. It is grouped into the sympathetic and parasympathetic systems. The sympathetic systems are known as "fight or flight" and the parasympathetic systems as "rest and digest." It functions without conscious control throughout the lifespan to control body systems, for example, the blood pressure.

Sympathetic nerve activity at rest is known to increase with aging (Hotta and Uchida 2010). There is an age-related increase in plasma noradrenaline concentration and discharge rate on muscle sympathetic nerve fibers measured by microneurography, see Figure 28 (Rowe and Troen 1980; Wallin et al. 1981; Hotta and Uchida 2010). A positive correlation was found between age and muscle sympathetic nerve activity in normal subjects (Iwase et al. 1991). From the animal study, aging is associated with an increase in sympathetic nerve outflow to the adrenal glands (Ito et al. 1986). The amount of tissue norepinephrine release, an indirect measure of sympathetic nerve activity innervating a tissue or organ, is higher in older adults than in young adults in the heart and liver but not in the kidney (Hotta and Uchida 2010). Thus, the age-related augmentation in sympathetic nerve activity appears to fluctuate depending on the tissue or organ system. It is postulated that a reduction of the sensitivity of the arterial baroreceptor reflex causes the age-related increase in resting sympathetic nerve activity (Rowe and Troen 1980). Moreover, there also a close relationship between an increase in visceral fat with aging and an increase in resting sympathetic nerve activity (Seals and Bell 2004). A correlation between body fat ratio and muscle sympathetic nerve activity was reported in every age group (Hotta and Uchida 2010). Lastly, leptin, which is released from adipocytes, also has sympathoexcitatory action (Haynes et al. 1997; Niijima 1999).

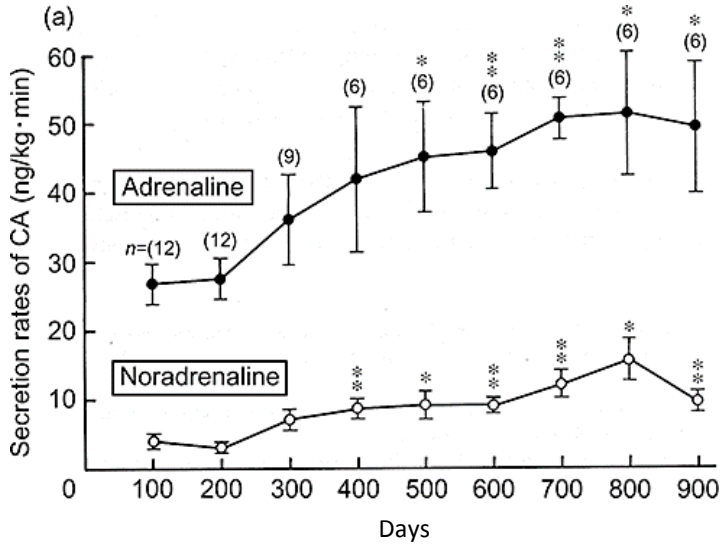


Figure 28. Secretion rates of adrenaline and noradrenaline at various age groups of Wistar rats (Modified from (Hotta and Uchida 2010)**)**

There is less research examining the association between aging and the parasympathetic nervous system. However, age-related declines in vagus nerve activities are shown as the vagal component of heart rate variability decreases with age and that heart rate changes in response to

muscarinic acetylcholine receptor blocking agents are reduced (Korkushko et al. 1991; Poller et al. 1997). In an animal study, aging also reported changing the conduction velocity of vagal tone (vagus nerve activity at rest). The maximum conduction velocity of vagus nerve decreases in old rats by about 10% (A. Sato, Sato, and Suzuki 1985).

3.6.4 Resume

- Cerebral blood flow (CBF) progressively decreases in aging,
- Women reported have higher levels of CBF than men.
- Effects of aging on determinants of CBF:
  - Total peripheral resistance and therefore mean arterial pressure are increase with age
  - Cardiac output at rest does not decrease with age
  - Sympathetic nerve activity at rest is increased with age
  - Conduction velocity of the parasympathetic nervous system is decreased with age.

3.7 Aging on Brain Structures and Functions

3.7.1 Effect of Aging on Grey Matter

Grey matter volume begins to decrease after the age of 20 (Terry and Katzman 2001). The amount of atrophy is most dominant in the prefrontal cortex. Age-related atrophy in the temporal lobes are more modest and involve decreases in the volume of the hippocampus (Raz et al. 2004). The entorhinal cortex, which functions as a relay center between the hippocampus and association areas, has been reported to experience early decreases in volume in Alzheimer's disease (AD), but not in normal aging (Braak and Braak 1996). The death of neurons has been implicated as a possible cause of grey matter volume loss. Neuronal death is particularly harmful, given infrequent cell division and accumulation of mutations (Uttara et al. 2009). The accumulation of beta-amyloid is reported in the brains of patients with AD. Beta-amyloid has been proposed to cause AD via neuronal death. The elevated presence of beta-amyloid in patients with mild cognitive impairment predicts conversion to AD. In recent years, neuroimaging techniques using positron emission tomography (PET) scanners have allowed to identify beta-amyloid plaques presence in cognitively normal older adults. Beta-amyloid is found in the cortex in 30% of normal adults (Rodrigue, Kennedy, and Park 2009). It has been hypothesized that the presence of beta-amyloid in cognitively normal individuals predicts the occurrence of AD on those individuals (Pike et al. 2007). One study showed an association between high levels of beta-amyloid and both decreased hippocampal volumes and episodic memory in cognitively normal individuals (Jack et al. 2008). The association suggests that amyloid may be early damage from cortical volume-loss processes that will lead to cognitive impairment. In conclusion, beta-amyloid can be found in the brain of cognitively normal individuals, but it may indicate a higher risk of developing cognitive impairment over time.

Despite the numerous theories explaining the neuronal loss, grey matter volume decline in older adults is best explained not by the death of neurons themselves but by a decrease in their size and the number of connections between them (Resnick et al. 2003; Terry and Katzman 2001). This reduction in synaptic density is well documented in older adults, and according to the model created by Terry and Katzman, by the age of 130 years, a cognitively normal adult will have a synaptic density equivalent to someone with AD (Terry and Katzman 2001). Neurons undergo morphologic changes with aging, including a decrease in the complexity of dendrite arborization, decreased dendrite length, and decreased neuritic spines (the major sites for excitatory synapses). These morphologic changes likely contribute directly to the reduction of synaptic density (Dickstein et al. 2007).

3.7.2 Effect of Aging on White Matter

White matter volume is decreased at a much higher rate than grey matter volume with increasing age (Salat, Kaye, and Janowsky 1999). This white matter atrophy has been studied with various neuroimaging techniques, but these investigations have been limited by low numbers of normal controls (O'Sullivan et al. 2001). In a study using morphometric methods from autopsy data of neurologically normal subjects, there was a decrease of 20% in white matter volume in older individuals over 70 years old compared to younger individuals. This white matter shrinkage was noted in the precentral gyrus, gyrus rectus, and corpus callosum, areas which reported having less than 6% declines in grey matter volume (Meier-Ruge et al. 1992). This finding has been supported by others. For example, Rogalski et al. reported that decreased parahippocampal white matter was leading to decreased neuronal activity with hippocampal structures and proposing a possible mechanism for age-associated memory impairment (Rogalski et al. 2012). In addition to a reduction in white matter volume, an impairment in the function of white matter has been studied using diffusion tensor imaging (DTI). DTI allowed us to observe the white matter integrity on a living organism directly. O'Sullivan et al. showed that age-related declines in white matter tract integrity are most marked in the anterior white matter and are associated with impairment in executive function (O'Sullivan et al. 2001). Madden et al. also reported that loss of integrity of the central portion of the corpus callosum might mediate age-related cognitive decline (Madden et al. 2009).

3.7.3 Resume

Grey matter

- Grey matter volume started to decrease from the third decade of life.
- The prefrontal cortex is a part of the brain that most related to grey matter volume decrease in aging.
- The decrease in grey matter volume is a decrease in size and numbers of connection between them not by the death of neurons.
- Beta-amyloid is associated with decreased brain volume, suggests that beta-amyloid may be related to cognitive aging.

White matter

- White matter volume decreases are much greater than grey matter volume decreases with increasing age.
- Precentral gyrus, gyrus rectus, and corpus callosum are part of the brain that related to white matter volume decrease in aging.
- The decrease in white matter integrity associated with a decline in cognitive function, including executive function.

3.8 Aging and Executive Function

Investigations about the age-related changes in executive functioning have yielded varied and often contradictory results. While some authors argue for a distinct decline of executive functions with aging (Plumet, Gil, and Gaonac'h 2005; Fisk and Sharp 2004). Others believe in a more global deterioration of cognitive skills (Salthouse 1996). A better understanding of the effects of age on executive control is important, as poor performance on executive measures is predictive of a decline in the functional living skills of elderly individuals (Grigsby et al. 1998). When compared to tasks that engage other cognitive domains, tests of executive function are more predictive of loss of instrumental activities of daily living in the elderly (Cahn-Weiner et al. 2000) as well as the quality of life as already explained in the first section in this manuscript. In the same way that maturation of the frontal lobe enables the development of executive skills in children, the decline of executive functions during aging is believed to be mediated by anatomical changes in the brain.

3.8.1 Working Memory

One model addressing neural activation differences between younger adults (typically 18–30 years old) and older adults (typically 60+ years old) during WM tasks is the Hemispheric Asymmetry Reduction in Older Age model (HAROLD) (Cabeza 2002). Findings in the HAROLD model reveal that, during WM tasks, young adults demonstrated left PFC activation during verbal WM tasks and right PFC activation during spatial WM tasks, while older adults display bilateral activation of the PFC during both spatial and verbal WM tasks (Figure 29 – point D) (Reuter-Lorenz et al. 2000; Cabeza 2002). Bilateral activation of PFC in older adults compensate for age-related decline by recruiting additional neural networks to maintain performance on the task.

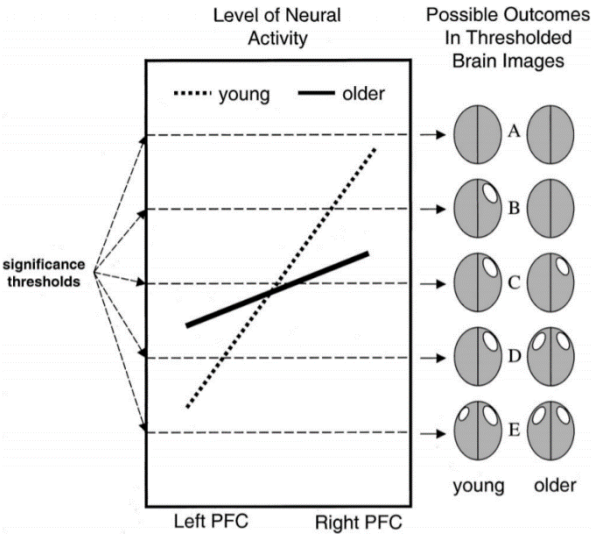


Figure 29. The Hemispheric Asymmetry Reduction in Older Age model (HAROLD) (Taken from [Cabeza 2002]). Point A indicates below threshold PFC activity, while point E indicates bilateral PFC activity in both young and older groups. Abbreviation: PFC, Prefrontal cortex

Clarifying the compensation view of the HAROLD model, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz and Cappell 2008) asserts that overactivation of neural circuits in healthy older adults, relative to healthy younger adults, is necessary for the completion of WM tasks and correlates with greater performance when normalized for task demand. Additionally, healthy older adults display bilateral overactivation of the frontal cortex, including the PFC, to compensate for decreased activity with age of more specialized regions such as the medial temporal lobes, relative to healthy younger adults (Gutchess et al. 2005). Payer et al. (2006) found that, during a visual WM task in older adults, underactivation of the ventral visual cortical (VVC) pathway, which includes areas of the occipital and temporal lobes, was accompanied by bilateral overactivation of the PFC (Payer et al. 2006). Findings from Schneider-Garces et al. (2000) further suggest that impaired WM capacity in older adults is due to reduced selective attention (Schneider-Garces et al. 2010). Older adults struggled with Sternberg task completion when the number of stimuli presented exceeded their working memory capacity, they also displayed slower response times and lower accuracy rates, especially at higher WM loads (4–6 item sets). Neurologically, this decrease in capacity and processing speed is associated with age-related changes in the dorsolateral PFC (Rypma and D'Esposito 2000).

As a summary, younger adults showed mainly left-hemispheric activation with some bilateral activation of frontal and parietal regions at high loads, suggesting that increasing task demand typically leads to recruitment of contralateral brain regions as posited by Reuter-Lorenz and Cappell (2008) in their CRUNCH model (Reuter-Lorenz and Cappell 2008). On the other hand, older adults exhibited bilateral-overactivation neural activity during low WM loads and

underactivation at high loads, suggesting that overactivation only occurs when tasks are easy enough for compensatory mechanisms to be beneficial.

3.8.2 Selective Attention and Inhibition Control

The most popular measure of inhibition is the Stroop task (Perret 1974), this condition requires participants to name the color of the ink of a written color word (for example, the word "RED" is written in green ink) demanding the suppression of the internal drift to read the color word. Many studies indicate greater age-related slowing on the inhibition condition of the Stroop task compared to a baseline condition. However, the inhibitory condition of this task takes considerably longer than baseline conditions not only in older adults but also in young adults, and so the aging effect may reflect a scalar factor of slowing (Rabbitt, Lowe, and Shilling 2001). Verhaegen and De Meersman (1998) showed through a meta-analysis of mean response times on the Stroop task that Stroop effects can be explained in terms of slowed information processing with age (Verhaeghen and De Meersman 1998).

The recent meta-analysis from Rey-Mermet & Gade (2018) demonstrates that for most inhibition tasks (i.e., the color Stroop task, the color-word Stroop test, the flanker task, the global task, as well as the task assessing n-2 repetition costs), no inhibition deficit in older age was observed (Rey-Mermet and Gade 2018). For other tasks (the Simon, global, positive, and negative compatibility tasks), more research is necessary to decide whether such a deficit occurs. In only two tasks (i.e., the stop-signal and go/no-go tasks), an age-related deficit was found. Together, these results indicate that no general inhibition deficit was observed in older age. Specifically, the stop-signal and go/no-go tasks are associated with the ability to suppress dominant responses, while the majority of other inhibition tasks are associated with the ability to ignore distracting information and response interference (Chuderski et al. 2012). Another explication is that in the stop-signal and go/no-go tasks, maintaining information and coordinating two sets of tasks are needed. Therefore, it is possible that the age-related deficit in those tasks related to a deficit in the ability to maintain and coordinate no-go/stop-signal information.

3.8.3 Cognitive Flexibility

Cognitive flexibility refers to the ability to switch rapidly between different response sets and is related to task-switching (Seniów 2012). Shifting attention between either different task sets or stimulus-response conditions is a key element of executive functioning (Miyake et al. 2000). Many studies have investigated the effects of aging on the ability to switch attention. Mejia et al. (1998) failed to find any significant differences in performance when comparing a young-old group (55-70) and an old-old group (71-85) (Mejia et al. 1998). Similarly, Haaland et al. (1987) found that older participants committed fewer perseverative errors and achieved more categories than younger ones with a decline only observed after the age of 80 (Haaland et al. 1987).

Contrary to those findings, Axelrod, Woodard & Henry (1992) found a significant increase in perseverative errors present after the age of 60 (Axelrod, Woodard, and Henry 1992). Similar results were obtained by Crawford et al. (2000), who found a significant decline among a sample

aged 60-75 when compared to a younger group (18-60 years) (Crawford et al. 2000). Significant differences between age groups were also reported by Plumet, Gaonac'h, and Gil (2005), in which older adults found to need more trials to complete a modified version of the Wisconsin Card Sorting Test (WCST) (Plumet, Gil, and Gaonac'h 2005). In general (with some exceptions from several studies (Mejia et al. 1998; Haaland et al. 1987)), as adults grow older, they become progressively susceptible to perseveration errors in the WCST and similar set-shifting tasks (Daigneault, Braun, and Whitaker 1992).

An explication of various results in switching results is presented by Kray and Lindenberger (2000), which investigated the age differences in general versus specific switching costs (Kray and Lindenberger 2000). General switch costs are costs associated with maintaining two different task-response sets (A and B) in mind, while specific switch costs are measured at the point of switching from one mental set to another. In the Kray and Lindenberger study, general switching costs were calculated by comparing the time taken to respond to single task set conditions (a series of only AAAAAA trials) compared to dual-task set (a series of AABBAABB), whereas specific switch costs were measured by comparing latencies of switch trials to those of non-switch trials within the AABBAABB condition. Aging resulted in increased general switch costs but did not affect specific switch costs, suggesting that age is associated with difficulty in maintaining two competing mental sets in mind, rather than the difficulty in the specific execution of the mental switch (for the results see Tabel 6) (Kray and Lindenberger 2000). This result was supported by a meta-analysis carried out by Verhaeghen and Cerelia (2002), in which they concluded that age effects were larger in the general cost as compared to the specific cost (Verhaeghen and Cerella 2002).

Tabel 7. General and specific switch costs between young-aged, middle-aged, and old aged (Modified from (Kray and Lindenberger 2000)**)**

	Costs type			
	General		Specific	
Group	*M*	*SD*	*M*	*SD*
Young	0.218	0.026	0.201	0.029
Middle	0.295	0.029	0.219	0.022
Old	0.328	0.027	0.230	0.021

Kray et al. (2002) suggest that, when switching is unpredictable, local switch costs are likely to be much higher for older adults, because multiple stimulus-response mental sets are not being actively maintained across the entire sequence of switches (Kray, Li, and Lindenberger 2002). Using meta-analytic techniques, Verhaeghen and Cerelia (2002) found that the age-deficit in global task switching exceeds the magnitude predicted by changes in general cognitive changes such as processing speed (Verhaeghen and Cerella 2002). The deficit suggests that the ability to juggle multiple task sets is impaired in aging, and this deficit is independent of more general cognitive changes with age. Reliable findings of age differences in global switch costs indicate

that older people may have difficulty in maintaining multiple action sets in mind. It has implications for everyday functioning in complex settings where attention·focus and action-sets must often be changed rapidly. However, so far, the literature on age and switching has concentrated on laboratory settings, so there is little empirical evidence available to evaluate the everyday importance of any deficit in task switching.

3.8.4 Resume

- Executive functions are more predictive of loss of instrumental activities of daily living in the elderly than other cognitive domains
- Younger adults showed mainly left-hemispheric activation with some bilateral activation of frontal and parietal regions at high loads. Older adults, on the other hand, exhibited bilateral-overactivation neural activity during low executive function loads and underactivation at high loads, suggesting that overactivation only occurs when tasks are easy enough for compensatory mechanisms to be beneficial
- In working memory, older adults showed slower response times and lower accuracy rates
- In inhibition, the age-related deficit in these tasks related to a deficit in the ability to maintain and coordinate information, and slowed information processing.
- In switching, the age-related deficit is associated with difficulty in maintaining two competing mental sets in mind, rather than the difficulty in the specific execution of the mental switch.

3.9 Summary of Section

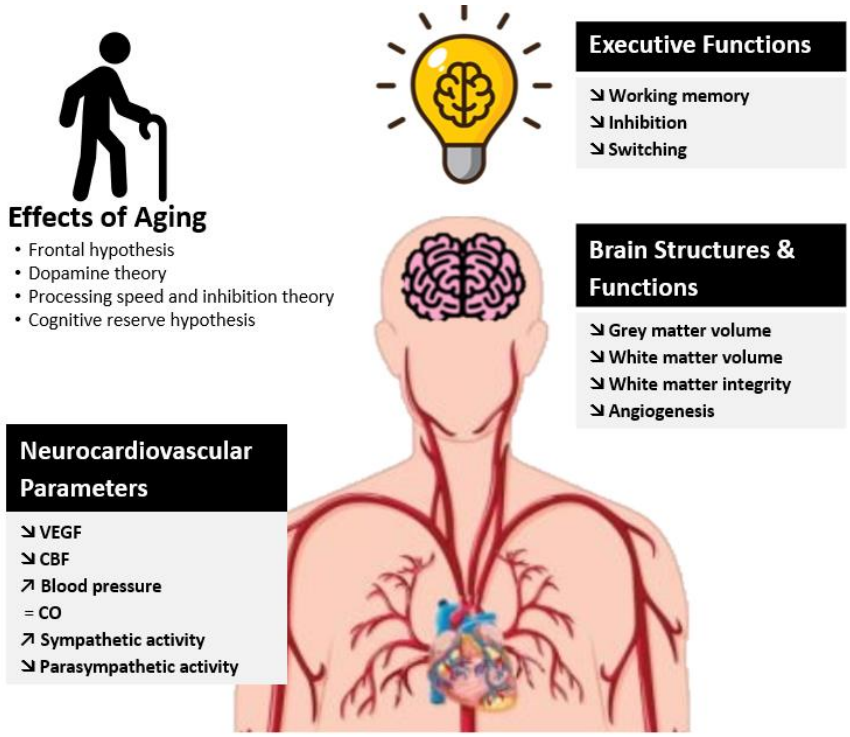


Figure 30. Summary of effects of aging on neuro-cardiovascular parameters, brain structures and functions, and executive functions. Abbreviation: CBF, cerebral blood flow; CO, cardiac output; VEGF, vascular endothelial growth factor.

In 2012, Michael R. Rose, an evolutionary biologist, defined aging as "a multifaceted phenomenon that deteriorate adaptation with adult age" (Rose et al. 2012). *Thus, it emphasized the "deteriorate adaptation" as a basis of aging processes. Cognitive aging is also a complex process of mental-structural deterioration that can be impede by certain adaptations. Physical activity has been established to offer numerous benefits to the body, including the brain, and is thought to be one of the adaptations needed to deter cognitive aging. Moreover, as some factors related to cognitive aging have been reported in young adults, the beneficial effects of physical activity to the brain and cognition seem not only limited to older adults but can also be observed in young ones.*

4 Physical Activity and Executive Function

Across age groups, previous meta-analyses have shown that enhanced cognitive functioning as a result of physical activity is most clearly seen in executive functions (Verburgh et al. 2014; S. J. Colcombe et al. 2004; Kramer and Colcombe 2018). These cognitive functions are indispensable for success throughout life and are often thought of as an important requirement for successful learning (Diamond 2013). According to the cardiovascular fitness hypothesis, an intervention program that contains continuous aerobic physical activity over several weeks (longitudinal physical activity program) is thought to improve aerobic fitness and consequently improve cognitive performance (Etnier et al. 1997). This hypothesis is supported by the argument that physical activity enhances angiogenesis and neurogenesis in areas of the brain (Dishman et al. 2006; Isaacs et al. 1992).

This section discusses the effect of physical activity on executive function. The implications of physical activity on executive function separated into three parts: physical activity and neuro-cardiovascular parameters, physical activity and brain structures-and-functions, physical activity and executive function. In this section, it will be discussed not only the effect of physical activity but also cardiorespiratory fitness (CRF) and exercise on executive function.

4.1 Physical Activity and Neuro-Cardiovascular Parameters

4.1.1 Physical Activity and Angiogenesis

Physical activity has been reported promoting cerebral vasculature angiogenesis (Cotman, Berchtold, and Christie 2007). Angiogenesis can occur by a mechanism of sprouting process in which a new branch sprouts from one capillary and merges with another (Makanya, Hlushchuk, and Djonov 2009). However, the physical activity increases the density of capillaries, while the volume of the molecular layer remains constant. Hence, the ratio of blood vessel volume to other components of the layer has increased. A study using macaques demonstrated the increase in vascular volume fraction in the motor cortex with five months of daily treadmill exercise.

Interestingly, this effect was found in older animals but not in the younger-aged animals (Rhyu et al. 2010). The mechanism of aerobic exercise increasing angiogenesis in the brain is not clearly understood yet. It is hypothesized that the mechanical shear stress on the walls of the capillaries and the hypoxia may play a role (Makanya, Hlushchuk, and Djonov 2009).

From a molecular perspective, exercise induces activation of peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC1α) through recruitment of estrogen-related receptor-α (ERRα) to the VEGF promoter (Silvennoinen et al. 2015; Pilegaard, Saltin, and Neufer 2003). This activation potentially increases the stabilization of hypoxia-inducible factor-1α (HIF1α), which culminates in the increased expression of VEGF and other pro-angiogenic factors (Gorski and Bock 2019). On the other site, estrogen-related receptor-γ (ERRγ) determines baseline muscle vascularization either via direct binding to the VEGF promoter or via controlling the activity of 5′-adenosine monophosphate-activated protein kinase (AMPK) (Gorski and Bock 2019). At the end of the sequence, the release of VEGF and other angiogenic factors from the exercising muscle

leads to increased vascularization through vessel sprouting or vessel splitting (see Figure 31 for the illustration) (Gorski and Bock 2019)

In the elderly, angiogenesis is impaired in response to ischemia or infarction (Rivard et al. 1999) but maybe intact in response to exercise. (Gavin et al. 2007; Parizkova et al. 1971; Coggan et al. 1992). Exercise appears to restore HIF1α activity and ischemia-induced neovascularization in aged animals through a PI3 kinase-dependent mechanism (Cheng et al. 2010). Swimming increases VEGF, Flt-1, Flk-1, and also increases capillary density in aged rat myocardium, similar to young controls (Iemitsu et al. 2006). The previous exercise improves recovery after hind limb ischemia in old rats by increasing HIF1α and VEGF-A expression, leading to an increase in capillary density in the ischemic limb (Leosco et al. 2007).

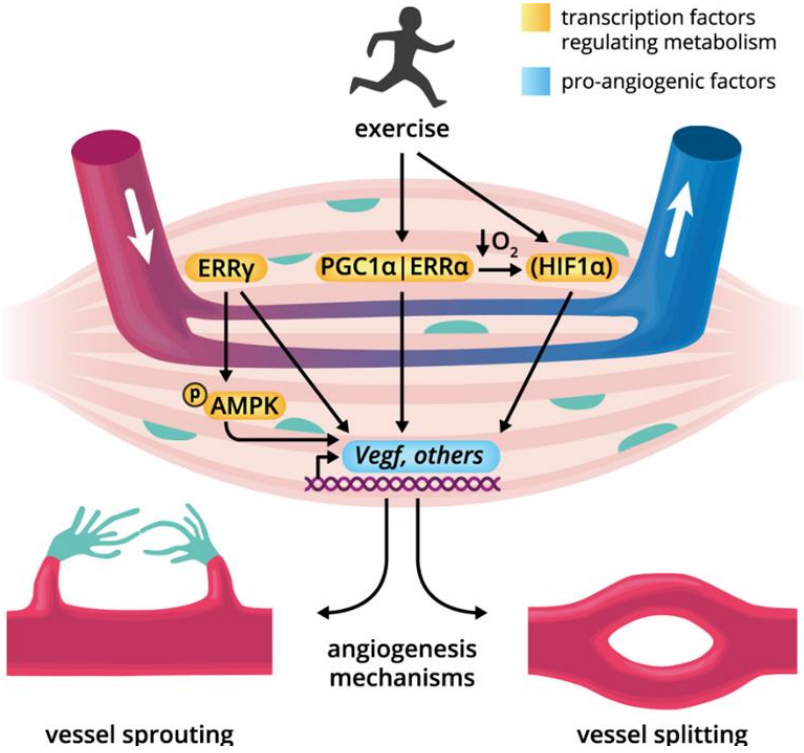


Figure 31. Exercise-induced activation of transcription factors in angiogenesis (modified from (Gorski and Bock 2019)**).** Abbreviation: AMPK, 5′ adenosine monophosphate-activated protein kinase; ERRα, estrogen-related receptor α; ERRγ, estrogen-related receptor γ; HIF1α, hypoxia-inducible factor 1α; PGC1α, peroxisome-proliferator-activated receptor-γ coactivator-1α; VEGF, vascular endothelial growth factor.

In conclusion, hypoxia or exercise increases expression of transcription factors or coactivators such as HIF1α and PCG-1α that, in turn, induce the production of angiogenic growth factors and angiogenesis (Fong 2008). Also, exercise mitigates many of the aging-related molecular defects seen in endothelial cells and angiogenesis.

4.1.2 Resume

- The physical activity increases the ratio of blood vessel volume to other components of the layer by increasing the density of capillaries.
- The hypothetical mechanism of exercise-induced angiogenesis in the brain is by mechanical shear stress on the walls of the capillaries and hypoxia.
- From a molecular perspective, exercise-induced angiogenesis comprises a sequence of higher activation of PGC1α, greater recruitment of ERRα, and increased expression of VEGF.
- In the elderly, angiogenesis is impaired in response to ischemia or infarction, but exercise mitigates the aging-related molecular defects seen in endothelial cells and angiogenesis.

4.1.3 Physical Activity and Cerebral Blood Flow

Regular aerobic exercise is an effective stimulation to enhance endothelial function and decrease arterial stiffness, oxidative stress, and vascular inflammation. As described in the previous section, resting CBF declines with age. Recently, Ainslie et al. (2008) examined the influence of fitness on basal CBF in men from 18 to 79 years old (P. N. Ainslie et al. 2008). CBF was found 17% higher in endurance-trained men compared with their sedentary counterparts after controlling mean arterial pressure and body mass index (P. N. Ainslie et al. 2008). Although the mechanism for CBF augmentation was not fully understood, animal study suggests that increased blood flow with increases in vascular shear stress may upregulate the expression of endothelial NOS, leading to an increase in NO-dependant vasodilation and an increase in basal CBF (Thomas et al. 2012).

4.1.3.1 Physical Activity and Blood Pressure

The regulation of blood pressure has been recognized as a complex mixture of neural, hormonal, and intrinsic factors involving the brain, heart, vasculature, and especially the kidneys due to its control of fluid balance (Hellsten and Nyberg 2016). It is well established that aerobic training reduces blood pressure at rest in both normotensive and hypertensive subjects, with a greater effect in hypertensive subjects (Cornelissen and Fagard 2005). The mechanisms underlying this effect of exercise training remain undisclosed, but are likely to be multifactorial and include vascular remodeling and changes in peripheral vascular function, sympathetic nervous activity, the renin-angiotensin system, and the function of the nitric oxide (NO) (Heerkens, Izzard, and Heagerty 2007; Mueller 2007; Nyberg et al. 2012; Hellsten and Nyberg 2016; Cornelissen and Fagard 2005). Concerning the sympathetic nervous system, the role of skeletal muscle sympathetic nervous activity (MSNA) for the training-induced reduction in blood pressure is likely to be limited as training does not reduce MSNA at rest (Hellsten and Nyberg 2016).

The age-related increase in BP is accompanied by an increase in cardiovascular risk that manifests beyond BP levels of 115/75 mmHg (Lewington et al. 2002). Evidence suggests that

the increase of BP is preceded by augmentation of the arterial stiffness (Kaess et al. 2012). To some extent, the age-related increase in arterial stiffness and BP are unavoidable. Nevertheless, a part of the causal of those conditions is more of the lifestyle characterized by physical inactivity and unhealthy diets (high-fat and high-sodium) than normal physiological processes of aging (McEniery et al. 2010; Thijssen et al. 2010). The exercise-induced shear stress and hypoxia seem to be the basis of physiological stimuli for the adaptations in endothelial function and vascular remodeling detected after exercise training in healthy subjects (Chobanian et al. 2003; Tinken et al. 2010).

Prehypertension which is defined as systolic BP levels of 120 to 139 mmHg or diastolic BP levels of 80 to 89 mmHg, is frequently a causal of hypertension (De Marco et al. 2009; Chobanian et al. 2003). Physical activity may attenuate the rate of progression from prehypertension to hypertension. This thought was investigated by Faselis et al. (2012) in 2303 prehypertensive, middle-aged male veterans that been followed for more than nine years. Higher cardiorespiratory fitness, as specified by peak metabolic equivalents (METs), was negatively associated with the rate of progression to hypertension (Faselis et al. 2012). Moreover, when compared with the individuals with the highest exercise capacity (>10 METs), the risk for developing hypertension was 36% higher for individuals with an exercise capacity between 8.6 and 10 METs; 66% for individuals with 6.6 to 8.5 METs, and 72% higher for individuals who has exercise capacity ≤6.5 METs (Faselis et al. 2012). This result is shown in Figure 32 (Faselis et al. 2012).

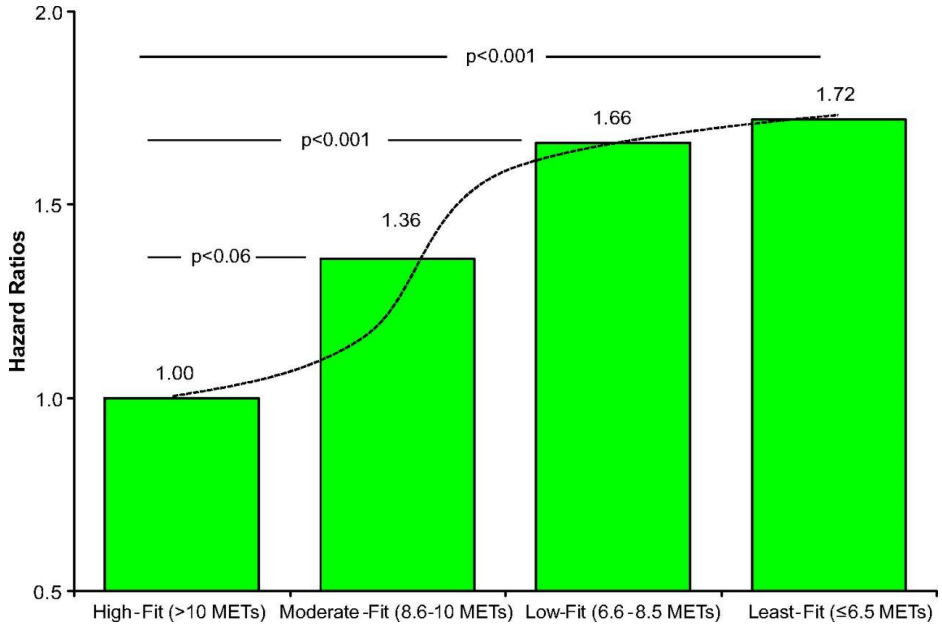


Figure 32. Risk of progression from prehypertension to hypertension group on fitness level categories (Taken from (Faselis et al. 2012)**)**

Collectively, those studies support that the age-related increases in arterial stiffness, systolic BP, and incident hypertension are not inevitable and that a physically active lifestyle or increased physical activity can lead to increased cardiorespiratory fitness, which attenuates the age-related vascular health problems.

4.1.3.2 Physical Activity and Cardiac Output

Systemic oxygen demand and cardiac output at rest are largely unaffected by exercise training (Figure 33) (Beere et al. 1999; Stratton et al. 1994). Also, bradycardia is likely secondary to the training-induced increase in stroke volume. The autonomic mechanisms underlying the decrease in heart rate at rest is a result of an increase in vagal tone and a decline in the intrinsic heart rate, while a reduction in sympathetic activity has a minimal impact (Rosenwinkel et al. 2001). The increase in heart rate following exercise onset is mediated by a combination of vagal withdrawal and β-adrenergic stimulation, and an essentially linear relationship exists between relative workload and heart rate during exercise that is independent of training status (Fu and Levine 2013, 2005). Similar to resting conditions, cardiac output at a given absolute submaximal workload is not significantly different following exercise training as oxygen demand is also unaltered (Beere et al. 1999). The unchanged cardiac output is the result of a larger stroke volume and lower heart rate (Gledhill, Cox, and Jamnik 1994).

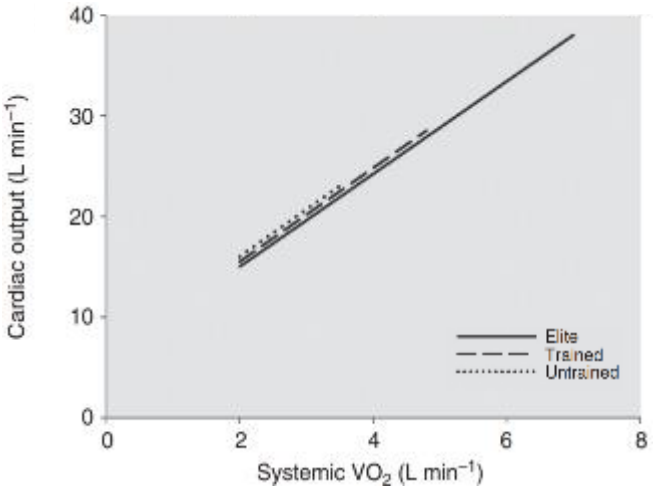


Figure 33. Cardiac output in relation to systemic $\dot{V}O_2$ in untrained and trained subjects and elite athletes (Modified from (Beere et al. 1999)

4.1.3.3 Physical Activity and Autonomic Nervous System

Recent research has indicated that exercise training remodels cardiorespiratory centers, and thereby reduces sympathetic and enhances parasympathetic (vagal) outflow (Billman and Kukielka 2007). Since the sympathetic nervous system is activated during each bout of exercise, repeated activation of this system may result in an attenuation of sympathetic activity (Fu and Levine 2013). On the other hand, exercise is protective against weight gain and visceral obesity, which may also contribute to the reduction in sympathetic activity (Joyner and Green 2009).

Moreover, exercise training decreases resting heart rate as a result of an increase in vagal tone and a decline in the intrinsic heart rate, while a reduction in sympathetic activity likely has, at most, minimal impact (Rosenwinkel et al. 2001). Trained individuals recover from an acute bout of exercise more rapidly than untrained individuals (Rosenwinkel et al. 2001).

Numerous studies have found that exercise training improves cardiac autonomic balance (increasing parasympathetic while decreasing sympathetic regulation of the heart) and increases heart rate variability (Iwasaki et al. 2003; Okazaki et al. 2005; Galbreath et al. 2011; Rennie et al. 2003). Exercise training improves baroreflex function in different populations and enhances protection against age-related reductions in baroreflex (Monahan et al. 2000; Iwasaki et al. 2003; Okazaki et al. 2005; Galbreath et al. 2011; Joyner and Green 2009). The improvement in baroreflex function with exercise training is a result of both greater blood vessel distensibility and better signal transduction in barosensitive areas of the carotid sinus and aortic arch (Tanaka

et al. 2000; Monahan et al. 2000). Also, the improvement in baroreflex function represents improved or maintained central integration in the brainstem cardiovascular centers (Joyner and Green 2009). In conclusion, exercise training related to reduce sympathetic activity and enhance parasympathetic tones, which in turn decreases resting heart rate, increases heart rate variability and improves baroreflex function.

4.1.4 Resume

- CBF was 17% higher in endurance-trained men compared with healthy but sedentary counterparts.
- Cardiac output at rest and submaximal exercise are largely unaffected by exercise training.
- A physically active lifestyle that leads to increased cardiorespiratory fitness can attenuate age-related augmentation in arterial stiffness, systolic BP, and incident of hypertension.
- Exercise training related to reduce sympathetic and enhance parasympathetic tones, which in turn decreases resting heart rate, increases heart rate variability, and improves baroreflex function.

4.2 Physical Activity on Brain Structures and Functions

4.2.1 Grey Matter

Studies compare cardiorespiratory fitness with grey matter consistently support the association between cardiorespiratory fitness and grey matter in older adults (V. J. Williams et al. 2017; Zlatar et al. 2015). Williams (2017) found a positive association between cardiorespiratory fitness and cortical thickness among older adults (V. J. Williams et al. 2017). More specifically, the association between cardiorespiratory fitness and cortical thickness appeared in the left parahippocampal, paracentral, precuneus, supramarginal cortices, right middle temporal, and lateral orbitofrontal areas (V. J. Williams et al. 2017). No difference in subcortical grey matter volumes was found between master athletes and healthy active older adult groups (Wood, Nikolov, and Shoemaker 2016). These results are suggesting that higher-order cortices may be sensitive to cardiorespiratory fitness.

On the other side, the results from studies of physical activity on the grey matter are less consistent than studies of cardiorespiratory fitness. Benedict (2014) asked the participants about their weekly physical activity, Arenaza-Urquinio (2016) used Modifiable Activity Questionnaire that assessed physical activity in the last 12 months and Wood (2016) grouped the participants based on their history of training and participation in sports events (Benedict et al. 2013; Arenaza-Urquijo et al. 2017; Wood, Nikolov, and Shoemaker 2016). All of them found that a higher score in physical activity was strongly correlated with higher grey matter volume (Arenaza-Urquijo et al. 2017; Benedict et al. 2013; Wood, Nikolov, and Shoemaker 2016). Meanwhile, several other studies have reported that physical activity is not significantly correlated with either grey matter

volume (Davis et al. 2012; Seider et al. 2016) or grey matter network (Kharabian Masouleh et al. 2018). The difference in the form used and the subjective nature of the physical activity questionnaire may influence the inconsistency on the correlation of physical activity and grey matter between studies in older adults. The positive association of physical activity on cortical grey matter volume was found when comparing a low to a high spectrum of physical activity (Benedict et al. 2013), and this association still appeared when comparing a very high level of physical activity in older adults (Wood, Nikolov, and Shoemaker 2016). Master athletes, which have a higher score in physical activity, showing a greater cortical grey matter compared to healthy active older adults, suggesting there is a possibility of the dose-response association on the relationship between physical activity and grey matter in older adults (Wood, Nikolov, and Shoemaker 2016). Also, Zlatar (2015) reported a relationship between grey matter density and age changed as a function of aerobic fitness, but not self-reported PA (Zlatar et al. 2015). These reports highlight the influence of fitness or physical activity measurement (subjective or objective measurement) since results vary depending upon the tools used.

In general, studies of cardiorespiratory fitness and physical activity on the grey matter have a positive association with the exception in some studies comparing physical activity and grey matter.

4.2.2 White Matter

Studies compare physical activity with white matter volume reported inconsistent results to support the association between physical activity and white matter volume in older adults (Davis et al. 2012; Seider et al. 2016; Benedict et al. 2013). The health risks in the characteristics of the participant in the studies need to be concerned. Unlike in the studies of Davis (2012) and Seider (2016) whose include only healthy older adults in their studies, Benedict (2014) did include participants with DM (Davis et al. 2012; Seider et al. 2016; Benedict et al. 2013). The deteriorating effect of DM to brain structure might accentuate the benefit of physical activity on white matter volume in older adults. In general, white matter studies regarding white matter hyperintensities and integrity as parameters of white matter's well-being.

4.2.2.1 White Matter Hyperintensities

White matter hyperintensities in the brain can be detected on MRI. The underlying pathology of these hyperintensities mostly reflects demyelination and axonal loss as a consequence of chronic ischemia caused by cerebral small vessel disease (microangiopathy) (Prins and Scheltens 2015). Research has shown that the presence and extent of white matter hyperintensities signals on MRI are essential for clinical outcomes, concerning cognitive and functional impairment (Debette and Markus 2010).

Studies in older adults compared cardiovascular fitness and physical activity with white matter hyperintensities gave consistent results (Vesperman et al. 2018; Tseng et al. 2013; Fleischman et al. 2015). Vesperman (2016) reported that higher cardiovascular fitness attenuates the adverse effect of age on White Matter Hyperintensities (WMH) (Vesperman et al. 2018). The results from the physical activity studies also support this relationship. Tseng (2013) reported an 83%

reduction in deep WMH volume in master athletes relative to their sedentary counterparts (Tseng et al. 2013). The utilization of actigraphy in the calculation of physical activity was added by Fleischman (2015) (Fleischman et al. 2015). In this study, Fleischman (2015) also supports that higher levels of physical activity may reduce the effect of WMH on motor function in healthy older adults (Fleischman et al. 2015). Only one study about physical activity and white matter hypointensity was reported since 2012. Wood (2016) reported no differences in white matter hypointensities between master athletes and healthy older adults (Wood, Nikolov, and Shoemaker 2016).

Studies compare cardiovascular fitness and physical activity with white matter hyperintensities supported the negative association between physical activity and white matter intensities in older adults.

4.2.2.2 White Matter Integrity

All studies in older adults compared cardiovascular fitness and physical activity with white matter integrity gave consistent results (Tseng et al. 2013; Gow et al. 2012; Burzynska et al. 2014; Oberlin et al. 2016; Johnson et al. 2012). The study in the relationship between cardiovascular fitness and white matter integrity by Oberlin (2016) reported higher VO_2max was associated with higher fractional anisotropy that suggests better white matter microstructural organization in healthy older adults (Oberlin et al. 2016). Johnson (2012) reported a positive correlation between VO_2peak and fractional anisotropy.(Johnson et al. 2012) Those studies showed that either higher VO_2max or VO_2peak had been associated with better white matter integrity in healthy older adults.

The effect of physical activity on white matter integrity reported by Tseng (2013) that masters athletes showed higher fractional anisotropy values compare to sedentary older adults (Tseng et al. 2013). Then, Gow (2012) reported that a higher level of physical activity was associated with higher fractional anisotropy (Gow et al. 2012). Last, Burzynska (2014), using an accelerometer to quantify physical activity for seven days, reported a positive association between physical activity and white matter integrity and also found that sedentary behavior was associated with lower white matter integrity in healthy low-fit older adults (Burzynska et al. 2014). All of those studies displayed a great range of physical activity of the participants, suggesting the advantage of physical activity on white matter integrity can be gained by participants with various physical activity levels from low to master athlete and not limited to just a certain level of physical activity.

Overall, cross-sectional studies of the relationship between physical activity on white matter volume have consistent results. Cardiovascular fitness or physical activity showed a promising effect on brain structure health, primarily to prevent or reduce white matter hyperintensities and maintain white matter integrity. The only inconsistent result is the relationship between physical activity and white matter volume. Again, as discussed in the grey matter section, the subjective nature of the self-reported physical activity questionnaire maybe varies the results. Other than that, the characteristics of participants need to be concerned as this also may vary the relationship between physical activity and white matter volume.

4.2.3 Resume

Grey matter

- In general, better CRF and higher PA associated with cortical but not subcortical thickness in older adults.
- The overlap of brain areas in which grey matter volume significantly associated with cardiorespiratory fitness and physical activity were left parahippocampal, precuneus, and right middle temporal area.

White matter

- Physical activity is negatively associated with white matter hyperintensities or hypointensities in older adults.
- The relationship between physical activity and white matter volume showed inconsistent results.

4.3 Physical Activity and Executive Function

Studies have been reported exercise-related benefits in brain structure and mechanical function, particularly in older adults (Stan J Colcombe et al., n.d.; Stanley J. Colcombe et al. 2006; Weinstein et al. 2012; Chaddock-Heyman et al. 2014). Aerobic fitness is associated with the efficacy of the overall cognitive performance in older adulthood (Brown et al. 2010; Netz et al. 2011). Specifically, studies have also reported association between aerobic fitness or exercise and older adults' performance on standard clinical tests of executive functioning, such as the Trails B test, the Digit Symbol test, the Wisconsin card sorting task, the REY Auditory Verbal Learning Test(Kramer et al. 2001), and the verbal fluency test (D. E. Barnes et al. 2003; Blumenthal et al. 1991; Gordon et al. 2008; Albinet et al. 2010; Kramer et al. 2001). Not only in older adults, but executive functions in children and early adulthood have also been positively linked to both acute and chronic engagement in physical activity (Tomporowski, Lambourne, and Okumura 2011; Castelli et al. 2007; Best 2011). Together, these data support the idea that regular exercise can aid performance concerning the broad construct of executive functioning. Below, the evidence from exercise–cognition research using simple cognitive tests to determine which components of executive functioning benefit from regular exercise are discussed. Therefore, in this part, the evidence from exercise–cognition research about the benefit of physical activity on three components of executive functioning (working memory, selective attention and inhibitory control, and cognitive flexibility) are discussed.

4.3.1 Working Memory

As discussed in the first section, working memory is defined as the capability to hold information in mind and to manipulate or to mentally work with it (Baddeley 1998; Smith and Jonidesl 1999). A popular working memory task in the exercise–cognition studies is the two-back task, in which

participants are asked to respond whenever the currently displayed stimulus matches the stimulus that appeared two stimuli back in a sequential presentation (Cohen et al. 1994; Guiney and Machado 2013). In older adults, cross-sectional research has reported that physical fitness is a significant predictor of accuracy on the two-back task (Voelcker-Rehage, Godde, and Staudinger 2010). In relatively young adults, exercise studies have shown that aerobic exercise programs can increase two-back accuracy and reduce reaction times (Hansen et al. 2004; Stroth et al. 2010). These findings suggest that both aerobic fitness and regular engagement in aerobic exercise are beneficial for two-back task performance.

Other tasks that have been used to assess the effects of physical activity on working memory are digit span and Sternberg tasks. A cross-sectional study showed that higher levels of physical activity in older women are associated with longer backward digit spans (Weuve et al. 2004). Furthermore, a 12-month intervention study involving 187 older women revealed that aerobic exercise could increase older adults' forward digit spans performance (P. Williams and Lord 1997). The modified Sternberg tasks, which depend more on memory capacity, have a relatively lower load of updating compared to two-back or digit span tasks. A cross-sectional fitness study in 64 young adults found no differences in Sternberg tasks performance between the high and low fitness groups (Kamijo et al. 2010). Overall, the results from the working memory tasks suggest that physical activity and physical fitness level can give benefits to the working memory performance in children and older adults, even type and load of the task need to be considered.

Selective Attention and Inhibitory Control

The most common test for selective attention and inhibitory control is the Stroop task. Performance during a Stroop task condition is considered an effective measure of executive functioning because participants have to respond to the color of the ink and inhibit the more dominant internal drift from reading the word (Miyake et al. 2000). A cross-sectional study involving older adults performing a Stroop task indicated that higher aerobic fitness was associated with smaller amounts of interference, greater accuracy, and greater task-relevant activation in the prefrontal cortex (Ruchika Shaurya Prakash, Michelle W. Voss, Kirk I. Erickson 2011). Importantly, findings from two randomized controlled trials in older adults investigating the effects of aerobic exercise on Stroop task performance support these results (Dustman et al. 1984; Smiley-Oyen et al. 2008). Several studies investigating the benefits of physical activity on inhibitory control have employed variations of the Eriksen flanker task (Eriksen and Eriksen 1974). Although flanker and Stroop tasks tap similar cognitive functions, the main difference is that in flanker tasks, the distracting information appears in the periphery, compared to the same location in the Stroop task. A cross-sectional study using a large sample size of older adults and measuring aerobic fitness produced evidence that in older adults, higher fitness predicts faster reaction time in flanker task (Voelcker-Rehage, Godde, and Staudinger 2010). Finally, a six-month intervention study in older adults revealed significantly greater reductions in the size of the flanker effect for the aerobic group, as compared with stretch and flexibility control group (Kramer et al. 2001).

Studies in children utilizing Stroop tasks have shown less promising results (Buck, Hillman, and Castelli 2008; Castelli et al. 2011). Otherwise, Buck et al. (2009) proposed that, in contrast to older adults, inhibition control in children and young adults may not be specially benefited by increased physical activity or fitness (Buck, Hillman, and Castelli 2008).

In conclusion, studies of inhibition control in older adults reported that physical activity and aerobic fitness are good predictors of selective attention and inhibition control performance (S. J. Colcombe et al. 2004). In contrast, current research in children and young adults offers only limited evidence for exercise-related benefits in selective attention and inhibitory control (J. R. Themanson, Pontifex, and Hillman 2008; Voss et al. 2011; Hillman et al. 2009; Jason R. Themanson, Hillman, and Curtin 2006). Intervention studies are needed in children and young adult populations to determine the association between physical activity and inhibition control in this population.

4.3.2 Cognitive Flexibility

The cognitive flexibility or task-switching paradigm underlies the ability to switch flexibly back and forth between tasks, operations, or mental sets (Miyake et al. 2000). Such mental-set-switch requires executive control, including working memory, inhibition, and mental flexibility. Therefore, smaller switching costs can be interpreted as more efficient executive functioning (Banich et al. 2009; Monsell 2003). On the contrary, larger switching costs have been reported in populations with impaired executive function, including older adults (Cepeda, Kramer, and Gonzalez de Sather 2001).

A large randomized controlled trial on which sedentary older adults engaged in either aerobic exercise (brisk walking) or strength and flexibility exercise for six months indicated that, at the end of the intervention, aerobic group showed a significantly greater reduction in the switching cost, as compared with those in the strength and flexibility group (Hawkins, Kramer, and Capaldi 1992; Kramer et al. 2001). Regarding children and young adults, the effect of physical activity on cognitive flexibility has been reported with inconsistent results (Guiney and Machado 2013; Kray, Karbach, and Blaye 2012; Kray and Lindenberger 2000; Kamijo and Takeda 2009).

In conclusion, it appears that older adults can get some benefits on cognitive flexibility performance from physical activity. However, it is not clear that young adults and children can gain such benefits given the lack of improvement in switching costs seen throughout childhood (Kray, Karbach, and Blaye 2012; Scisco, Leynes, and Kang 2008).

4.3.3 Resume

- Regular physical activity has been reported improved performance of executive functioning.
- In working memory, Aerobic fitness and regular engagement in aerobic exercise are beneficial for the updating component of working memory in young and older adults.
- In inhibition and flexibility, physical activity and exercise give benefit to selective inhibitory control processes in older adults but show inconclusive results in children and young adults.

4.4 Summary of Section

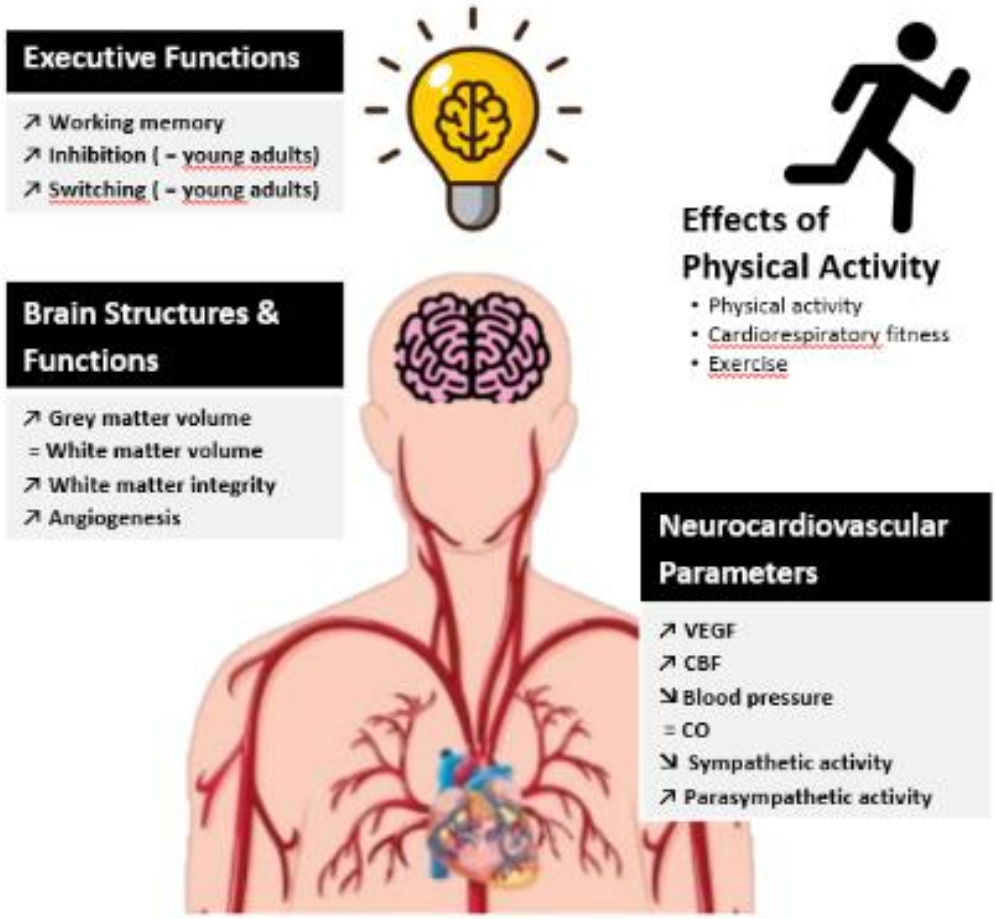


Figure 34. Summary of effects of physical activity on neuro-cardiovascular parameters, brain structures and functions, and executive functions. Abbreviation: CBF, cerebral blood flow; CO, cardiac output; VEGF, vascular endothelial growth factors.

5 Summary of the Literature Review

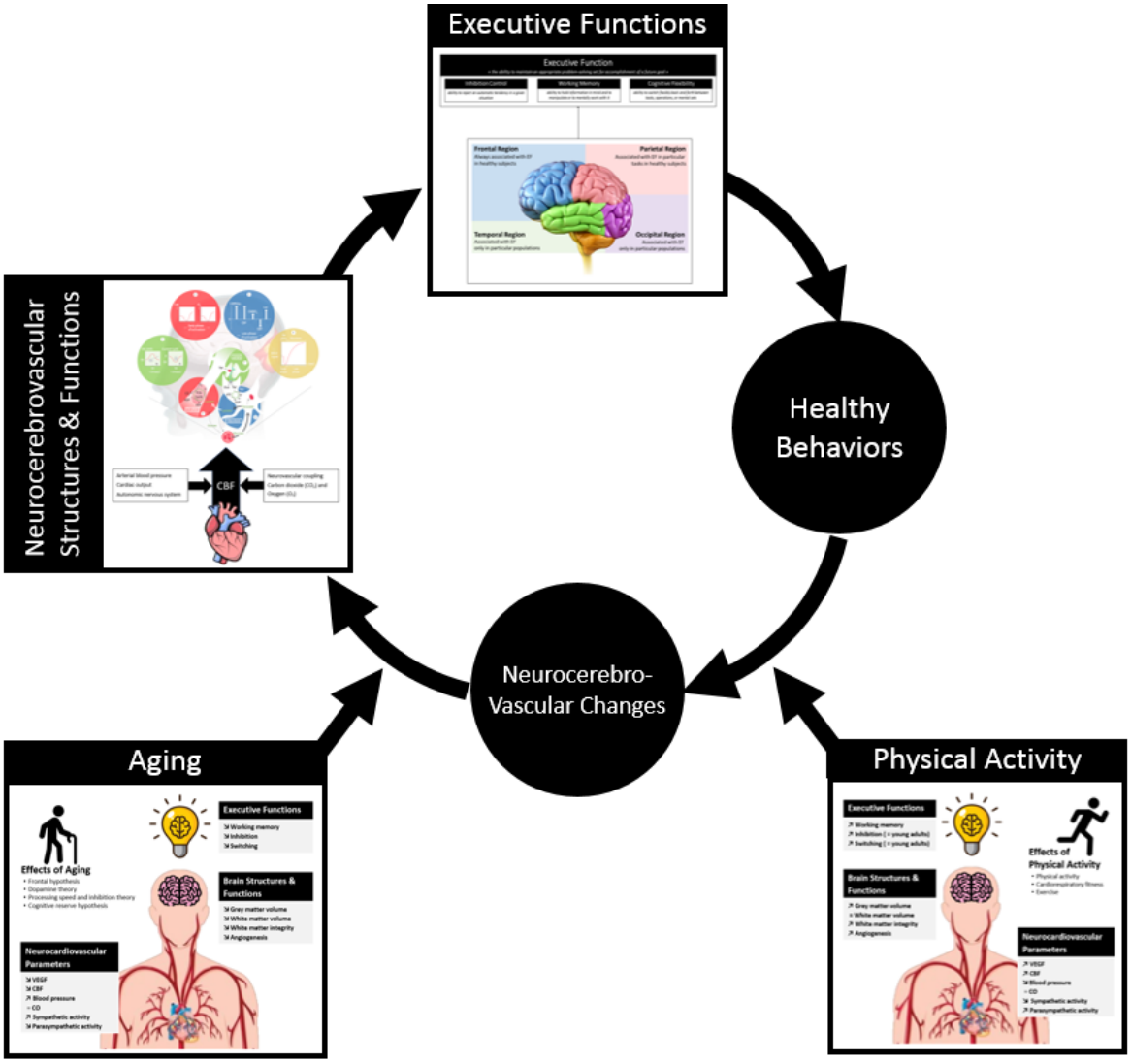


Figure 35. Integrated-algorithm of physical activity and aging effects on neuro-cardiovascular parameters, brain structures and functions, and executive functions. Abbreviation: CBF, cerebral blood flow; CO, cardiac output; VEGF, vascular endothelial growth factor.

OBJECTIVE, MATERIALS, AND METHODS

All of the information mentioned in the literature review allowed us to understand the executive functions and how it been processed in the brain, also to identify the influence of age and physical activity on the brain, specifically on executive functions. However, this interaction needs to be studied in a comprehensive study to clarify the interaction of the vascular-neural-cognition axis in controlled subjects, materials, and methods. Through this thesis, we hope to provide in-depth observation about the relationship between aging and physical activity on executive function in healthy males.

This thesis will be presented with the format of "thesis by articles". After objectives and hypotheses, we will describe methods that were used in this thesis. Each study will be presented as a summary with a copy of the accepted article or manuscript of the results.

6 Objective and Hypotheses

6.1 Objective

This thesis has several objectives. First, to understand the effect of age and physical activity on cerebral oxygenation and executive function in males. Secondly, to identify the influence of age on the interaction between vascular health and executive function. To obtain those objectives, five studies were conducted.

6.1.1 Studies of the Association between Physical Activity, Cerebral Oxygenation, and Executive Function in Young Males (Study 1 and 2)

1. To investigate the association between physical activity, cerebral oxygenation, and inhibition control-and-cognitive flexibility. This study is a cross-sectional study.
2. To investigate the association between cardiorespiratory fitness, cerebral oxygenation, and dual-task paradigms. This study is a cross-sectional study.

6.1.2 Studies of the Association between Physical Activity, Cerebral Oxygenation, and Executive Function in Older Males (Study 3 and 4)

3. To review the effect of physical activity on brain structure, brain function, and executive function performance in older adults. This study is a literature review study.
4. To investigate the association between cardiorespiratory fitness, cerebral oxygenation, and inhibition control-and-cognitive flexibility. This study is a cross-sectional study.

6.1.3 Studies of the Influence of Vascular Health on the Interaction between Age, Physical Activity, and Executive Function (Study 5)

5. To observe the association between vascular parameters and executive performances. This study is a cross-sectional study.

Scheme of the studies is illustrated in Figure 36 as follows:

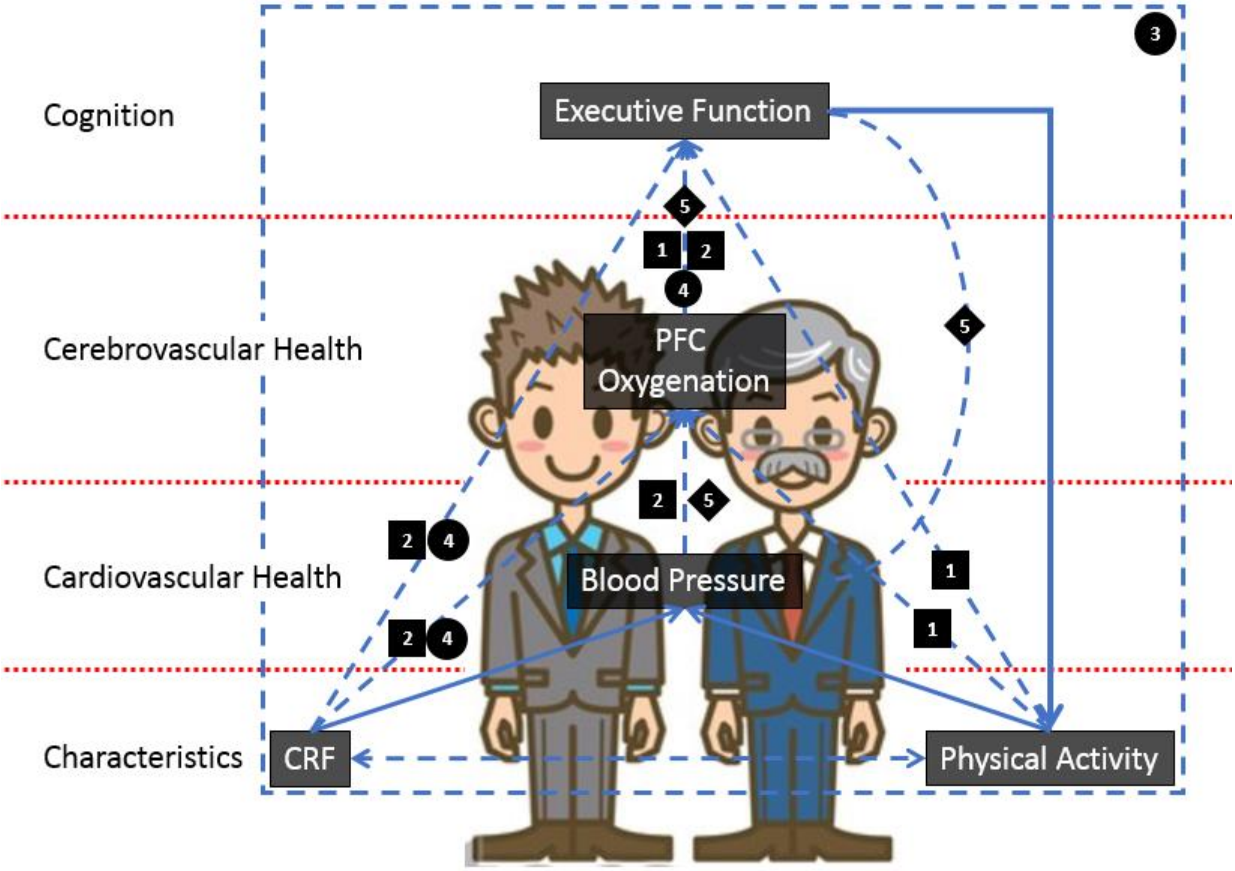


Figure 36. Schematic illustration of relations of each study to research topics. Abbreviation: CRF, cardiorespiratory fitness; PFC, prefrontal cortex; ■, study in young males; •, study in older males; ♦, study in both young and older males; ——, established relation from previous studies; – – –, observed relation in this thesis.

6.2 Hypotheses

1. Higher physical activity levels associated with better executive function in young males.
2. Higher cardiorespiratory fitness levels gave greater benefit in the dual-task condition compared to the single-task condition in young males.
3. Benefits of physical activity to the brain structures, brain functions, and executive function performances in older adults could be explained by change in cerebrovascular dynamics.
4. Higher cardiorespiratory fitness levels associated with better inhibition control and cognitive flexibility in older males.

5. Vascular parameters are related to executive function, and the age influences the association between vascular parameters and executive function.

7 Materials and Methods

7.1 Materials and Methods for Experimental studies

7.1.1 Participants

For all the studies in the thesis, 87 males were recruited to be participated in the experimentations. The characteristics of the participants in each study were presented in Table 8.

Table 8. Characteristics of participants in the experimental studies

Study	Number (person)	Age (years)	Height (cm)	Weight (kg)	Group	Cardiorespiratory fitness level
Study 1	56	22.6 ± 2.3	178.5 ± 5.3	78.2 ± 18.7	Young males	Mixed
Study 2	24	23.8 ± 4.8	175.5 ± 6.5	74.1 ± 13.6	Young males	Mixed
Study 4	24	62.0 ± 6.4	175.4 ± 6.2	80.9 ± 12.4	Older males	Mixed
Study 5	29	23.4 ± 4.4	175.1 ± 6.3	73.9 ± 13.2	Young males	Mixed
	24	61.5 ± 5.7	173.8 ± 6.2	81.6 ± 12.4	Older males	Mixed

(Age, height, and weight presented in $M \pm SD$)

7.1.2 General Protocols

7.1.2.1 Study 1:

Young male participants need to complete a 35-minute visit to the laboratory. The details of the visit are described as follows:

The protocol started with giving a written informed consent form to the participants. After written informed consents were obtained, anthropometric data were taken to acquire the characteristics of the participants. Subsequently, physical activity assessments were measured using the French version of the Global Physical Activity Questionnaire (GPAQ). Last, the cognitive assessments were obtained with the computerized modified Stroop task in several conditions (naming, inhibition, and flexibility) while assessing for the change of HbO_2 and HHb in PFC with the fNIRS system. Illustration of the study design in Study 1 and Study 4 is shown in Figure 38.

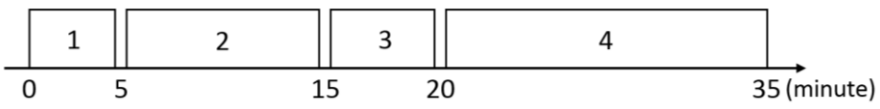


Figure 37. Study design for Study 1.
Abbreviation: 1, informed consent; 2, anthropometry measurement; 3, physical activity assessment; 4, cognitive assessment**.**

7.1.2.2 Study 2:

Young male participants need to complete two visits to the laboratory. The first day was assigned to cognitive and blood pressure assessments, while the second day was dedicated to the cardiorespiratory fitness assessment. The details of the visit are described as follows:

First-day visit

The protocol started with giving a written informed consent form to the participants. After written informed consent was obtained, a cognitive screening test was taken using the Montreal Cognitive Assessment (MoCA). Probe placement was performed to prepare for cerebral oxygenation measurements that are taken during the cognitive assessment. The cognitive assessment was performed using the 2-back task in two different conditions: single-task and dual-task to test the effect of the complexity of the task. At the end of the first-day visit, 24-h blood pressure measurement using an ambulatory blood pressure monitoring (ABPM) was started until the next day.

Second-day visit

The participants returned the ABPM from the previous visit. Afterward, they were asked to prepare for the cardiovascular test and were explained about the protocol of the cardiovascular test. The cardiovascular test was performed using the modified Balke walking protocol on a motorized treadmill to measure peak oxygen consumption ($\dot{V}O_2$peak). Illustration of the study design in Study 2 is shown in Figure 39.

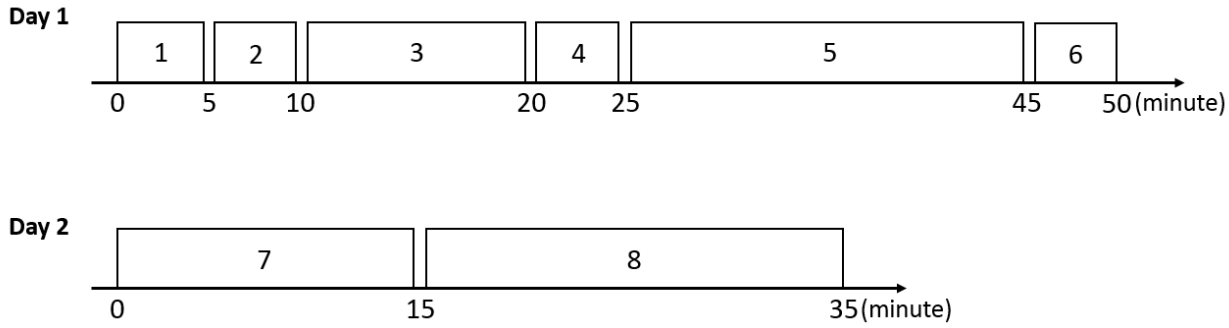


Figure 38. Study design for Study 2 and Study 5.
Abbreviation: 1, informed consent; 2, cognitive screening test; 3, anthropometry measurement; 4, probe placement; 5, cognitive assessment; 6, the start of 24-h blood pressure measurement; 7, preparation for the cardiorespiratory test; 8, cardiorespiratory test**.**

7.1.2.3 Study 4:

Older male participants need to complete two visits to the laboratory. The first day was assigned to cognitive assessments, while the second day was dedicated to the cardiorespiratory fitness assessment. The detail of the visits are described as follows:

First-day visit

The protocol started with giving a written informed consent form to the participants. After written informed consent was obtained, a depression screening test was taken using the Beck's

Depression Inventory (BDI). Subsequently, a cognitive screening test was assessed with the Montreal Cognitive Assessment (MoCA). After that, anthropometric data were taken to acquire the characteristics of the participants. Last, the cognitive assessments were obtained with the computerized modified Stroop task in several conditions (naming, inhibition, and flexibility).

Second-day visit

The participants were asked to fill the physical activity form using the French version of the Global Physical Activity Questionnaire (GPAQ). The next 15 minutes were dedicated to prepare for the cardiovascular test and to explain about the protocol of the cardiovascular test. The cardiovascular test was performed using the modified Balke walking protocol on a motorized treadmill to measure peak oxygen consumption ($\dot{V}O_2peak$). Illustration of the study design in Study 4 is shown in Figure 41.

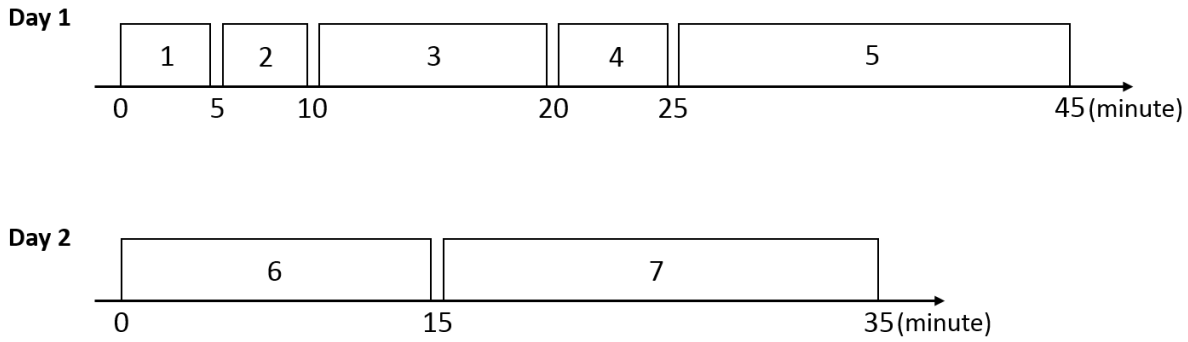


Figure 39. Study design for Study 4
Abbreviation: 1, informed consent; 2, depression screening test; 3, cognitive screening test; 4, anthropometry measurement; 5, cognitive assessment; 6, preparation for the cardiorespiratory test; 7, cardiorespiratory test**.**

7.1.2.4 Study 5:

Young male and older male participants need to complete two visits to the laboratory. The first day was assigned to cognitive and blood pressure assessments, while the second day was dedicated to the vascular and baroreflex sensitivity assessment. The detail of the visits are described as follows:

First-day visit

The protocol started with giving a written informed consent form to the participants. After written informed consent was obtained, a depression screening test was taken using the Beck's Depression Inventory (BDI). Subsequently, a cognitive screening test was assessed with the Montreal Cognitive Assessment (MoCA). Then, anthropometric data were taken to acquire the characteristics of the participants. After that, the cognitive assessments were obtained with the computerized modified Stroop task in several conditions (naming, inhibition, and flexibility). At the end of the first-day visit, 24-h blood pressure measurement using an ambulatory blood pressure monitoring (ABPM) was started until the next day.

Second-day visit

The participants were asked to fill the physical activity form using the French version of the Global Physical Activity Questionnaire (GPAQ). The next part is dedicated to the vascular assessment, started with central pressure and arterial stiffness measurement with a pressure transducer (tonometer), and finished with a continuous non-invasive blood pressure monitoring to measure baroreflex sensitivity. Illustration of the study design in Study 5 is shown in Figure 42.

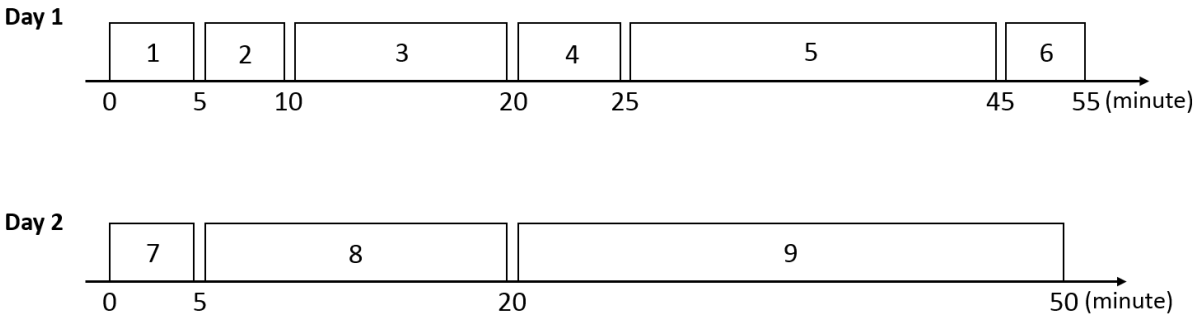


Figure 40. Study design for Study 5
Abbreviation: 1, informed consent; 2, depression screening test; 3, cognitive screening test; 4, anthropometry measurement; 5, cognitive assessment; 6, the start of 24-h blood pressure measurement; 7, physical activity assessment; 8, central pressure and arterial pressure measurement; 9, baroreflex sensitivity measurement**.**

7.1.3 Physical Activity Measurement

- Global Physical Activity Questionnaire (GPAQ)

Physical activity was assessed using the French version of the Global Physical Activity Questionnaire (GPAQ). The French version of the GPAQ gives acceptable reliability and validity for the measurement of PA and sedentary time in adults (Rivière et al. 2018). The French version of the GPAQ was shown in Figure 43. The GPAQ was developed by the WHO for PA surveillance. It collects information on PA participation in three settings – PA at work, recreational activities, and travel to and from places as well as sedentary behavior. The questionnaire consists of 16 questions covering both vigorous and moderate-intensity PA.

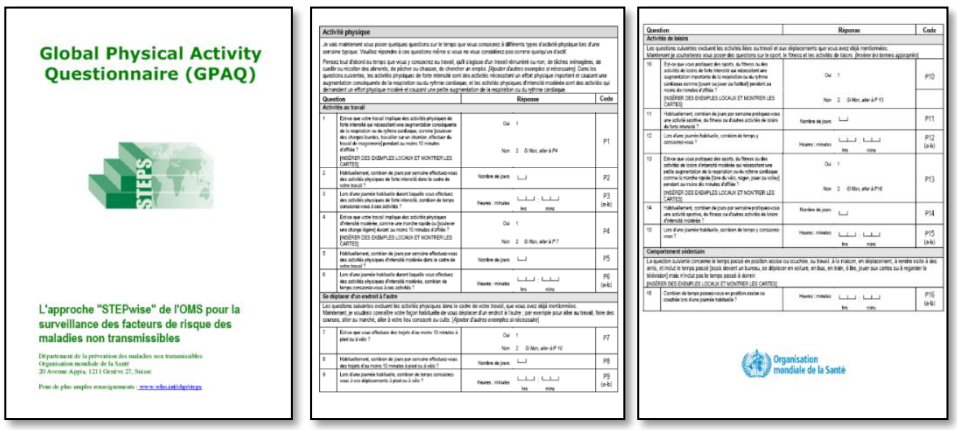


Figure 41. The French version of the Global Physical Activity Questionnaire (GPAQ) (Taken from (WHO 2012)**)**

7.1.4 Physiological Measurement

- Anthropometry measurements

The anthropometry of the participants will be measured by a Leicester portable height measurer (shown in Figure 44) and a bioelectrical impedance analysis device Tanita® BC-418 (Tanita, Japan; shown in Figure 45) and to estimate height, weight, body mass index (BMI), and percentage of fat. To ensure accuracy, participants will be informed to wear light clothing and well-hydrated. Participants are always asked to remove his shoes and socks or stockings and be sure the soles of their feet are clean before stepping on the measuring platform. Heels of the participants must be correctly aligned with the electrodes on the measuring platform. The readings of the measurements will be attempted at the considered same time of the day. The grips must be grasped with both hands and placed on the side of the body.

Figure 42. Image of Leicester Height Measure (Taken from (Homecare Medical Supplies 2018)**)**

Figure 43. Image of Tanita® BC-418 (Taken from (Tanita 2019)**)**

- Central arterial pressure waveform analysis

The assessment of the central blood pressure is measured by a non-invasive diagnostic tool by placing a pressure transducer (tonometer) over the radial artery and recording 11 seconds of quality radial waveforms by SphygmoCor® system (AtCor Medical, Australia; shown in Figure 46). Before the measurement, the participant was lying down on a bed in a comfortable room for around 15 minutes. Measurements are performed by recording pressure waveforms at the carotid artery followed by the femoral artery, with an ECG signal recorded simultaneously. Any pulse wave measurements not considered of sufficient quality, based on the following quality control criteria, will be repeated. The SphygmoCor software regularly calibrated by enters the mean arterial pressure (MAP) and diastolic blood pressure (DBP) values from a calibrated sphygmomanometer.

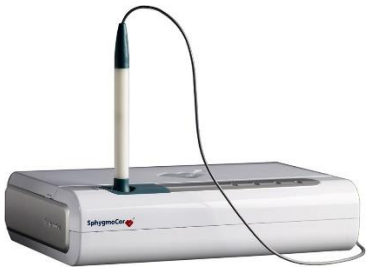


Figure 44. Image of the SphygmoCor® system (Taken from (MDS Cardio 2019)**)**

- 24-hour blood pressure monitoring (ABPM)

  Blood pressure parameters were measured for 24 hours with an ambulatory blood pressure monitor Mobil-O-Graph (I.E.M GmbH, Stolberg, Germany; shown in Figure 47). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP; MAP = 1/3 SBP + 2/3 DBP) were measured every 20 minutes during a 24-h period and were divided into daytime (8 am to 10 pm) and night-time (from 10 pm to 8 am) periods. The participant must bring the ABPM that he wears on his next visit to the MOVE laboratory.

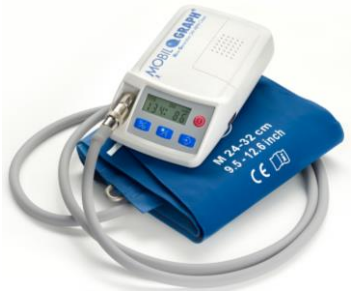


Figure 45. Image of Mobil-O-Graph 24-hour Ambulatory Blood Pressure Monitor (AMBP) (Taken from (Techmed 2019)**)**

- Continuous non-invasive blood pressure monitoring (FINAPRES)

  The continuous blood pressure monitoring was performed to obtain baroreflex sensitivity data. It measured by s a non-invasive continuous blood pressure monitor Finapres® NOVA system (Finapres Medical System, Netherlands; shown in Figure 48). Arterial blood pressure recorded uses Finapres Medical Systems Finometer MIDI hardware and Beatscope software. Non-invasive continuous arterial blood pressure and heart rate will be measured beat-to-beat using the Finapres finger cuff on the middle finger and a height correction system.

Figure 46. Image of Finapres® NOVA (Taken from (FMS 2019)**)**

- Maximal continuous graded exercise test

This test was performed on a motorized treadmill Valiant 2 sport (Lode B.V., Groningen, Netherlands; shown in Figure 49). Modified Balke walking protocol was used to measure peak oxygen consumption ($\dot{V}O_2$peak). The walking protocol was chosen because it does not require running and has a slow increase in workload. This test is well suited to evaluate aerobic fitness in heterogeneous populations that vary in terms of fitness level, age, adiposity, or health status in general (G. F. Fletcher et al. 2013). The velocity was set at 5.6 km/h throughout the test, with an initial 0% grade. The inclination was increased by 6% after the first minute, and then by 2% every minute until voluntary exhaustion. The protocol of the Modified Balke walking test is displayed in Figure 50. Verbal encouragement was given every minute throughout the test (Andreacci et al. 2010)

Figure 47. Image of motorized treadmill Valiant 2 sport (**Taken from** [Lode for Life 2019])

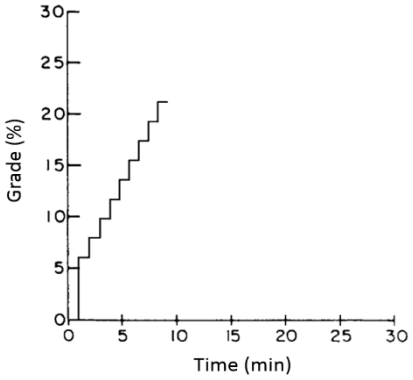


Figure 48. Illustration of the Modified Balke walking protocol (Taken from (Marinov, Kostianev, and Turnovska 2003)**)**

- Cerebral oxygenation

The concentration changes of HbO_2 (ΔHbO_2) and HHb (ΔHHb) were measured with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands; shown in Figure 51). This system utilizes near-infrared lights, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in the cortical layer. The lights were transmitted with two different wavelengths, 760 and 850 nm. A probe of PortaLite has three transmitters and one

receiver, with transmitter-receiver distances of 30, 35, and 40 mm. Two probes were placed on the forehead of the participants, at a height corresponding to 10 % of the nasion-inion distance from nasion, and the middle of the device was placed at 5 % of the head circumference to the left and right from midline, corresponding to the Fp1 and Fp2 according to the international EEG 10–20 system. These locations roughly target left and right Brodmann's areas 9 and 10, which represent the dorsolateral and anterior PFC. Probes were shielded from ambient light with a black cloth fixed by an elastic strap. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection.

Figure 49. Image of PortaLite fNIRS system (Taken from (Cortech 2019)**)**

- Walking performance

Temporal and spatial parameters of motor performances of walking were studied using an instrumented walkway GAITRite® system (CIR Systems Inc, Clifton, NJ, USA; shown in Figure 52). This system consists of a 4.6 m electronic walkway with sensors arranged in a grid-like pattern to identify footsteps contacts.

Figure 50. Image of the GAITRite® system (Taken from (EMS 2019)**)**

7.1.5 Psycho-Cognitive Measurement

The Cognitive tests were given in randomized order, and since some study stated that depression affects cognitive performances, Beck's Depression Impression (BDI) was given before the cognitive tests to measure the depression score of the participant. Cerebral oxygenation was measured using the NIRS system during cognitive tests.

- Beck's Depression Impression (BDI)

The level of depression was measured by the Beck Depression Inventory (BDI), a 21-question multiple-choice self-report inventory, one of the most widely used psychometric tests for measuring the severity of depression. The BDI is designed for individuals aged 13 and over and is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The form of BDI is displayed in Figure 53.

Echelle de Beck (BDI : Beck Depression Inventory)

A
0 Je ne me sens pas triste
1 Je me sens cafardeux ou triste
2 Je me sens tout le temps cafardeux ou triste et je n'arrive pas à en sortir
3 Je suis si triste et si malheureux que je ne peux pas le supporter

B
0 Je ne suis pas particulièrement découragé ni pessimiste au sujet de l'avenir
1 J'ai un sentiment de découragement au sujet de l'avenir
2 Pour mon avenir, je n'ai aucun motif d'espérer
3 Je sens qu'il n'y a aucun espoir pour mon avenir et que la situation ne peut s'améliorer

C
0 Je n'ai aucun sentiment d'échec de ma vie
1 J'ai l'impression que j'ai échoué dans ma vie plus que la plupart des gens
2 Quand je regarde ma vie passée, tout ce que j'y découvre n'est qu'échecs
3 J'ai un sentiment d'échec complet dans toute ma vie personnelle (dans mes relations avec mes parents, mon mari, ma femme, mes enfants)

D
0 Je ne me sens pas particulièrement insatisfait
1 Je ne sais pas profiter agréablement des circonstances
2 Je ne tire plus aucune satisfaction de quoi que ce soit
3 Je suis mécontent de tout

E
0 Je ne me sens pas coupable
1 Je me sens mauvais ou indigne une bonne partie du temps
2 Je me sens coupable
3 Je me juge très mauvais et j'ai l'impression que je ne vaux rien

F
0 Je ne suis pas déçu par moi-même
1 Je suis déçu par moi-même
2 Je me dégoûte moi-même
3 Je me hais

G
0 Je ne pense pas à me faire du mal
1 Je pense que la mort me libérerait
2 J'ai des plans précis pour me suicider
3 Si je le pouvais, je me tuerais

Figure 51. Image of the form of the French version of Beck's Depression Impression (BDI) (Taken with modification from (Isab61 2014)**)**

Montreal Cognitive Assessment (MoCA)

The final version of the MoCA (available at www.mocatest.org) is a one-page 30-point test administered in 10 minutes. Details on the specific MoCA items are as follows. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).

Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points). The form of MoCA is displayed in Figure 54.

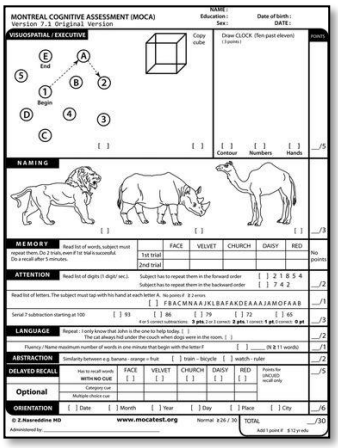


Figure 52. Image of the form of the French version of Montreal Cognitive Assessment (MoCA) (taken from ("Montreal Cognitive Assessment (MoCA) Test French Version" 2005)**)**

- Trail Making Test parts A and B

Trail Making Test (TMT) is a measure of attention, speed, and mental flexibility. It requires the participant to connect by making pencil lines, 25 encircled numbers and letters in alternating order. A time limit of 5 minutes (300 seconds) added to reduce testing time and participant frustration. Participants who cannot complete the TMT within 5 minutes are assigned a time of 300 or 301 seconds. The form of TMT part B is displayed in Figure 55.

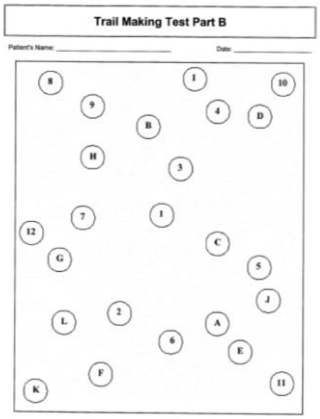


Figure 53. Image of form Trail Making Test B (TMT B) (Taken from (Hoffer 2016)**)**

- Stroop Tests

The Computerized Modified Stroop task used in this study is based on the Modified Stroop Color Test (Bohnen et al., 1992) and included three experimental conditions: naming, inhibiting, and switching/flexibility (Shown in Figure 56). Participants provided their responses with two fingers (index and major finger) from each of their hands on an AZERTY

keyboard. In the Naming block, participants were presented with a visual stimulus of the name of colors (RED/BLUE/GREEN/YELLOW) in French presented in congruent color with the word, and participants were asked to identify the color of the ink with a button press. In the Inhibition block, each stimulus consisted of a color-word (RED/BLUE/GREEN/YELLOW) printed in the incongruent ink color (i.e., the word RED was presented in blue ink). Participants were asked to identify the color of the ink (i.e., blue). In the Switching block, in 25% of the trials, a square in place of the fixation cross appeared before the word. When this occurred, participants were instructed to read the word instead of identifying the color of the ink (i.e., RED). As such, within the Switching block, there were both inhibition trials in which the participant had to inhibit their reading of the word and correctly identify the color of the ink, and there were switch trials in which the participant had to switch their response mode to read the word instead of identifying the color of the ink when a square appeared before the word presented. Visual feedback on performance was presented after each trial. A practice session was completed before the acquisition run to ensure the participants understood the task. The practice consisted of a shorter version of the task. Dependent variables were reaction times (ms) and the number of errors committed (%). This task and procedure have been used successfully in previous studies (Dupuy et al. 2010, Dupuy et al. 2015).

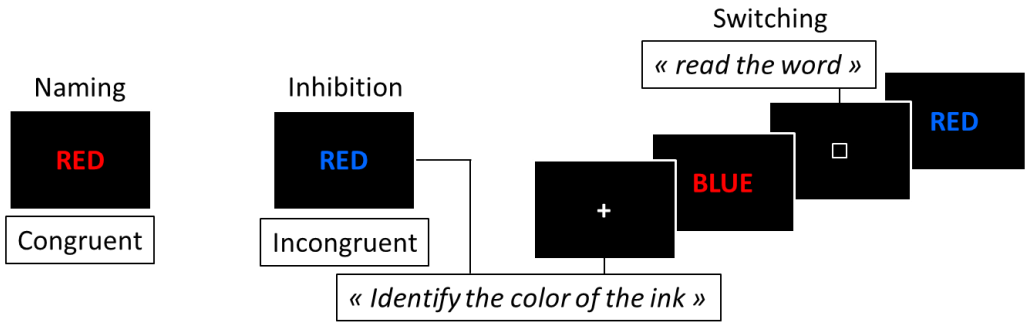
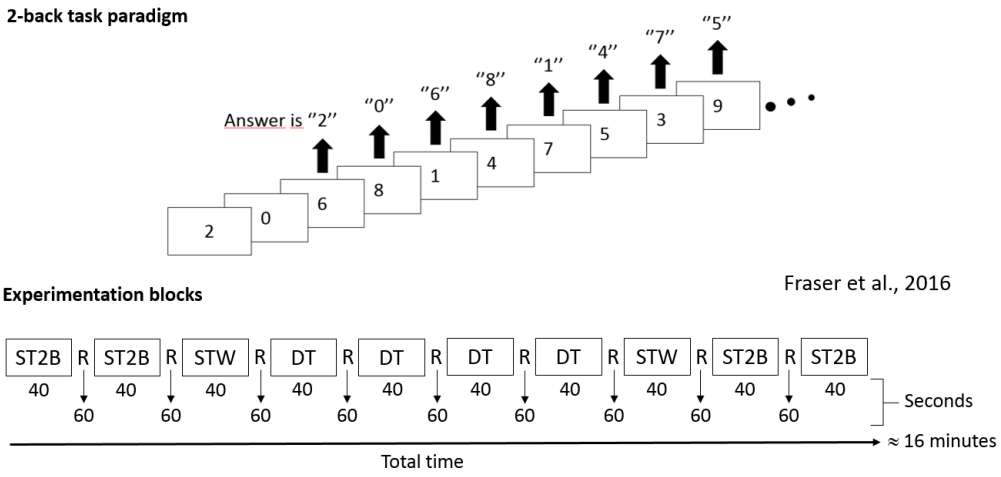


Figure 54. Paradigms of Stroop task in naming, inhibition, and switching (flexibility) conditions

- 2-back Tests

The participant will be instructed to respond to auditory stimuli. The participant will be asked to give the same emphasis on both tasks. In the beginning, the participant will be given time to practice and getting used to the test. The headphones Sennheiser® RS-165 (Sennheiser, Germany) will be applied, and a series of numbers will be played through them in the regular rhythm. The participant must repeat, with a clear voice, the number that he heard two numbers before the number he is listening in the headphones. The visual explanation and examples will be given if the participant has difficulties to understand the verbal instructions of the task. The practice will be repeated three times (to maximum 15 times) or until he feels ready to start the real test. The emphasis scale form will be given at the end of the tests for evaluation.



R = Rest; ST2B = single task 2-back, STW = single task walking; DT = dual task

Figure 55. Paradigm and protocol of 2-back task

STUDIES OF THE THESIS

1 Study 1

1.1 Resume

Prefrontal Oxygenation Reserve: The Relationship between Physical Activity Level and the Cognitive Load during a Stroop Task in Healthy Young Males

Description of Study 1

Many studies have reported that regular physical activity was associated with cognitive performance and more selectively with executive functions. However, a large bulk of the knowledge concerning the effects of physical activity level on executive performance in younger adults remains unclear. Among many physiological mechanisms that may influence executive function, prefrontal (PFC) oxygenation seems to play a major role. The immediate energy needs of activated neurons are met by oxidation of lactate present in the extracellular space, resulting in a transient decrease in lactate levels and oxygen concentrations in PFC (Pellerin and Magistretti 1994).

Although the studies in the fNIRS field is growing exponentially (Yucel et al. 2017; Herold et al. 2018; Leff et al. 2011), most of the studies that address the relationship between PA and the prevention of cognitive impairment measured in older adults (Erickson, Hillman, and Kramer 2015; Prakash et al. 2015). Little is known about the relationship between the participation in regular PA and cerebral oxygenation, more specifically prefrontal cortex (PFC) during cognitive processing in young adults, probably because the cerebrovascular reserve is not considered as a limiting factor in this period of life (Lu et al. 2011). Steadily decreased physical activity in the last several decades, suggest that the research effort on the link between PA and executive performance should not be limited to the elderly, but be concerned with all ages of life.

The current study aimed to assess whether physical activity level is associated with executive function and prefrontal oxygenation in healthy young males. Fifty-six healthy young males (22.1±2.4yrs) were classified as active (n=26) or inactive (n=30) according to the recommendations made by the WHO and using the Global Physical Activity Questionnaire (GPAQ). Bilateral PFC oxygenation was assessed using functional near infra-red spectroscopy (fNIRS) during a computerized Stroop task (which included naming, inhibition, and switching conditions). Accuracy (% of correct responses) and reaction times (ms) were used as indicators of cognitive performances. Two-way ANOVA (Physical activity level x Stroop conditions) was performed to test the null hypothesis of an absence of interaction between physical activity level and executive performance and prefrontal oxygenation.

The main results from this study are:

- The interaction between physical activity level and Stroop conditions on reaction time was found (p = .04; ES = 0.7), in which physical activity level had a moderate effect on reaction time in the switching condition (p = .02; ES = 0.8) but not in naming and inhibition conditions
- The interaction between physical activity level and Stroop conditions on ΔHbO_2 was found in the switching condition in the right PFC (p = .04; ES = 0.8) and left PFC (p = .02; ES = 0.96), but not in other conditions.
- A large physical activity level effect was found on ΔHHb in the inhibition condition in the right PFC (p < .01; ES = 0.9), but not in the left PFC or other conditions.
- The active young males performed better in executive tasks than their inactive counterparts and had a larger change in oxygenation in the PFC during the most complex conditions.

1.2 Article

Cerebral oxygenation reserve: the relationship between physical activity level and the cognitive load during a Stroop task in healthy young males

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INTRODUCTION

Participation in regular physical activity (PA) has been shown to reduce the incidence of many chronic diseases and mental disorders (Pedersen and Saltin 2015), therefore contributing to decreasing all-cause and cardiovascular mortality (World Health Organization 2009). Regular PA has also been shown to influence cognitive performance throughout the lifespan (Berryman, Pothier, and Bherer 2018), contributing to improve academic achievement in children, adolescents or young adults (Santana et al. 2017; Donnelly et al. 2016) and preventing cognitive decline and dementia in older adults (Chodzko-Zajko et al. 2009). This beneficial effect on cognition is more specific to executive functions, a subset of high-order cognitive functions including planning, inhibition or switching, that are mainly supported by the prefrontal regions of the cortex (Kramer et al. 1999; Miyake et al. 2000).

Several underlying mechanisms have been put forward to explain this link between regular PA and executive performance (Hillman, Erickson, and Kramer 2008; Hayes et al. 2013). Cerebral oxygenation is considered as one of the cornerstones of this relationship (Cameron, Lucas, and Machado 2015). It is determined in part by the interaction between cerebral vasculature and the regulation of cerebral blood flow, which defines the magnitude of the cerebrovascular reserve (Ainslie et al. 2008; Davenport et al. 2012b), and by the capacity of cerebral blood vessels to increase cerebral blood flow (CBF) as a response to metabolic demand in activated brain regions (Brown et al. 2010). Cerebral oxygenation is also determined by the availability of oxygen in the environment, as suggested by a study showing cognitive performance impairments in hypoxia (Ando, Yamada, and Kokubu 2010).

Cerebral oxygenation reserve refers to the capacity of prefrontal cortex blood vessels to increased blood flow as a response to increased metabolic demands during increased neuronal activity in the prefrontal cortex. Several stimuli, such as cognitive tasks, can activate neurons leading to electrical and chemical activities. The immediate energy needs of activated neurons are met by oxidation of lactate present in the extracellular space, resulting in a transient decrease in lactate levels and oxygen concentrations (Pellerin and Magistretti 1994). As oxygen concentrations decrease, the lack of energy for (adenosine triphosphate) ATP synthesis via oxidative phosphorylation causes an increase in the level of extracellular adenosine and lactate. These conditions resulting in larger arteriole dilation and greater blood flow at the activated brain regions, thus providing a transient increase in oxyhemoglobin (HbO_2) and a relative decrease in deoxyhemoglobin (ΔHHb), due to the increased HbO_2 concentration (Magistretti and Allaman 2015). Neuroimaging technologies such as near-infrared spectroscopy (NIRS), which provide a measure of concentration changes in HbO_2 and HHb, respectively, allow for the investigation of the specific role of cerebral oxygenation during cognitive processing (Yanagisawa et al. 2010).

Although the studies in the fNIRS field are growing exponentially (Yucel et al. 2017; Herold et al. 2018; Leff et al. 2011), most of the studies that address the relationship between PA and cerebral oxygenation have the goal of measuring these factors in older adults to prevent or reduce cognitive impairment (Erickson, Hillman, and Kramer

2015; Prakash et al. 2015). Little is known about the relationship between the participation in regular PA and cerebral oxygenation, more specifically prefrontal cortex (PFC) during cognitive processing in young adults, probably because the cerebrovascular reserve is not considered as a limiting factor in this period of life (Lu et al. 2011). Nevertheless, it is well established that the cardiovascular fitness of children and adolescents (Tomkinson et al, 2007, Olds et al, 2006), and consequently of young adults (Lamoureux et al. 2019), has been steadily decreasing for several decades, probably due to a significant decrease in weekly physical activity. The potential consequences on the cerebrovascular reserve are obvious (i.e., stroke, transient ischemic attack, cognitive issues, etc.) (Gupta et al 2012; Davenport et al. 2012), and suggest that the research effort on the link between PA and executive performance should not be limited to the elderly, but be concerned with all ages of life. Mechanisms should be explored to determine if there are age specificities. In all cases, mechanisms affecting cognitive performance in young adults should be studied in order to make appropriate recommendations. Therefore, the purpose of this study was to determine the relationship between physical activity, cerebral oxygenation, and executive performance in healthy young males. We hypothesized that 1) executive performance would be better in participants with a higher level of PA and that 2) changes in cerebral oxygenation during the task in the PFC would be greater in participants with higher PA level and better executive performance.

METHOD

PARTICIPANTS

Considering that PFC functions were influenced by the concentration of estrogen, we decided to focus specifically on males (Keenan et al. 2001; Jacobs and D'Esposito 2011; Hausmann 2017). 56 healthy young males (aged: 22.1 ± 2.1, range [18–26 years]) participated in this study. All participants signed a written statement of informed consent. They were non-smokers, did not undergo major surgery in the 6 months prior to the experiment, did not report any neurological or psychiatric disorders, and were not taking medication known to affect cognition. Moreover, given the physical implications of the study, participants were also screened and excluded for cardiovascular disease, and moderate to severe hypertension based on self-report. The protocol was reviewed and approved by a national ethics committee for non-interventional research (CERSTAPS # 2017-23-11-17) and was conducted in accordance with recognized ethical standards and national/international laws.

STUDY DESIGN

Participants completed all the tests within the same session. It included a physical activity measurement as well as a cognitive assessment. The study design is presented in Figure 1.

PHYSICAL ACTIVITY ASSESSMENT

Physical activity was assessed using the French version of Global Physical Activity Questionnaire (GPAQ). The French version of the GPAQ gives acceptable reliability and validity for the measurement of PA and sedentary time in adults (Rivière et al. 2018). The GPAQ was developed by the WHO for PA surveillance. It collects information on PA participation in three settings – PA at work,

recreational activities, and travel to and from places as well as sedentary behavior. The questionnaire consists of 16 questions covering both vigorous and moderate-intensity PA.

Based on the recommendation levels of physical activity for health from WHO (2009), participants were categorized as active, meeting the physical activity recommendations ($\geq$150 min/week) or inactive (<150 min/week).

CARDIORESPIRATORY FITNESS ASSESSMENT

The maximal continuous graded exercise test was performed on a motorized treadmill (Valiant 2 sport, Lode B.V., Groningen, Netherlands). The velocity was set at 5.6 km/h throughout the test, with an initial inclination of 0% grade. The inclination was increased by 6% after the first minute, and then by 2% every minute until voluntary exhaustion. Verbal encouragement was given every minute throughout the test (Andreacci et al. 2010). Oxygen uptake ($\dot{V}O_2$, in ml.kg-1.min-1) was determined continuously on a 30-s basis using a portable cardiopulmonary exercise testing system (MetaMax Cortex 3B, CORTEX Biophysik GmbH, Germany). Gas analyzers were calibrated before each test using ambient air and a gas mixture of known concentration (15% O_2 and 5% CO_2). The turbine was calibrated before each test using a 3-l syringe at several flow rates. The highest $\dot{V}O_2$ over a 30-s period during the test was considered as the peak oxygen uptake ($\dot{V}O_2$peak, in ml.kg-1.min-1). Perceived exertion was assessed at the end of the test with the 15-point Borg scale (in which higher scores represent higher perceived exertion) (Borg 1982).

COGNITIVE ASSESSMENT

The Computerized Modified Stroop task used in this study is based on the Modified Stroop Color Test (Bohnen et al., 1992) and included three experimental conditions: naming, inhibiting, and switching. Each block lasted between 2-4 minutes and was interspersed with 60-s resting blocks. Overall, there were three experimental task blocks (1 naming, 1 inhibiting, and 1 switching) and 2 resting blocks, for a total length between 8-14 min. In total, there were 60 Naming trials, 60 Inhibiting trials, and 60 Switching trials. All trials began with a fixation cross (or square for switching condition) for 1.5 s, and all visual stimuli appeared in the center of the computer screen for 2.5 s. Participants provided their responses with two fingers (index and major finger) from each of their hands on an AZERTY keyboard. In the Naming block, participants were presented with a visual stimulus of the name of colors (RED/BLUE/GREEN/YELLOW) in French presented in congruent color with the word and participants were asked to identify the color of the ink with a button press. In the Inhibition block, each stimulus consisted of a color-word (RED/BLUE/GREEN/YELLOW) printed in the incongruent ink color (i.e., the word RED was presented in blue ink). Participants were asked to identify the color of the ink (i.e., blue). In the Switching block, in 25% of the trials, a square in place of the fixation cross appeared before the word. When this occurred, participants were instructed to read the word instead of identifying the color of the ink (i.e., RED). As such, within the Switching block, there were both inhibition trials in which the participant had to inhibit their reading of the word and correctly identify the color of the ink, and there were switch trials in which the

participant had to switch their response mode to read the word instead of identifying the color of the ink when a square appeared before the word presented. Visual feedback on performance was presented after each trial. A practice session was completed before the acquisition run to ensure the participants understood the task. The practice consisted of a shorter version of the task. Dependent variables were reaction times (ms) and the number of errors committed (%). This task and procedure have been used successfully in previous studies (Dupuy et al. 2010, Dupuy et al. 2015).

The Stroop task is frequently used to examine executive function, as certain components of this task require extensive executive control (Dupuy 2015; Lague-Beauvais 2013; Scarpina and Tagini 2017). The relationship between physical activity and executive function has been confirmed in systematic review studies, including the one measured by the Stroop task (Verburgh et al. 2014; Cox et al. 2016). Those studies indicate that Stroop task can be used to observe the relationship between PA and executive function. Again, as studies about the relationship between PA and executive function in young adults, moreover using Stroop task, are limited, findings in this topic will be compelling.

PFC OXYGENATION

The concentration changes of HbO_2 (ΔHbO_2) and HHb (ΔHHb) were acquired with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands). This system utilizes near-infrared light, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in capillary, arteriolar and venular beds (Ferrari and Quaresima 2012). The light was transmitted with two wavelengths, 760 and 850 nm, and data were sampled with a frequency of 10 Hz. The PortaLite uses wireless technology (Bluetooth), which allows participants to walk and move without the restriction of wires. Two sensors were placed on the forehead of the participants, one on the right and one on the left side. Both devices were positioned at the height of 10% of the nasion-inion distance from nasion, and the middle of the device was placed at 5% of the head circumference to the left and right from midline, to avoid measuring the midline sinus. Those positions correspond to the Fp1 and Fp2 according to the international EEG 10–20 system and target left and right Brodmann's areas 9 and 10, which roughly represent the dorsolateral and anterior prefrontal cortex (PFC). The sensors were shielded from ambient light with a black cloth and fixed with an elastic strap. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection. This protocol for optode positioning was used successfully in a recent study (Hermand et al. 2019).

Based on different Hb absorption spectra, concentration changes of HbO_2 and HHb in the PFC area were calculated from the changes in detected light intensity. The calculation was conducted with the modified Lambert-Beer law, assuming constant light scattering (Sakatani et al. 2006). A PortaLite has three transmitters and one receiver, with transmitter-receiver distances of 30, 35, and 40 mm. The change in prefrontal oxygenation was calculated as the average of the three channels of NIRS on the same side of the prefrontal cortex. NIRS data analysis was performed on unfiltered data. Each block of the task was calculated by averaging blocks on each task condition. The artifacts in the signals were identified by visual inspection and

replaced by interpolation of adjacent data. The differential pathlength factor (DPF), which accounts for the increased distance traveled by light due to scattering, was set based on the age of participants. The differential pathlength factor (DPF) was specified for DPF807, which is determined using the formula: DPF807 = 4.99 + (0.067 x $Age^{0.814}$) (Duncan et al. 1996). Variables of interest were relative changes in concentration of ΔHbO_2, ΔHHb, and ΔtHb compared to the baseline (1 min at rest before the computerized Stroop task) (Dupuy et al. 2015; Gagnon et al. 2012; Laguë-Beauvais et al. 2013). Relative changes in concentration were measured because continuous-wave technology does not allow for the quantification of absolute concentrations due to its inability to measure optical path lengths (Ferrari and Quaresima 2012; Delpy and Cope 1997; Hoshi 2003).

STATISTICAL ANALYSiS

Standard statistical methods were used for the calculation of means and standard deviations. Normal Gaussian distribution of the data was verified by the Shapiro–Wilks test and homoscedasticity by a modified Levene Test. The compound symmetry, or sphericity, was checked by the Mauchly's test. Several t-tests for independent samples were used to explain the characteristics of PA groups. An analysis of variance (ANOVA) with Bonferroni post-hoc tests were conducted to test the interaction of PA level (active/inactive) by Stroop's performance (naming, inhibition, switching) and PFC oxygenation. The magnitude of the difference was assessed by the Cohen's d (*d*). The magnitude of the difference was considered either small ($0.2 < d < 0.5$), moderate ($0.5 < d < 0.8$), or large ($d > 0.8$) (Cohen, 1988). The significance level was set at $p < .05$ for all analyses. All calculations were made with Statistica 7.0 (StatSoft, Tulsa, USA).

RESULTS

Participants' characteristics are presented in Table 1. We found a large difference in GPAQ score ($t_{(54)} = 6.35$, $p < .001$, $d = 1.77$) and in $\dot{V}O_2$peak [$t(54) = 5.31$, $p < 0.001$]. There were no other differences between groups.

Computerized Stroop task results

Concerning the reaction times on the computerized Stroop task, the ANOVA showed a marginal effect of physical activity level ($F_{(1, 54)} = 3.72$, $p = .06$), in which active individuals had faster overall reaction times than inactive individuals (726ms ± 95 and 784ms ± 82, respectively; $d = 0.65$). There was also a main effect of Stroop condition ($F_{(2, 54)} = 225.66$, $p < .001$). Participants completed the naming condition faster than inhibition and switching conditions (605ms ± 84, 707ms ± 92, and 958ms ± 146, respectively, $1.17 < d < 2.99$). Moreover, there was a significant physical activity level by Stroop's condition interaction ($F_{(1, 54)} = 3.40$, $p = .04$). Bonferroni post-hoc analysis revealed a moderate difference in reaction time in which active individuals were faster than inactive individuals in the switching condition (901ms ± 146 and 1008ms ± 138, respectively; $p = .05$; $d = 0.77$). We found no difference in reaction time between active and inactive individuals for naming and inhibition Stroop condition.

The ANOVA assessing differences in accuracy on the computerized Stroop task revealed a main effect of Stroop condition ($F_{(2, 54)} = 40.65$, $p < .001$). Participants completed naming and inhibition conditions

with significantly higher accuracy than switching condition (96.7% ± 2.2, 97.4% ± 2.4, and 92.6% ± 4.2, respectively, $0.29 < d <$, 1.41). There were no effects of physical activity level on accuracy and no significant interactions. These results are presented in Table 2.

PFC oxygenation results

Total PFC oxygenation changes during Stroop task are presented in Figure 2, and the detail for the right and left hemisphere are presented in Table 3.

For ΔHbO_2, the ANOVA indicated a main effect of Stroop condition in the left PFC ($F_{(2, 54)} = 44.78$, $p < .001$) and the right PFC ($F_{(2, 54)} = 72.89$, $p < .001$). We also found interaction of physical activity level by Stroop condition in left PFC ($F_{(2, 54)} = 6.77$, $p < .01$) and right PFC ($F_{(2, 54)} = 16.05$, $p < .001$), in which the ΔHbO_2 in active individuals was greater than inactive individuals in switching condition. Post-hoc analysis revealed a large difference in which active individuals had greater ΔHbO_2 than inactive individuals in the switching condition (6.16umol.L^{-1} ± 2.38 and 3.73umol.L^{-1} ± 2.67, respectively; $p = .05$; $d = 0.77$). Manipulations of cognitive load revealed that between the naming and inhibition condition, there was a greater ΔHbO_2 in the right and left PFC in both physical activity groups. However, between inhibition and switching condition, we found greater ΔHbO_2 in the right and left PFC in active individuals but not in inactive individuals.

For ΔHHb, the ANOVA revealed a main effect of Stroop condition in the left PFC ($F_{(2, 54)} = 4.07$, $p = .02$) and in the right PFC ($F_{(2, 54)} = 4.57$, $p = .01$). We also found interaction of physical activity level by Stroop condition in right PFC ($F_{(2, 54)} = 3.25$, $p = .04$), in which between naming and inhibition condition, we found greater ΔHHb in right PFC in active individuals but not in inactive individuals.

The typical response of cerebral oxygenation during the Stroop procedure is presented in Figure 3.

DISCUSSION

The aim of this study was to assess the association between physical activity level, PFC oxygenation, and cognitive performances in healthy young males. Based on the existing literature, we hypothesized that the physical activity level would enhance performance in executive conditions (inhibition and switching conditions) in a computerized Stroop task. Secondly, we hypothesized that better executive control in active individuals would be related to increased PFC oxygenation. The results of this study supported our first hypothesis, as we found that active individuals performed better in the executive condition of the computerized Stroop task than inactive individuals. However, this effect was specific to the switching condition (the most complex condition) and did not emerge in the inhibition condition. Regarding our second hypothesis, we found a greater amplitude response in PFC oxygenation during the Stroop task in active young males when compared to inactive.

Regarding our cognitive performance results, both groups had higher accuracy scores and shorter reaction times in the naming condition compared to the inhibition and switching conditions. This finding indicates that non-executive condition (naming condition) was less demanding than the executive conditions and the manipulation

of the cognitive load was successful as the inhibition and switching conditions require executive functions and the naming condition does not. The condition effect in our study is in accordance with the Stroop task findings in healthy younger and older females (Dupuy et al. 2015). When compared to the overall cognitive performance, the active group had the same accuracy but with shorter reaction times than the inactive group. More specifically, this difference in performance emerged in the switching condition but not in the naming and inhibition conditions. In addition, we also found an interaction of physical activity level by condition in reaction times, such that the increasing executive function load resulted in longer reaction times for the inactive individuals compared to active individuals. These data suggest that when the condition requires greater executive control, the active individuals demonstrate better executive functioning in the form of faster performances than inactive individuals. These results are in line with a longitudinal study that reported a specific physical activity level effect on the switch and mixing costs in task switching in young adults (Kamijo and Takeda 2010). Further, in line with other findings using the Stroop task, this result is in accordance with a cross-sectional study of younger adults and older adults (Dupuy et al. 2015) and a longitudinal study of older adults (Predovan et al. 2012).

In line with our previous study in females (Dupuy et al. 2015), no interaction of physical activity level by condition in the accuracy performance was found in our participants, suggesting that the computerized Stroop task is more sensitive to reaction time changes than accuracy when testing the effect of physical activity level on Stroop performances in young males. All these results suggest that fulfilling physical activity recommendations (of $\geq$ 150 mins/week) has a positive impact on cognition in healthy young males, specifically in the executive function domain.

Moreover, we found no difference between the groups in inhibition performance. As the inhibition performance requires a smaller cognitive load than the switching condition (Proctor 1995), it is possible that inhibition condition was not cognitively challenging enough for healthy young males. Our result is in line with another study in older adults, Coubard et al. (Coubard et al. 2011) evaluated executive functions after contemporary dance training and demonstrated an executive function improvement after contemporary dance training that was seen only in a switching condition (rule shift cards sorting test) but not in an inhibition condition (Stroop task). The best of our knowledge, this is the first study that compared the effect of physical activity level on inhibition condition and switching condition in healthy young males.

Regarding PFC oxygenation, both groups had greater ΔHbO_2, ΔHHb, and ΔtHb, on the executive conditions when compared with the naming condition. This result supports our cognitive load manipulation since participants' increased PFC oxygenation in the more cognitive demanding executive conditions. Such an observation has already been reported in the literature (Fraser et al. 2016; Herff et al. 2014; Mirelman et al. 2014). In addition, we also found an interaction between physical activity level and condition of the Stroop task on PFC oxygenation changes. This interaction showed that increased executive function load during inhibition and switching conditions resulted in greater ΔHbO_2 in left and right PFC, greater ΔHHb in the right PFC, and greater ΔtHb in

left and right PFC in active individuals when compared with inactive individuals. These results suggest that active individuals have a higher capacity to regulate the PFC oxygenation necessary to deal with increasing cognitive demand in computerized Stroop task, hence proposing a mechanism by which physical activity affects executive performances. Beyond this potential link between PA level, PFC oxygenation and cognitive performance, the scientific literature of the last decade has also suggested a similar link with cardiorespiratory fitness (CRF) (Albinet et al. 2014; Dupuy et al. 2015), which is regularly considered as one of the determinants of PA level (Martínez-vizcaíno and Sánchez-lópez 2008; Schmidt et al. 2017). In our study, physically active participants also displayed greater CRF (as measured by peak oxygen uptake) and presented a higher PFC oxygenation during cognitive task. These results are in accordance with previous studies (Dupuy et al. 2018; Albinet et al. 2014; Fabiani et al. 2014) which reported that participants with the highest CRF also presented a higher PFC or occipital cortex oxygenation during cognitive or visual task, whatever the age, thus supporting the cerebrovascular reserve hypothesis (Davenport et al. 2012b). Also, Agbangla et al. (2019) found a similar pattern in working memory task (n-back) and reported that high-fit older adults had a higher response to PFC oxygenation than low-fit older adults (Agbangla et al. 2019). More specifically, active individuals displayed a greater decrease of ΔHHb then inactive individuals during inhibition condition, which represents greater oxygenation. A previous fNIRS study reported that the right inferior gyrus of the prefrontal cortex, which is known to contribute to inhibition process, was more active during an executive task in higher-fit individuals (Dupuy et al. 2015)

Theoretically, the present results combine some hypotheses from the previous studies, such as the compensation-related utilization of neural circuits hypothesis (CRUNCH), which stipulates that some cerebral regions will be more activated as specific task load increases (Reuter-Lorenz and Lustig 2005), astrocyte-neuron lactate shuttle (ANLS) (Pellerin and Magistretti 1994), and cerebrovascular reserve (Davenport et al. 2012a). In the CRUNCH model, cerebral activation should increase until a certain cognitive capacity is reached (Reuter-Lorenz and Lustig 2005). Afterward, cerebral activity should stop increasing, either because there are no further resources available or because there is no performance benefit in using brain resources any further. Additionally, according to the ANLS mechanism, this dynamics of cerebral activity is coupled with energy metabolism in the brain (Pellerin and Magistretti 1994). As a consequence, cerebral activation could be restricted by the availability or reserve of metabolic substances in the brain (i.e., oxygen, glucose, and lactate). The availability of these substances in the brain depends on brain perfusion and how cerebral blood vessels respond to metabolic demand. The cerebrovascular reserve hypothesis proposes that cerebrovascular control is positively associated with cognitive function (Davenport et al. 2012a). Thus, a higher physical activity level, which is related to better cerebrovascular health, should be associated with better cognitive function.

In this study, we found that the interaction in cognitive performance, more specifically reaction time performance, was concurrent with the pattern of PFC oxygenation between physical activity level groups. One important finding to note from the present study is that inactive individuals

had a poorer performance in switching condition, which is the most complex condition, than their active counterpart but not in the other conditions. In parallel, there was an absence of increased oxygenation in response to the increased complexity of the Stroop task during switching condition in inactive individuals. It is suggested that inactive individuals had reached their cognitive capacity limit in a less complex condition than active individuals, and this alteration may be due to a lower capacity to increase PFC oxygenation in this group. The difference in the PFC oxygenation could be explained by the difference in cerebrovascular control as postulated in the cerebrovascular reserve theory.

Limitations

The objective of participants' recruitment as all males is to limit the gender bias due to the influence of estrogen on PFC, but we aware that this method will limit the generalizability of findings in young adults. A follow-up study, using the same design, which recruits younger female participants is needed to compare to the current findings. The proportion of aerobic and resistance activity was not determined in this study, development of protocols or questionnaires that can address this issue will be beneficial for future investigation on this topic. In addition, objective measures of exercise intensity such as accelerometry, heart rate or oxygen uptake should be used to complement the questionnaire-based physical activity recording and provide a better view of exercise intensity. Furthermore, the continuous-wave fNIRS technique has several limitations, first, lower spatial resolution and poorer depth penetration than other brain imaging techniques (Bakker, Smith, Ainslie, & Smith, 2012). Secondly, this technique can be influenced by changes in blood flow on extra-cerebral tissue such as extra-cerebral tissue included the scalp, skull and cerebrospinal fluid (Strangman et al. 2002; Kirilina et al. 2012). In this study we did not control the superficial skin blood flow but the influence of changes in scalp blood flow is likely to be minimal since participants remained in a seated position during entire protocol. Thirdly, the fNIRS device used quantifies changes in cerebral oxygenation and not absolute oxygenation. Therefore, group comparisons using this type of fNIRS should be interpreted with caution, as it is possible that in certain protocols group differences exist already in baseline tissue oxygenation and blood volume, and also optical properties of the brain and superficial layers (Bakker, Smith, Ainslie, & Smith, 2012). Also, in this study, we have underestimated the impact of physiological noise on fNIRS data since our results are in accordance with the results of literature and so we have not performed the filtering of the NIRS signals and detrending of segments. The results obtained in the present study concern only the PFC (not deep brain structures) and not whole of the brain, since the cognitive task used strongly stimulates this region of interest. Combining the results of NIRS with electroencephalogram (EEG) and functional MRI will provide a more comprehensive understanding of the dynamics of cerebral activation. Also, the utilization of a multi-channel NIRS setup can help to observe the oxygenation profiles and activities of other brain regions compared to the two-channel setup in this study.

CONCLUSION.

In conclusion, this study supports the positive effect of PA on executive performances in healthy young males. The

results showed that the active young males performed better in switching condition than inactive young males. Furthermore, greater increase of PFC oxygenation, especially ΔHbO_2, was associated with a higher PA also in switching condition. Accordingly, fulfilling the physical activity recommendation of 150 MVPA/week may be able to support healthy young males to increase their PFC oxygenation and to perform better in activities that require executive function.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure captions:

Figure 3: Typical response of cerebral oxygenation during the Stroop procedure. (PT= practice trials)

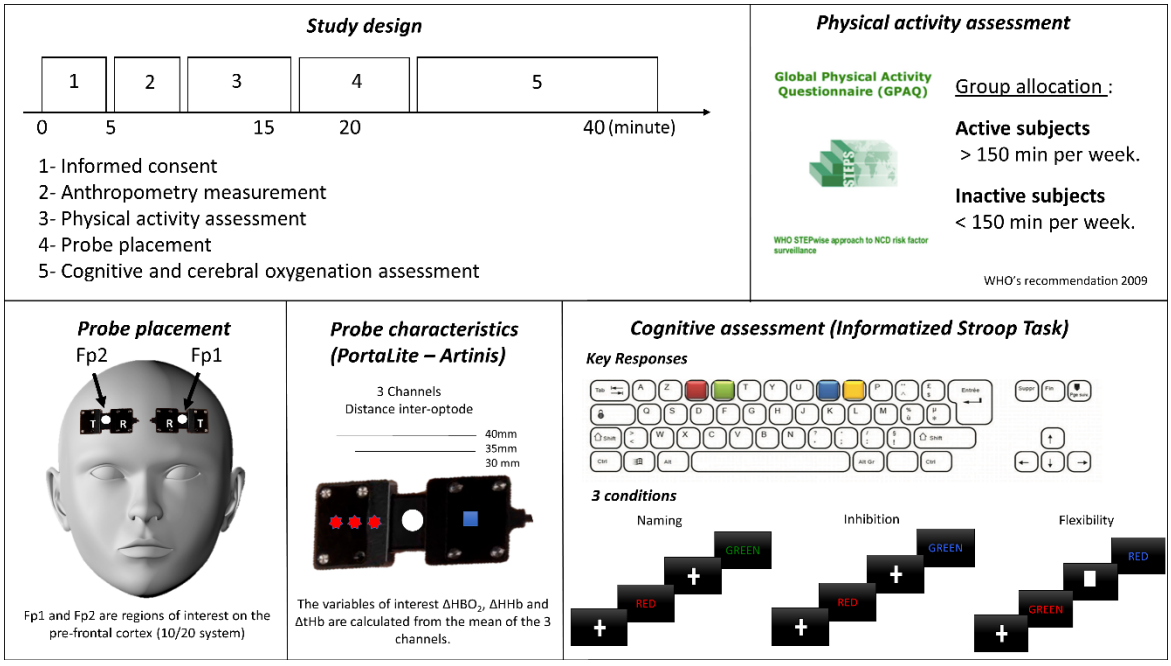

Figure 1: Study design and methodological information

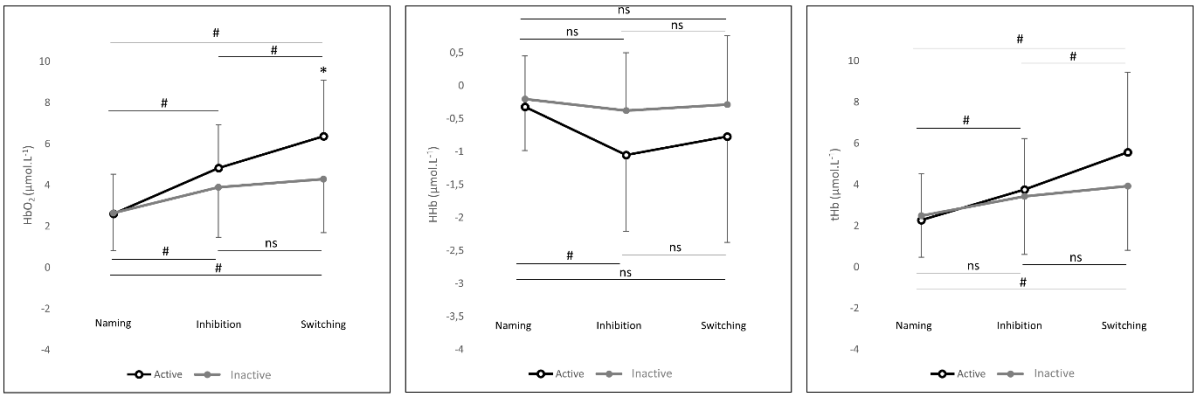

Figure 2: Total cerebral oxygenation (both hemispheres of PFC) during Computerized Stroop task conditions. (A) Change in total HbO_2, (B) Change in total HHb, (C) Change in total tHb. Data are presented as means and SDs; *p < 0.05 between active and inactive group. #: p < 0.05 between Stroop conditions.

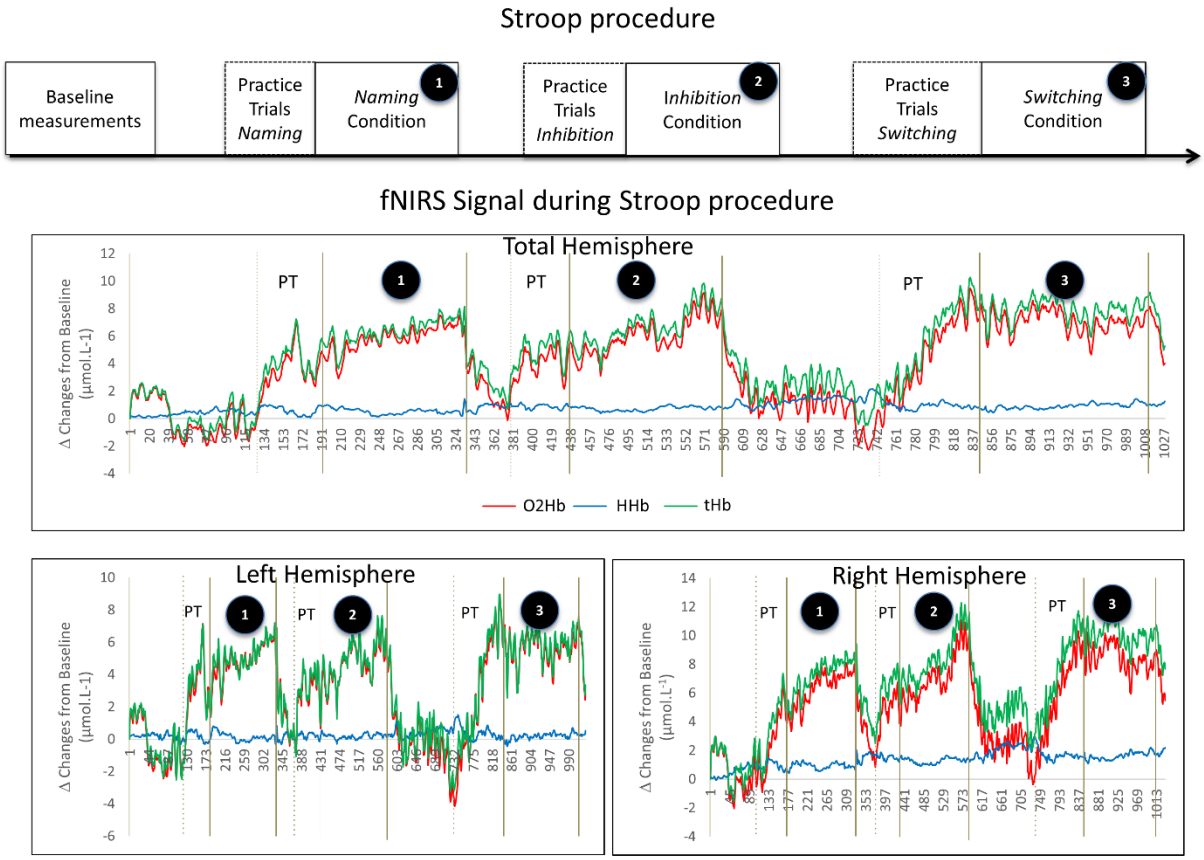

Figure 3: Typical response of cerebral oxygenation during the Stroop procedure. (PT= practice trials)

Table 1: Characteristics of Study Participants. Data are presented as mean (SD)

	Active (n=26)		Inactive (n=30)		Cohen's d
Age (yrs)	21.8	(2.0)	23.3	(2.5)	0.66
Height (cm)	177.0	(5.2)	180.0	(5.4)	0.56
Weight (kg)	74.4	(15.1)	81.9	(22.2)	0.35
GPAQ (METS.min.week^{-1})	5165.6	(3842.8)	536.0	(275.2) *	1.77
($\dot{V}O_2$peak (ml.kg^{-1}.min^{-1})	49.8	(8.5)	38.6	(7.2)*	2.9

GPAQ, Global Physical Activity Questionnaire ; $\dot{V}O_2$peak, peak oxygen uptake
*different from Active (p<0.05)

Table 2. Accuracy and reaction time during Stroop tasks. Data are presented as mean (SD)

	Overall (n=56)		Active (n=26)		Inactive (n=30)		Cohen's d^{+}
Accuracy (% correct responses)							
Naming	96.7	(2.2)	96.7	(2.4)	96.7	(2.5)	0.0
Inhibition	97.4	(2.4)	96.5	(2.6)	97.8	(3.1)	0.5
Switching	92.6	(4.2)	91.4	(5.9)	93.7	(4.9)	0.4
Reaction Time (ms)							
Naming	605.4	(83.5)	594.4	(105.8)	614.9	(63.2)	0.2
Inhibition	707.2	(91.9)	682.9	(94.0)	728.3	(92.7)	0.5
Switching	958.4	(145.9)	901.3	(137.6)	1007.8	(138.2)*	0.7

*different from active group (p<0.05); $^{+}$effect size between active and inactive group

Table 3. Cerebral oxygenation changes from baseline during computerized Stroop tasks. Data are presented as means (SDs).

	Active (n=26)		Inactive (n=30)		Cohen's d
Naming					
Right PFC					
ΔHbO_2 (umol.L^{-1})	2.29	(2.06)	2.48	(1.99)	0.1
ΔHHb (umol.L^{-1})	-0.44	(0.69)	-0.32	(0.66)	0.2
Left PFC					
ΔHbO_2 (umol.L^{-1})	3.13	(1.90)	2.81	(1.85)	0.2
ΔHHb (umol.L^{-1})	-0.15	(0.75)	-0.14	(0.68)	0.0
Inhibition					
Right PFC					
ΔHbO_2 (umol.L^{-1})	4.75	(2.27)	3.54	(2.42)	0.5
ΔHHb (umol.L^{-1})	-1.32	(1.19)	-0.42	(0.83)*	0.9
Left PFC					
ΔHbO_2 (umol.L^{-1})	5.14	(2.22)	4.02	(2.40)	0.5
ΔHHb (umol.L^{-1})	-0.75	(1.25)	-0.38	(0.86)	0.4
Switching					
Right PFC					
ΔHbO_2 (umol.L^{-1})	6.16	(2.38)	3.73	(2.67)*	0.8
ΔHHb (umol.L^{-1})	-1.11	(1.70)	-0.26	(1.10)	0.6
Left PFC					
ΔHbO_2 (umol.L^{-1})	6.87	(3.21)	4.45	(2.81)*	0.8
ΔHHb (umol.L^{-1})	-0.37	(1.67)	-0.37	(1.05)	0.0

PFC, Prefrontal cortex; ΔHbO_2, changes in oxyhemoglobin concentrations; ΔHHb, changes in deoxyhemoglobin concentrations

The results of dual-task condition are the difference from the baseline

*different from active group ($p<0.05$)

2 Study 2

2.1 Resume

Cardiorespiratory Fitness, Blood Pressure, and Cerebral Oxygenation during a Dual-task in Healthy Young Males

Description of Study 2

There is an increasing amount of knowledge supporting a close relationship between cardiorespiratory fitness (CRF), brain health, and cognitive performance in older adults (Hayes, Forman, and Verfaellie 2016; Hillman, Erickson, and Kramer 2008b; S. J. Colcombe et al. 2004; Hayes et al. 2013; Tamura et al. 2015). Working memory (WM), which is the executive function that correlates the most with fluid intelligence, represents the ability to hold short-term information in mind while using that information to accomplish a task (Miyake et al. 2000). Several studies have shown that n-back task performance, which is under the control of the prefrontal cortex (PFC), was a predictor of inter-individual differences in fluid intelligence and was associated with CRF in older adults (Voelcker-Rehage, Godde, and Staudinger 2010; Agbangla et al. 2019). On the other side, inconsistency in the younger adult findings relating to CRF and WM initiates a debate on the potential links between CRF, PFC, and WM, especially in younger adults. Younger adults typically have better WM performance than older adults (Stern 2009). Therefore, considering their larger cognitive reserve and physical performance capacity, the level of task complexity required for the CRF to become a limiting factor is much greater in younger adults compared to older adults (Stern 2009; Davenport et al. 2012). In this regard, the dual-task walking paradigm may provide the increased task complexity needed for younger adults (Woollacott and Shumway-Cook 2002).

Several underlying mechanisms, involving both the structure and the function of the brain, have been proposed to explain this beneficial effect of exercise on executive functions (Hillman, Erickson, and Kramer 2008a; S. J. Colcombe et al. 2004; Hayes et al. 2013; Kramer and Colcombe 2018). From a functional point of view, oxygen availability appears to play a major role in cerebral functioning (Obrig and Villringer 2003). Cerebral oxygen availability is determined in part by the interaction between cerebral vasculature and the regulation of cerebral blood flow (CBF) but also by the availability of oxygen in the environment as suggested by studies showing cognitive performance impairments during hypoxia (Ando, Yamada, and Kokubu 2010; P. N. Ainslie et al. 2008; Novak and Hajjar 2010a). Differences in CRF seem to play a key role in cerebral oxygenation since high-fit older adults display higher cerebral oxygenation during a cognitive task (Dupuy et al. 2015; Agbangla et al. 2019; Albinet et al. 2014). In parallel, some evidence has suggested that blood pressure is involved in the association between CRF and executive performance, including WM (Novak and Hajjar 2010b). Both hypertension and hypotension have been associated with alterations in CBF,

which may lead to a decrease in perfusion and oxygenation of the brain, a decrease in a vascular reserve capacity, and ultimately a decrease in executive performance capacity (Novak and Hajjar 2010b). This potential role of blood pressure has also been supported by the association between blood pressure and cognitive impairment, even in normotensive individuals (J. N. Barnes and Corkery 2018). However, the degree to which CRF and blood pressure associated with the PFC oxygenation and dual-task performance remains to be determined, particularly in younger adults.

The current study aimed to evaluate the effects of CRF and mean arterial pressure (MAP) on the PFC oxygenation and dual-task performance in healthy young males. Thirty-six young males (23.8 ± 4.8yrs) were ranked according to their $\dot{V}O_2peak$. The second tertile was excluded to generate two groups of different CRF: high fit group (n = 12; $\dot{V}O_2peak$ = 56.0±6.7 ml.kg-1.min-1) and low-fit group (n = 12; $\dot{V}O_2peak$ = 36.7±4.1 ml.kg-1.min-1). The CRF groups were further split into two subgroups according to their 24-hour MAP (higher-MAP and lower-MAP). Changes in the concentration of oxygenated (ΔHbO_2) and deoxygenated hemoglobin (ΔHHb) in the right and left PFC were examined during a cognitive auditory 2-back task. Cognitive performance (2-back task's accuracy) and walking motor performances were measured in single-tasks (single motor and single cognitive) and dual-task (2-back task + walking). Three-way ANOVA (CRF x MAP x n-back conditions) was performed to test the null hypothesis of an absence of interaction between CRF level, MAP, and PFC oxygenation on executive performance.

The main results of this study are:

- The interaction between the CRF and cognitive task condition on 2-back accuracy was found ($p < .01$), in which CRF level had a moderate effect on 2-back accuracy in the dual-task condition ($p = .04$) but not in single-task condition.
- The interaction between the CRF, PFC oxygenation, and cognitive task condition on 2-back accuracy was found on ΔHHb in the right PFC ($p = .01$), and the left PFC ($p = .04$), but not on ΔHbO_2
- The interaction between CRF, MAP and cognitive task conditions on 2-back accuracy does not reach statistical significance ($p = .06$)
- The dual-task costs in accuracy (dual-task < single-task) only demonstrated in low-fit young males.
- Greater ΔHHb on both sides of PFC was shown in high-fit young males compared with the low-fit ones.
- Neither interaction nor effect of MAP on cerebral oxygenation and 2-back accuracy was found

2.2 Article

Cardiorespiratory fitness, blood pressure, and cerebral oxygenation during a dual-task in healthy young males

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INTRODUCTION

There is an increasing amount of knowledge supporting a close relationship between cardiorespiratory fitness (CRF), brain health, and cognitive performance in older adults [1]–[5]. This link is particularly well-established for fluid intelligence. This high-level cognitive function, which declines with aging [6], refers to the ability to solve novel problems [7] and is commonly used as a predictor of general intelligence [8]. Working memory (WM), which is the executive function that correlates the most with fluid intelligence, represents the ability to hold short-term information in mind while using that information to accomplish a task [9]. One of the typical tests used to assess WM is the n-back task, which consists in presenting a series of stimuli and ask the participant to respond to the stimuli they saw or heard "n" items-back. Several studies have shown that n-back task performance, which is under the control of the prefrontal cortex (PFC), was a predictor of inter-individual differences in fluid intelligence and was associated to CRF in older adults [10], [11]. Studies in younger adults have reported a lack of association between CRF and n-back task performance [12], [13] even though higher-fit younger adults have exhibited better WM performance than lower-fit young adults using a different WM tasks such as: the Automatic Operation Span (Aospan) task [14] and Sternberg's Working Memory Search (SMS) task [15]. This inconsistency in the younger adult findings relating to CRF and WM initiates a debate on the potential links between CRF, PFC, and WM, especially in younger adults.

Younger adults typically have better WM performance than older adults [16]. Therefore, considering their larger cognitive reserve and physical performance capacity, the level of task complexity required for the CRF to become a limiting factor is much greater in younger adults compared to older adults [16], [17]. In this regard, the dual-task walking paradigm may provide the increased task complexity needed for younger adults [18]. The dual-task walking paradigm is a procedure that requires an individual to perform a motor and a cognitive task simultaneously (or dual-task), in order to compare performance with single-task conditions (i.e., walking alone or responding to cognitive task alone). Considering the high cognitive demands of this task, a reduced cognitive reserve may result in an alteration of motor performance, cognitive performance or both [19]–[21]. In addition, low CRF has been associated with less automaticity in movement and greater cognitive control during complex motor tasks [22]. It has recently been suggested that increased gait instability and higher stride variability that has been observed in individuals with low CRF could be partly compensated by cognitive strategies, thus replacing automated sensorimotor processing with effortful higher-order functions [19]. When cognitive resources are allocated for locomotion, capacity theories [23] propose that these cognitive resources are less available for other activities while walking. Therefore, regardless of age, individuals with low CRF may have more difficulty than those with a high CRF to walk and concurrently engage in a cognitive activity [24], [25].

Several underlying mechanisms, involving both the structure and the function of the brain, have been proposed to explain this beneficial effect of exercise on executive functions [3], [4], [26], [27]. In fact, CRF has been positively associated with white matter integrity, cortical thickness, and gray matter

volume of the PFC in older adults [28], [29]. From a functional point of view, oxygen availability appears to play a major role in cerebral functioning [30]. Cerebral oxygen availability is determined in part by the interaction between cerebral vasculature and the regulation of cerebral blood flow (CBF) but also by the availability of oxygen in the environment as suggested by studies showing cognitive performance impairments during hypoxia [31]–[33]. Differences in CRF seem to play a key role in cerebral oxygenation since high-fit older adults display higher cerebral oxygenation during a cognitive task [11], [34], [35]. In parallel, some evidence has suggested that blood pressure is involved in the association between CRF and executive performance, including WM [36]. In fact, both hypertension and hypotension have been associated with alterations in CBF which may lead to a decrease in perfusion and oxygenation of the brain, a decrease in a vascular reserve capacity, and ultimately a decrease in executive performance capacity [36]. This potential role of blood pressure has also been supported by the association between blood pressure and cognitive impairment, even in normotensive individuals [37]. Finally, some studies reported that a higher CRF predicted a lower mean arterial pressure (MAP) [38] and CBF regulation [39] in healthy young adults. However, the degree to which CRF and MAP associated with the PFC oxygenation and dual-task performance still remains to be determined, particularly in younger adults.

Therefore, the purpose of this study was to determine the interactions between CRF, MAP and PFC oxygenation during dual-task walking in healthy young males. Considering the literature and previous studies, we expected that a higher CRF level would be associated with a better 2-back accuracy in healthy young males especially in the dual-task condition. Secondly, we expected that a higher CRF level would also be associated with a greater change on ΔHbO_2 and ΔHHb during 2-back task performance especially in dual-task condition. Thirdly, we expected that MAP would influence the relationship between CRF, cerebral oxygenation and WM in healthy young males. We hypothesized that: 1) WM assessed in dual-task would be better in high-fit individuals compared to low-fit, 2) PFC oxygenation would be greater in individuals with better WM, and 3) MAP would affect the link between WM, cerebral oxygenation, and CRF.

2. MATERIAL AND METHODS

2.1 Participants

In this study, considering the influence of estrogen on PFC, we decided to focus specifically on males [40]–[42]. Young healthy males aged between 18 and 35 years old were considered for inclusion in this study. Thirty-nine young males were recruited for this study. All participants were university students in Poitiers (France) and were recruited via announcements in university's media. Participants were excluded if they had cardiovascular, musculoskeletal or rheumatoid disorders that are exacerbated by exercise, a psychiatric disorder, a gait abnormality or were currently being treated for a cardiovascular disease or psychiatric disorder. After inclusion, 2 participants were unable to perform the dual-task correctly and one participant did not complete the study. Therefore, the final sample of participants are thirty-six young males who have completed this protocol. All participants provided written

informed consent under an approved ethical board protocol from the research ethics board in physical activity and sports sciences (CERSTAPS #2017-231117).

2.2 Experimental design

On day one, participants came to the lab and completed the informed consent form. Afterwards, a Beck's Depression Inventory-II questionnaire was given and all participants underwent cognitive screening (Montreal Cognitive Assessment). Then, participants completed anthropometry measurements to measure height, weight, body fat percentage using the Leicester height measure and a bioelectric impedance device (Tanita BC418, Tanita Corp., Tokyo, Japan). Following, these questionnaires and measures, the dual-task protocol was performed by the participants. At the end of the first session, all participants were given a 24-h ambulatory blood pressure monitor. The arm cuff was attached and instructions were provided so that 24-h blood pressure monitoring could be started. On day two, participants completed the maximal continuous graded exercise test. To avoid any residual fatigue induced by recent workout, participants were asked to refrain from strenuous exercise the day before each session. They were also asked to abstain from alcohol and caffeine-containing beverages 24 hours before the test in order to avoid any influence of these beverages on the regulation of the cardiovascular system. All sessions were administered between 8:00 a.m. to 4:00 p.m.

Once the experimental sessions were completed, participants were sorted according to their peak oxygen uptake ($\dot{V}O_2$peak). Based on the participants' $\dot{V}O_2$peak, the sample was split into tertiles. The second tertile was excluded to generate two groups of different physical fitness (high and low-fit). Then, a median split was performed to generate two subgroups with different MAP (higher and lower-MAP) within each physical fitness group. In the end, 4 groups (higher-MAP low-fit; lower-MAP low-fit; higher-MAP high-fit; and lower-MAP low-fit) of 6 participants were generated to test our hypotheses. Their characteristics are presented in Table 1.

2.3 Maximal continuous graded exercise test

This test was performed on a motorized treadmill (Valiant 2 sport, Lode B.V., Groningen, Netherlands). Modified Balke walking protocol was used to measure peak oxygen consumption ($\dot{V}O_2$peak). Walking protocol was chosen because it does not require running and has a slow increase in work load. This test is well suited to evaluate aerobic fitness in heterogeneous populations that vary in terms of fitness level, age, adiposity or health status in general [43]. The velocity was set at 5.6 km/h throughout the test, with an initial 0% grade. The inclination was increased by 6% after the first minute, and then by 2% every minute until voluntary exhaustion. Verbal encouragement was given every minute throughout the test [44]. Oxygen uptake ($\dot{V}O_2$, in $ml.kg^{-1}.min^{-1}$) was determined continuously on a 30-s basis using a portable cardiopulmonary exercise testing system (MetaMax Cortex 3B, CORTEX Biophysik GmbH, Germany). Gas analyzers were calibrated before each test using ambient air and a gas mixture of known concentration (15% O_2 and 5% CO_2). The turbine was calibrated before each test using a 3-l syringe at several flow rates. The highest $\dot{V}O_2$ over a 30-s period during the test was considered as the peak oxygen uptake ($\dot{V}O_2$peak, in $ml.kg^{-1}.min^{-1}$). Perceived exertion (RPE) was assessed at the end of the test with the 15-point

Borg scale (in which higher scores represent higher perceived exertion) [45].

2.4 Blood pressure measurement

Blood pressure parameters were measured with an ambulatory blood pressure measurement device (Mobil-O-Graph, I.E.M GmbH, Stolberg, Germany). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP; MAP = 1/3 SBP + 2/3 DBP) were measured every 20 minutes during a 24-h period and were divided into daytime (8 am to 10 pm) and night-time (from 10 pm to 8 am) periods.

2.5 Measurement of motor and cognitive performances

The n-back task is a cognitive task which frequently used to measure working memory [46]. A series of numbers (0-9) were presented auditorally, and the participants were asked to respond to the stimuli that they heard "n" items-back (0-back or 2-back). In the lowest load version (0-back), participants were asked to remember and say the number they just heard. As the number of items-back increases, the working memory load increases the attentional demands of the individual [47]. The dual-task condition with 2-back version of n-back task has a better reliability than the 1-back or 3-back version [20]. Previous work with this task [24] has shown that the 2-back version of this task adequately challenges younger adults and therefore this was the version used in this study. In this study, the cognitive load was manipulated by using two different conditions: single- and dual-task, and not by manipulating the n-back load. In the single task condition, participants were instructed to perform either a self-paced walk (motor task) or the 2-back task (cognitive task). In the dual-task condition, participants performed both self-paced walking and 2-back task simultaneously.

The numbers were pseudo-randomly ordered to ensure that there were no repeats (1–1) and no sequenced series (1–2–3). The numbers were recorded with a female voice, and sound files (wav files) of lists of numbers were created with Audacity version 2.2.6 (general public license). The numbers were presented through wireless headphones (RS 165, Sennheiser Electronic, Wedemark, Germany). In the 2-back version, a participant might hear the series "0 – 4 – 1 – 5…..", once they heard "1", they would have to say "0", and once they heard "5" they would have to say "4", always keeping in mind the digit heard two positions back. The experimenter noted the participants' responses and their accuracy. A 0-back version of the task with 12 items was used in single-task condition and only in practice session to ensure an adequate hearing for testing. All participants were given instructions before each task condition (0-back single-task, 2-back single-task, self-paced walking, and 2-back dual-task walking). The practice trial consisted of two trials for each task condition. All participants reached 100% accuracy on a 0-back version during practice. Then, the experimental test consisted of 10 blocks organized as follows: single-task 2-back (2 blocks), single-task (self-selected pace) walking (1 block), dual-task 2-back (4 blocks), single-task (self-selected pace) walking (1 block), and single-task 2-back (2 blocks). Each block of single and dual-task 2-back consisted of 12 items. Each item was presented in 1.5 s, and there was a 1 s response interval (total trial time 2.5 s) before the next item was presented. Each block lasted 40 seconds with a 60-second rest period between blocks. The protocol for 2-back task and the general experimentation are presented in Figure 1.

Cognitive performance was measured as a percentage of correct responses out of all possible responses on the 2-back task. Single-task cognitive performance is the percentage of participants' correct responses on the 2-back tasks while seated on a chair. The dual-task cognitive performance is the percentage of participants' correct responses on the 2-back tasks while walking at their self-selected pace. In this study, participants were given instructions to give equal priority for both cognitive and motor tasks.

Temporal and spatial parameters of motor performances of walking were studied using an instrumented walkway system (GAITRite system; CIR Systems Inc, Clifton, NJ, USA). This system consists of a 4.6 m electronic walkway with sensors arranged in a grid-like pattern to identify footsteps contacts. Participants stood a distance of 5 meters away from the beginning of the walkway and were instructed to walk at their self-selected pace across the instrumented walkway. Participants began and finished walking according to the sound cues from the headphones.

Walk speed and stride length variability were quantified to represent motor performances. Single-task motor performance was the speed and stride length variability of their self-selected-pace walk (alone). The dual-task motor performance wa the walking speed and stride length variability at their self-selected-pace walk while responding to the 2-back task.

2.6 Measurement and analysis of PFC oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb)

The concentration changes of HbO_2 (ΔHbO_2) and HHb (ΔHHb) were measured with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands). This system utilizes near-infrared lights, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in the cortical layer. The lights were transmitted with two different wavelengths, 760 and 850 nm. Based on different Hb absorption spectra, concentration changes of HbO_2 and HHb in the PFC area are calculated from the changes in detected light intensity. The calculation was done using the modified Lambert-Beer law, assuming constant light scattering [48]. A probe of PortaLite has three transmitters and one receiver, with transmitter-receiver distances of 30, 35, and 40 mm. The differential pathlength factor (DPF) was specified for DPF807, which is determined using the formula: DPF807 = 4.99 + (0.067 x $Age^{0.814}$) [49], and data were sampled with a frequency of 10 Hz.

Two probes were placed on the forehead of the participants, at a height corresponding to 10 % of the nasion-inion distance from nasion, and the middle of the device was placed at 5 % of the head circumference to the left and right from midline, corresponding to the Fp1 and Fp2 according to the international EEG 10–20 system. These locations roughly target left and right Brodmann's areas 9 and 10, which represent the dorsolateral and anterior PFC. Probes were shielded from ambient light with a black cloth fixed by an elastic strap. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection.

Measurement started with a measure of resting PFC oxygenation in a sitting condition for 2 minutes. During the practice phase, no PFC oxygenation data was acquired. During the 2-back task conditions, the last 30 s of each block was used as a measurement of PFC oxygenation. In the dual-task condition,

the PFC oxygenation values from the self-selected pace walking block were subtracted to isolate the dual-task condition. The PortaLite uses wireless technology (Bluetooth), gives a possibility to measure the cerebral oxygenation during walking without restriction of wires. During the experimentation, tight fitting band and no long wires pulling on optode were applied in order to minimize noise in the hemodynamic signals. For the same objective, our participants were asked to always facing forward during the test, avoid making a sudden head movement, clenching their jaw, frowning, and other facial expressions.

NIRS data analysis was performed on unfiltered data. The artifacts in the signal were identified by visual inspection and replaced by interpolation of adjacent data. Conversion of optical density to HbO_2 and HHb signals occurred in the oxysoft software with the modified Beer-Lambert law. The change in prefrontal oxygenation was calculated as the average of the three channels of NIRS in the same side of prefrontal cortex. As in all fNIRS calculations the experimental condition activity was subtracted from the baseline activity in order to have a change in cerebral oxygenation for each condition.

2.7 Statistical Analysis

Normal Gaussian distribution of the data was verified by the Shapiro-Wilk test, and homogeneity of variance by a modified Levene test. Independent t-test was used to compare means between characteristics of groups and subgroups. Mann-Whitney Test was used when homogeneity of variance or normality of distribution between groups or subgroups was violated. The magnitude of the difference for each test was assessed by Cohen's *d*. The scale proposed by Cohen [50] was used for interpretation. The magnitude of the difference was considered small (0.2), moderate (0.5), or large (0.8). Three-way 2 x 2 x 2 ANOVAs with the following design: fitness (high-fit vs. low-fit) x MAP (higher-MAP vs. lower-MAP) x 2-back conditions (single-task vs. dual task) as independent variables, with 2-back accuracy and PFC oxygenation parameters (HbO_2, HHb, and tHb) as dependent variables. Tukey's post-hoc test were conducted for the cognitive performance, motor performance, and PFC oxygenation data. Since there was no control group, the pooled standard deviation was used to compute this statistic. The association between CRF or MAP and cognitive performance was tested using nonparametric Spearman's rank correlation test using the data from all participants as a continuum. Statistical significance was set at $\alpha \leq 0.05$ level for all analysis. All calculations were made with Statistica 7.0 (StatSoft, Tulsa, USA). The values are presented as mean ± SD.

3. RESULTS

Characteristics of our participants are presented in Table 1. As expected, we found a large difference in the VO_{2peak} for high-fit (M = 56.0, SD = 6.7) and low-fit (M = 36.7, SD = 4.1) group, $t(22) = 8.54$, $p < .001$, $d = 3.5$. Average $\dot{V}O_2peak$ of the high-fit group corresponded to the 90th percentile of the ACSM norm [51], while the low-fit group was ranked in the 20th percentile. Although both groups could be considered as normotensive (i.e., 24-hour APBM < 130/80 mmHg), low-fit individuals had higher MAP levels (M = 90.8, SD = 6.1) than high-fit individuals (M = 82.8, SD = 5.9), $t(22) = -3.23$, $p = .003$, d = 1.3. More precisely, the difference was

reported in the diastolic blood pressure in high-fit (M = 67.6, SD = 6.8) and low-fit (M = 80.3, SD = 7.9) group, $t(22) = -4.18$, $p < .001$, $d = 1.7$, but not in the systolic blood pressure. The characteristic differences between CRF groups were also found in weight; high-fit (M = 68.3, SD = 5.8) and low-fit (M = 79.8, SD = 16.8), $t(22) = -2.23$, $p = .04$, $d = 0.9$, and in body mass index (BMI); high-fit (M = 21.9, SD = 2.4) and low-fit (M = 26.2, SD = 5.3), $t(22) = -2.52$, $p = .02$, $d = 1.0$.

Within the CRF category, in the high-fit group, we found a large MAP difference between lower-MAP (M = 78.3, SD = 4.7) and higher-MAP (M = 87.3, SD = 2.9) group, $t(10) = -3.95$, $p < .002$, $d = 2.3$. Also a large difference in systolic blood pressure; lower-MAP (M = 110.0, SD = 4.8) and higher-MAP (M = 116.2, SD = 3.1), $t(10) = -2.66$, $p = .02$, $d = 1.5$, and in diastolic blood pressure; lower-MAP (M = 62.5, SD = 5.0) and higher-MAP (M = 72.8, SD = 3.7), $t(10) = -4.06$, $p < .002$; $d = 2.3$. In the low-fit group, we found a large MAP difference between lower-MAP (M = 86.9, SD = 1.8) and higher-MAP (M = 94.6, SD = 6.6) group, $t(10) = -2.73$, $p = .02$, $d = 1.6$. As well a large difference in the diastolic blood pressure, lower-MAP (M = 75.2, SD = 4.6) and higher-MAP (M = 85.5, SD = 7.3), $t(10) = -2.91$, $p = .01$, $d = 1.7$, but not in the systolic blood pressure.

No differences were found in age, height, MoCA score and years of education both between CRF groups and MAP subgroups.

Characteristics of the CRF groups and MAP subgroups are presented in Table 1. Cognitive and motor performances during single-task and dual-task conditions are presented in Table 2, Figure 2 and Figure 3, while PFC oxygenation characteristics are shown in Table 3.

Motor Performance

There was a main effect of task condition on motor performance ($F_{(1,20)}$ = 68.02, p = 0.001), indicating that the stride length variability (CoV) for single-task motor condition (M = 0.9, SD = 0.2) was significantly lower than the dual task condition (M = 1.4, SD = 0.4). No interaction was found between cognitive task condition and CRF on the stride length variability. Neither main effect nor interaction was found between walking speed and CRF.

CRF and Cognitive Performance

The ANOVA revealed a main effect of condition on 2-back accuracy ($F_{(1,20)} = 4.45$, p = .047), indicated that the accuracy for the single task condition (M = 97.73%, SD = 3.03) was significantly greater than the dual task condition (M = 95.73%, SD = 5.84). Also, there was a main effect of CRF on 2-back accuracy ($F_{(1,20)}$ = 8.49, p = .009), showing that the overall accuracy for the high-fit participants (M = 98.58%, SD = 3.07) was significantly greater than the low-fit participants (M = 94.88%, SD = 5.36). The ANOVA also revealed a significant interaction between the cognitive task condition and CRF on 2-back accuracy ($F_{(1,20)}$ = 8.93, p = .007). Post-hoc analyses indicated that low-fit participants was significantly less accurate in dual-task condition, as compared to single-task condition (p = .02), but there was no difference between conditions in high-fit participants. Also, post-hoc analyses revealed that dual-task performance are better for higher fit participants compared to lower fit participants (p = .04). These results are presented in the Figure 2. These results were

confirmed by a positive correlation between $\dot{V}O_2$peak and 2-back accuracy (r = .57, p = .003).

CRF and Cerebral Oxygenation

Neither main effect nor interaction was found in both side of PFC on ΔHbO_2. The ANOVA performed on relative changes in ΔHHb showed a main effect of CRF on ΔHHb ($F_{(1,20)}$ = 7.98, p = .01) in the right PFC, indicating that the ΔHHb for the high-fit participants (M = -0.31, SD = 0.28) was significantly greater than the low-fit participants (M = -0.11, SD = 0.21). A correlation between $\dot{V}O_2$peak and ΔHHb was confirmed (r = -.43, p = .03). In the left PFC, there was a main effect of CRF on ΔHHb ($F_{(1,20)}$ = 4.43, p = .048), indicating that the ΔHHb for the high-fit participants (M = -0.21, SD = 0.15) was significantly greater than the low-fit participants (M = -0.12, SD = 0.13). A correlation between $\dot{V}O_2$peak and ΔHHb was also confirmed (r = -.46, p = .02).

MAP and Cognitive Performance

The ANOVA reported a significant interaction between the cognitive task condition and MAP on 2-back accuracy ($F_{(1,20)}$ = 4.27, p = .04) in healthy younger adults, in which higher-MAP participants were significantly less accurate in dual-task condition, compared to single-task condition (p = .03), but there were no differences between conditions in lower-MAP participants. The results are presented in the Figure 2. Again, these results were further supported by a significant correlation between MAP and dual task 2-back accuracy (r = -.55, p = .005).

Finally we performed an exploratory analysis to test the possible interaction between CRF, MAP and cognitive task condition on 2-back accuracy. The results are presented in Figure 3. Although the interaction does not reach statistical significance ($F_{(1,20)}$ = 3.91, p = .06)., it seems that MAP modulates the general effect described previously between CRF and cognitive performance. This result seems to support that lower-fit with higher-MAP group have poorer dual-task performance compared to others groups. The small sample size does not allow to provide a definitive answer, but this results underscore the need for further investigations.

MAP and Cerebral Oxygenation

The ANOVA revealed no effect of MAP on cerebral oxygenation.

4. DISCUSSION

The study investigated the interactions between CRF, MAP, PFC oxygenation and WM performances in healthy young males. Based on the literature, we hypothesized that individuals with high-CRF would have better WM performances than individuals with low-CRF. Our main findings were that 1) only lower fit participants demonstrated dual-task performance costs in WM (Dual task < Single), while higher-fit participants maintained their performance level and 2) PFC oxygenation during the dual-task condition, specifically in ΔHHb, was greater in high-fit participants compared to lower fit. 3) Neither walking speed nor stride length variability during the 2-back task was associated with CRF. 4) MAP did not

significantly change association between CRF and WM performances.

Regarding motor performance, although there was a main effect of conditions that both groups had better motor control in single-task condition than in dual-task condition, no significant main effects of CRF or interactions with CRF and conditions were found suggesting that task conditions had the same effect in both CRF-group. The increased stride length variability in dual-task condition in both groups suggests that, even in healthy young males, walking is not a purely motor task. A dual-task study by Bloem et al. (2001) in 50 healthy young and 13 healthy elderly participants showed that healthy participants prioritize performance of motor tasks over performance of cognitive tasks [52]. Moreover, the younger participants were more likely to use this strategy than older adults. Based this finding, it seems that in healthy young individuals, a self-paced motor task may be a less sensitive parameter than cognitive task performance when examining the influence of CRF on dual-task performance.

Regarding 2-back accuracy, we found a main effect of CRF, since high-fit individuals were more accurate than low-fit individuals. We also found an interaction between CRF and 2-back conditions, suggesting that this effect of CRF was specific to the dual-task condition. Specifically, the increased the complexity of the task (i.e., from a seated single-task to dual-task walking) resulted in a higher error rate in low-fit individuals than high-fit individuals. This finding is in line with the literature on CRF-related differences in working memory in Agbangla et al. (2019), in which high-fit older adults showed were more accurate in the 3-back condition but not in 1- or 2-back condition [28]. This higher sensitivity of highly demanding cognitive tasks to CRF has already been underscored in older adults [53]. Indeed, Dupuy et al [53], reported that higher fit older adults had better cognitive performance and lesser error rate in visual-auditory dual-task performance than lower fit counterparts. All these results suggest that a good CRF allows for better cognitive performance in cognitively demanding tasks that involve executive functions. These results support the hypothesis, that executive function is the most sensitive cognitive function to CRF [54].

Several underlying neurophysiological mechanisms could explain our results. The CRF is associated to greater white and grey matter of the brain and more particularly of the PFC [28]. Also, structural modifications in the blood vessels are observed in subjects with better CRF [55]. These changes are often accompanied by increased cerebral blood flow and brain oxygenation in older subjects [32], [35], [53]. Neuronal activation consumes energy which are met by oxidation of lactate present in the extracellular space, resulting in a temporary decrease in lactate levels and oxygen concentrations [56]. Neurovascular response resulting in larger arteriole dilation and greater blood flow at the activated brain regions, consequently providing a temporary increase in HbO_2 and relative decrease in HHb, due to the increased HbO_2 concentration [57].

It is a continuing discussion in the fNIRS studies to determine which parameter (HbO_2 or HHb) is best for capturing relevant cerebral hemodynamic changes. HbO_2 is reported produce higher signal-to-noise ratio [58], higher reproducibility [59], [60], and be more sensitive to the changes in regional

blood flow [61] especially in participants with pathologies [62] than HHb. HHb described to have less physiological noise [30], [63] and spatially more focused than HbO_2 [64], [65]. Also, the inverse relationship between HHb and blood oxygenation level dependent (BOLD) signal of fMRI has been reported by Ekkekakis (2009) and Strangman et al. (2002) [58], [66].

In our study, concerning the changes in PFC oxygenation, we found that high-fit individuals had a greater decrease in ΔHHb than low-fit individuals in both hemispheres. The absence of interaction between CRF and task conditions on ΔHHb suggested that this difference was true for both. single-task and dual-task. This observation was supported by the association between $\dot{V}O_2$peak and dual-task ΔHHb in the right and left PFC. Altogether, these results showed that healthy young males with greater CRF displayed a greater decrease of ΔHHb in both hemispheres of PFC during a dual-task. Moreover, this relation supports the CRF hypothesis that PFC hemodynamic is influenced by the regulation of the cardiovascular system [67]. According to this hypothesis, high-fit individuals have a greater regional cerebral blood flow and therefore a greater potential for PFC activation, which could contribute to their better executive performances [32].

Using fNIRS technique, this study confirms that higher fit participants displayed greater cortical activation during executive task [68]. Furthermore, in contrast to a recent study that reported a greater ΔHbO_2 during n-back task in higher-fit older adults compared to their lower-fit counterpart [11], our study reports no difference in ΔHbO_2 between groups in both task conditions. Aside from a difference in age group, it should be noted that the change in PFC hemodynamics in this study was measured in dual-task walking paradigm whereas the participants were sitting in study of Agbangla et al. [11]. An alternate explanation for these differences between studies is the duration of our dual-task condition. Indeed, Agbangla et al [11], reported the evolution of PFC hemodynamics during 0-,1-,2 and 3-back tasks and showed that ΔHbO_2 concentration increased progressively from the beginning to the end of their task, which lasted 140-seconds [11]. Considering these results, the shorter duration (30 seconds) of 2-back task in this study may not allow us to observe the complete kinetics of HbO_2 concentration.

In our study, we were also interested in determining the effect of MAP on cognitive performance during a dual-task. We observed that participants with a lower-MAP had a better WM performance during the dual task than those with a higher-MAP. This result supports previous studies examining the relationship between elevated resting blood pressure and poorer cognitive performance on attention [69] and visualization/fluid score of the Wechsler Adult Intelligence Scale (WAIS) [70] in young adults. One of the potential physiological mechanisms involved in this relationship is altered cerebrovascular reactivity [71]. In the study of Settakis et al. (2003) which investigated 113 hypertensive and 58 normotensive young adults, there investigators reported that the hypertensive group have smaller change in mean and diastolic blood flow velocities after breath-holding compared to the normotensive group [72]. This result suggesting decreased cerebrovascular reactivity in hypertensive young adults compared to their normotensive counterparts. Another study from Wong et al. (2011) investigated relationship between blood pressure and cerebral vasoreactivity in 56 children and adolescents [73]. All of the

subjects in this study were examined by transcranial Doppler in the middle cerebral artery while rebreathing carbon dioxide with a plastic bag [73]. The result shown that baseline diastolic blood pressure (DBP) was inversely related to cerebral vasoreactivity [73]. All of those results displayed evidence of a relationship between hypertension and altered cerebrovascular reactivity in young adults. However, we also observed that CRF could modulate this effect of MAP on WM. Although these results should be viewed as exploratory considering the small sample size of subgroups (n=6), we found a tendency toward an interaction between CRF, MAP and cognitive performance. Low-fit participants with a higher MAP displayed poorer 2-back accuracy than all other profiles. Taken together, our results suggest that high CRF in young males is associated with greater PFC oxygenation (ΔHHb) and better WM performance in a dual-task condition.

4.1 Limits and perspectives

The focus of this study on a single sex (males) is to limit the gender bias due to influence of estrogen on PFC, but we aware that this limits generalizability of findings in younger adults. A replication of this study with young females is needed. The small sample size of subgroups (n=6) necessitates caution in interpreting the results of the 3-way ANOVA. However, they provide very interesting outcomes that should be tested in a larger sample. CRF is determined by life habits, including physical activity (PA), and genetic factors. Since we have no direct measure of both PA and genetic factors, it is not possible to determine the extent by which they contribute to the observed differences in cognition. Regarding cognitive performance, there is a possibility that CRF and/or MAP could also influence the reaction time in the 2-back task. Therefore, we highly recommend future studies using a 2-back task to investigate both reaction time and accuracy. In addition, NIRS is an indirect measure of brain or neuronal activities. It has several limitations such as lower spatial resolution and lack of sensitivity to deeper brain areas.

The fNIRS signal pre-processing that was used in this study may have underestimated the impact of motion artifacts. In this study we have not performed the filtering of the NIRS signals and detrending of segments that could lead to contamination of the fNIRS data with physiological or body movement noise. Converging evidence from NIRS with EEG and fMRI is need to provide a more comprehensive understanding of the dynamics of cerebral activation. Also, the utilization of a multi-channel NIRS setup can also help to observe the oxygenation profiles and activities of other brain regions compared to the two-channel setup in this study. Analyzing PFC hemodynamic in dual-task walking with longer duration (> 3 minutes) is needed to understand the complete hemodynamic profile of this paradigm. As differences in PFC oxygenation could be interpreted as a difference in concentration of oxyhemoglobin (ΔHbO_2) and deoxyhemoglobin (ΔHHb), their values are relative to their total concentration in blood and CBF. Therefore, measurements of total hemoglobin and CBF are needed in further studies to obtain a comprehensive understanding of the role of cerebral oxygenation. We did not have a wide range of blood pressure levels (from hypotension to hypertension) in participants of our study. This may underestimate the effect of blood pressure on brain activation and cognitive performance. In future studies, it would be beneficial to include a broader range of blood pressure levels in young adults to observe the

relationship between blood pressure and cognitive performance on dual-task condition.

5. CONCLUSION

This study supports the positive effect of higher CRF on WM performance in healthy young males. The results indicated that the high-fit individuals performed better in dual-task conditions than low-fit individuals. Moreover, greater PFC oxygenation in the ΔHHb measure was demonstrated in higher CRF group. Also, lower blood pressure tends to be associated with better dual-task performance. Consequently, healthy young males with high cardiorespiratory fitness may be able to perform better in the activities that require working memory, especially while walking.

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Figure caption

Figure 4: Conceptual framework for links between fitness level, cognitive performance in dual-task condition, mean arterial blood pressure and PFC oxygenation.

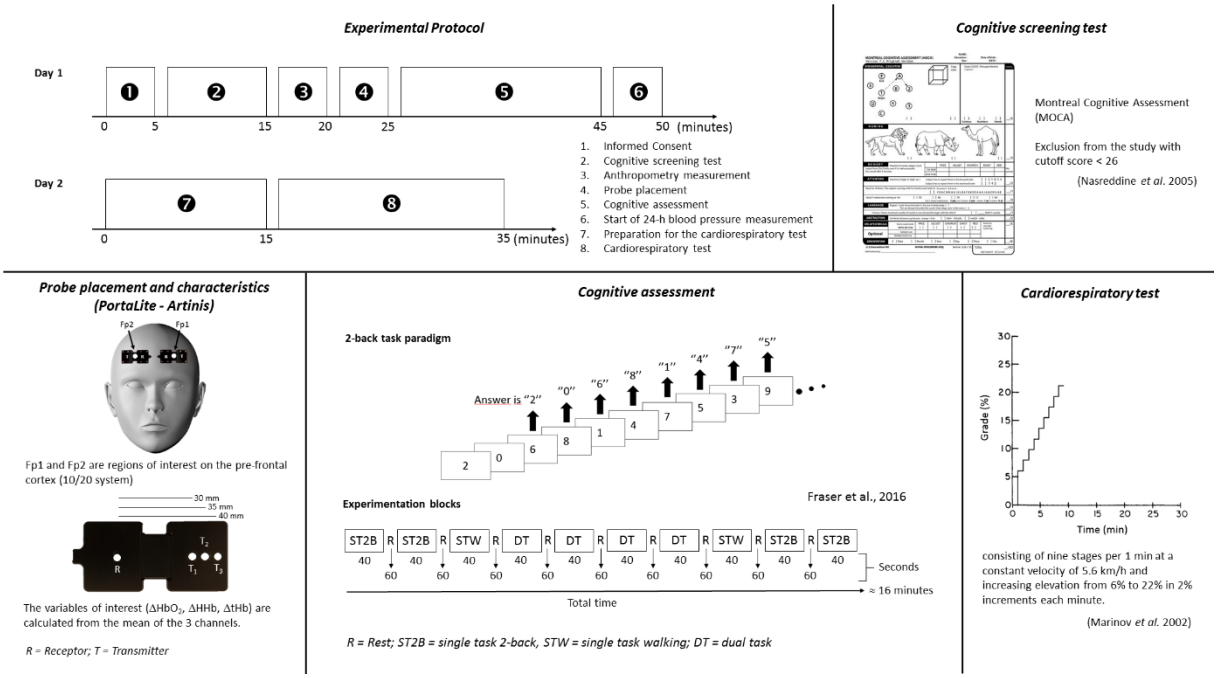

Figure 1: Experimentation protocol and information of methods

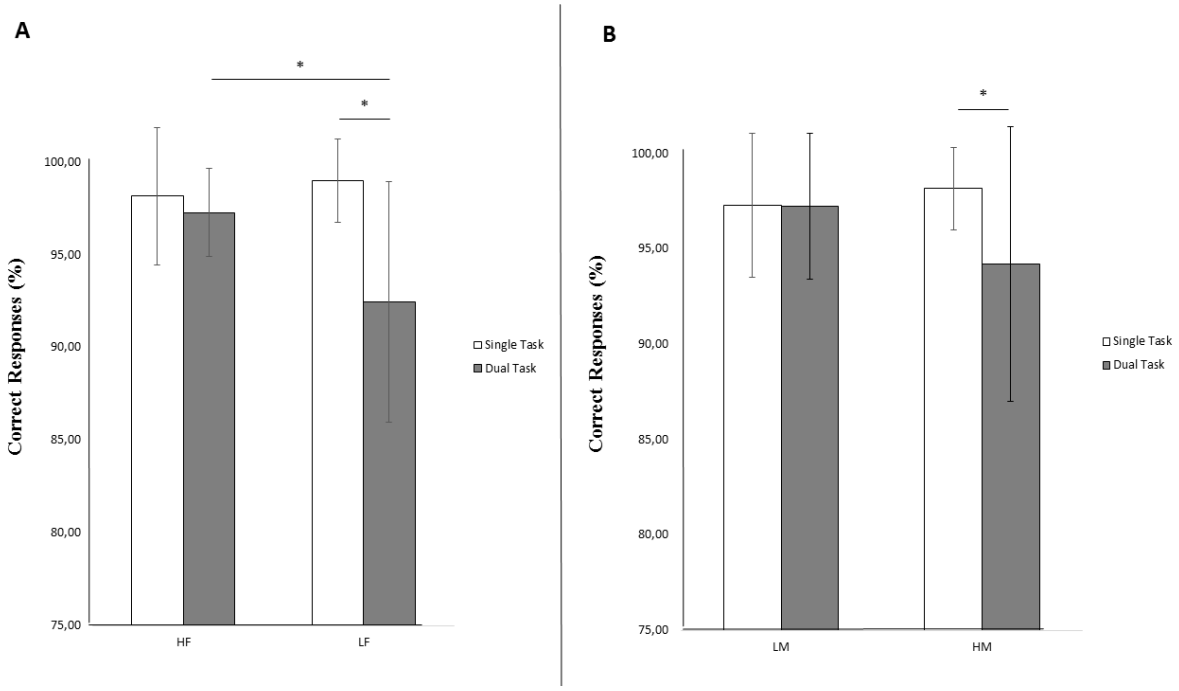

Figure 2: Impact of cardiorespiratory fitness (A) and mean arterial pressure (B) on cognitive performance (% correct responses) during single and dual-task conditions. Data are presented as mean and SD. *: $p < 0.05$. (HF: High-fit; LF: Low-fit; LM: Low mean arterial pressure; HM: High mean arterial pressure)

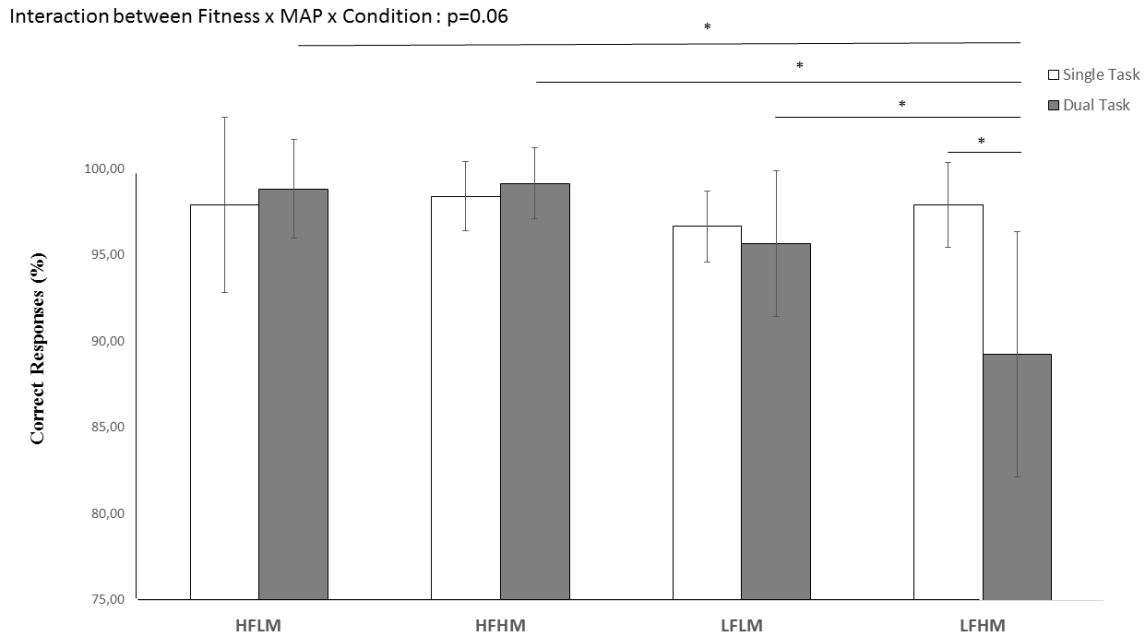

Figure 3: Cognitive performance (% correct responses) during single and dual-task for HFLM, HFHM, LFHM, LFLM participants. Data are presented as mean and SD. *: $p < 0.05$. (HFLM: High-Fit Low-MAP; HFHM: High-Fit High-MAP; LFLM: Low-Fit Low-MAP; LFHM: Low-Fit High-MAP)

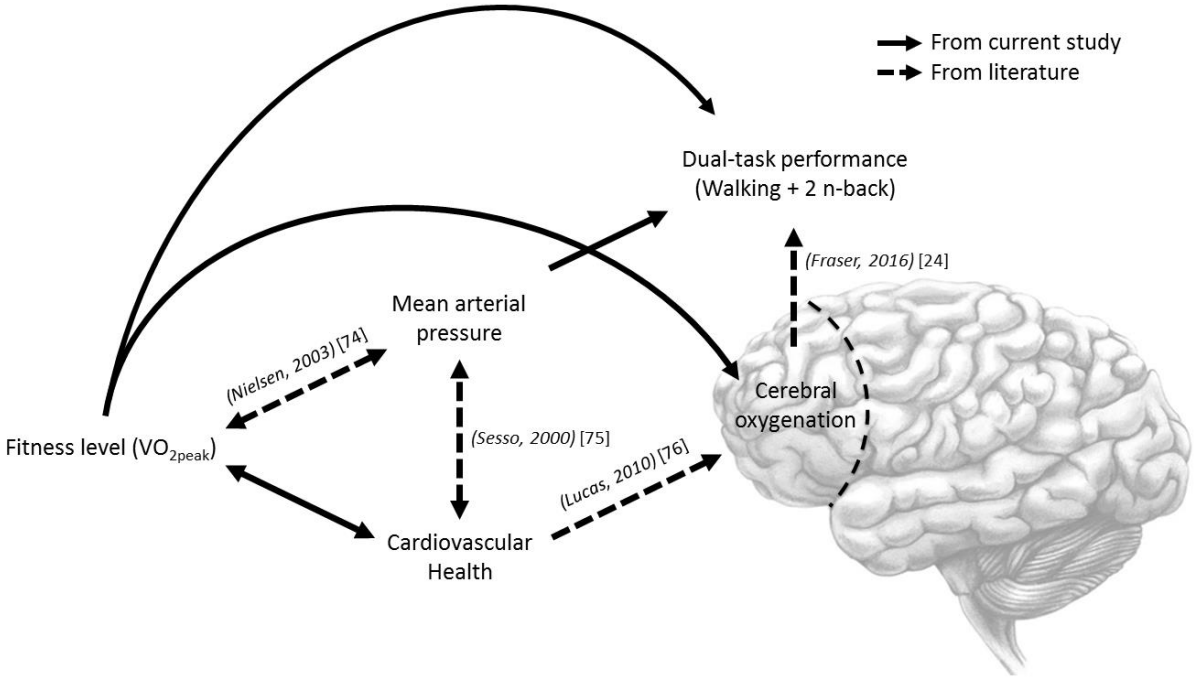

Figure 4: Conceptual framework for links between fitness level, cognitive performance in dual-task condition, mean arterial blood pressure and PFC oxygenation.

Table 1. Characteristics of study participants. Data are presented as means and standard deviations (SD)

	Overall (n=24)	High-Fit (n=12)	Low-Fit (n=12)	Cohen's d +	High-Fit (n=12)		Cohen's d	Low-Fit (n=12)		Cohen's d
					Lower MAP (n=6)	Higher MAP (n=6)		Lower MAP (n=6)	Higher MAP (n=6)	
Age	23.8	22.8	24.8	0.4	23.8	21.7	0.5	22.7	26.8	0.8
(yr)	(4.8)	(4.2)	(5.1)		(5.3)	(2.7)		(4.7)	(5.0)	
Height	175.5	176.6	174.5	0.3	178.3	174.8	0.5	173.3	175.7	0.3
(cm)	(6.5)	(6.5)	(6.7)		(7.0)	(6.0)		(6.5)	(7.2)	
Weight	74.1	68.3	79.8 *	0.9	70.4	66.2	0.8	70.7	88.9	1.2
(kg)	(13.6)	(5.8)	(16.9)		(3.9)	(6.9)		(9.7)	(18.2)	
BMI	24.1	22.0	26.2 *	1.0	22.2	21.7	0.2	23.5	28.9	1.1
(%)	(4.0)	(2.4)	(5.3)		(1.3)	(3.3)		(3.0)	(6.0)	
Overweight & Obese (n;%)	(3;13%)	(0;0%)	(3;25%)		(0;0%)	(0;0%)		(1;17%)	(2;33%)	
$\dot{V}O_2$peak	46.1	56.0	36.7 *	3.5	58.8	53.2	0.9	37.7	35.7	0.5
($ml.kg^{-1}.min^{-1}$)	(9.9)	(6.7)	(4.1)		(6.4)	(6.2)		(3.0)	(5.0)	
RER	1.19	1.23	1.18	0.6	1.25	1.21	0.5	1.17	1.19	0.2

	(0.09)	(0.08)	(0.08)		(0.08)	(0.07)		(0.09)	(0.07)	
RPE	16.2	16.6	15.9	0.5	17.0	16.7	0.5	15.3	16.3	0.8
	(1.4)	(1.6)	(1.3)		(1.8)	(1.5)		(0.8)	(1.6)	
MAP24h	86.9	82.8	90.8 *	1.3	78.3	87.3 #	2.3	86.9	94.6 #	1.6
(mmHg)	(7.0)	(6.0)	(6.1)		(4.7)	(3.0)		(1.8)	(6.6)	
Systolic Pressure (mmHg)	112.4	113.8	111.7	0.2	110.0	116.2 #	1.5	110.5	112.8	0.3
	(6.7)	(5.0)	(7.7)		(4.8)	(3.1)		(7.4)	(8.5)	
Diastolic Pressure	74.0	67.7	80.3 *	1.7	62.5	72.8 #	2.3	75.2	85.5 #	1.7
(mmHg)	(9.2)	(6.8)	(8.0)		(5.0)	(3.7)		(4.6)	(7.3)	
MoCA	28.6	28.4	28.8	0.3	28.8	28.0	0.6	28.3	29,2	0.8
(points)	(5.4)	(1.5)	(1.1)		(1.6)	(1.4)		(1.2)	(1.0)	
Education	14.5	13.9	15.1	0.5	14.2	13.7	0.1	14.2	16.0	0.6
(years)	(2.3)	(2.2)	(2.2)		(2.5)	(2.2)		(2.2)	(2.0)	
0-back	100	100	100	0.0	100	100	0.0	100	100	0.0
(% correct)	(0)	(0)	(0)		(0)	(0)		(0)	(0)	

$\dot{V}O_2$peak, peak oxygen uptake; RER, respiratory exchange ratio; RPE, rated perceived exertion; MAP24h, mean arterial pressure over 24-hour. * different from High-Fit ($p < 0.05$); # different from Lower-MAP in same group ($p < 0.05$); + effect size of the difference between high-fit and low-fit groups

Table 2. Cognitive and motor performance during single task and dual-task conditions. Data are presented as mean (SD)

	Overall (n=24)	High-Fit (n=12)	Low-Fit (n=12)	Cohen's d [+]
2-back accuracy (% of correct responses)				
Single task	97.9 (2.9)	98.2 (3.7)	97.3 (2.3)	0.3
Dual task	95.9 (5.5)	99.0 (2.4)	92.5 (6.5) *	1.3
Walking speed ($m.s^{-1}$)				
Single task	1.42 (2.9)	1.45 (3.7)	1.41 (2.3)	0.5
Dual task	1.37 (5.5)	1.39 (2.4)	1.36 (6.5) *	0.7
CoV of stride length				
Single task	0.9 (0.2)	1.0 (0.2)	0.9 (0.1)	0.5
Dual task	1.4 (0.4)	1.4 (0.3)	1.4 (0.3)	<0.2

$m.s^{-1}$, meter per second; CoV, coefficient of variation

* different from High-Fit ($p < 0.05$);

Table 3. Cerebral oxygenation changes from baseline during the 2-back task in single and dual-task conditions. Data are presented as mean (SD).

	Overall (n=24)		High-Fit (n=12)		Low-Fit (n=12)		Cohen's d [+]	High-Fit (n=12)				Cohen's d	Low-Fit (n=12)				Cohen's d
								Lower MAP (n=6)		Higher MAP (n=6)			Lower MAP (n=6)		Higher MAP (n=6)		
Single Task																	
Right PFC																	
ΔHbO_2 (umol.L^{-1})	0.64	(0.89)	0.52	(1.24)	0.67	(0.57)	0.2	0.84	(1.63)	0.19	(0.69)	0.5	0.90	(0.56)	0.45	(0.52)	0.8
ΔHHb (umol.L^{-1})	-0.25	(0.23)	-0.29	(0.27)	-0.15	(0.20)	0.6	-0.37	(0.33)	-0.22	(0.19)	0.6	-0.22	(0.08)	-0.07	(0.25)	0.8
$\Delta HbDiff$ (umol.L^{-1})	0.79	(1.04)	0.81	(1.45)	0.82	(0.65)	<0.2	1.21	(1.94)	0.41	(0.66)	0.6	1.13	(0.64)	0.52	(0.55)	1.0
Left PFC																	
ΔHbO_2 (umol.L^{-1})	0.35	(0.44)	0.24	(0.54)	0.42	(0.46)	0.4	0.31	(0.71)	0.17	(0.36)	0.2	0.58	(0.58)	0.27	(0.26)	0.7
ΔHHb (umol.L^{-1})	-0.19	(0.14)	-0.19	(0.12)	-0.14	(0.16)	0.4	-0.24	(0.13)	-0.15	(0.10)	0.7	-0.20	(0.16)	-0.08	(0.15)	0.8
$\Delta HbDiff$ (umol.L^{-1})	0.54	(0.53)	0.43	(0.61)	0.56	(0.59)	0.2	0.55	(0.78)	0.32	(0.41)	0.4	0.78	(0.72)	0.34	(0.36)	0.7

Dual Task																
Right PFC																
ΔHbO_2 (umol.L^{-1})	0.50	(0.90)	0.30	(1.07)	0.99	(0.54)	0.8	-0.10	(1.02)	0.70	(1.05)	0.7	1.20	(0.66)	0.77	(0.32)	0.8
ΔHHb (umol.L^{-1})	-0.17	(0.27)	-0.33	(0.29)	-0.06	(0.21) *	1.1	-0.28	(0.25)	-0.38	(0.34)	0.3	-0.22	(0.11)	0.09	(0.17) #	2.1
ΔHbDiff (umol.L^{-1})	0.67	(1.00)	0.63	(1.21)	1.05	(0.69)	0.4	0.18	(1.20)	1.08	(1.15)	0.7	1.42	(0.73)	0.68	(0.42)	1.2
Left PFC																	
ΔHbO_2 (umol.L^{-1})	0.21	(0.47)	0.16	(0.59)	0.50	(0.27)	0.7	-0.09	(0.48)	0.40	(0.62)	0.9	0.60	(0.32)	0.39	(0.17)	0.8
ΔHHb (umol.L^{-1})	-0.15	(0.16)	-0.23	(0.17)	-0.09	(0.14) *	0.9	-0.21	(0.18)	-0.25	(0.19)	0.2	-0.17	(0.11)	0.00	(0.12) #	1.5
ΔHbDiff (umol.L^{-1})	0.35	(0.54)	0.39	(0.70)	0.58	(0.36)	0.3	0.13	(0.58)	0.65	(0.75)	0.7	0.77	(0.36)	0.39	(0.26)	1.2

MAP, mean arterial pressure over 24-hour; PFC, Pre-frontal cortex; ΔHbO_2, changes in oxyhemoglobin concentrations; ΔHHb, changes in deoxyhemoglobin concentrations; ΔHbDiff, (ΔHbO_2-ΔHHb) as an index of brain oxygenation.

* different from Higher-Fit ($p < 0.05$); # different from lower MAP in same group ($p < 0.05$); + between Higher-Fit and Lower-Fit

3 Study 3

3.1 Resume

Master Athletes and Cognitive Performance: What are the Potential Explanatory Neurophysiological Mechanisms?

Description of Study 3

Regular physical activity has been recognized as an effective strategy for limiting the cognitive decline observed during aging. Much evidence has supported that maintaining a high level of physical activity (PA) and cardiorespiratory fitness (CRF) is associated with better cognitive performances across the lifespan. From childhood to adulthood, a high level of physical activity will have a positive impact on cerebral health. More specifically, executive performance seems to be preferentially affected by the level of fitness. This is partly because the prefrontal cortex, which governs these functions, seems to be very sensitive to physical activity levels. A question then arises as to what the neurophysiological mechanisms that explain the improvement of the cognitive performance as well the optimal dose of physical activity is to observe these effects on our brain. An example of successful aging is the Master Athletes. This category of people who have been training and competing throughout their lives and demonstrate high levels of fitness induced by a high level of physical activity. Some studies seem to confirm that Master Athletes have better cognitive performances than sedentary or less active subjects. This review aims to identify studies assessing the cognitive performance of Master Athletes and report on the probable neurophysiological mechanisms that explain the cognitive benefits in this population.

The main results of this study are:

- In older adults, higher fitness level is associated with better performance in several executive function tests. Even though the limited number of studies available makes it difficult to draw definitive conclusions.
- Greater gray matter volume and white matter integrity were related to the CRF but less consistently related to PA, and at least 12 weeks of aerobic exercise program are required for giving advantageous effects compared to control.
- Several authors reported that better cognitive performance in master athletes was associated with the greater amplitude of cerebral oxygenation during exercise or cognitive tasks.

- CRF appears to improve arterial stiffness and vascular reactivity thus preserving cognitive decline in the elderly
- Acute and chronic exercise influence the brain through several factors, such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF)

3.2 Article

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ARTICLE

Master Athletes and cognitive performance: What are the potential explanatory neurophysiological mechanisms?

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Abstract - Regular physical activity has been recognized as an effective strategy for limiting the cognitive decline observed during aging. Much evidence has supported that maintaining a high level of physical activity and cardiorespiratory fitness is associated with better cognitive performances across the lifespan. From childhood to adulthood, a high level of physical activity will have a positive impact on cerebral health. More specifically, executive performance seems to be preferentially affected by the level of fitness. This is partly because the prefrontal cortex, which governs these functions, seems to be very sensitive to physical activity levels. Today many neurophysiological mechanisms that explain the improvement of the cognitive performance are relatively well identified. A question then arises as to what is the optimal dose of physical activity to observe these effects on our brain. An example of successful aging is the example of the Master Athletes. This category of people who have been training and competing throughout their lives, demonstrate high levels of fitness induced by a high level of physical activity. Some studies seem to confirm that Master Athletes have better cognitive performances than sedentary or less active subjects. The aim of this review is to identify studies assessing the cognitive performance of Master Athletes and report on the probable neurophysiological mechanisms that explain the cognitive benefits in this population.

Key words: Master Athletes, cognition, brain, neurophysiology, mechanisms

Résumé - Master Athletes et performances cognitives : quels sont les mécanismes neurophysiologiques explicatifs potentiels ? L'activité physique régulière est reconnue comme une stratégie efficace pour limiter le déclin cognitif observé au cours du vieillissement. De nombreuses preuves scientiques ont démontré que le maintien d'un niveau élevé d'activité physique et d'une bonne condition cardiorespiratoire étaient associés à de meilleures performances cognitives tout au long de la vie. De l'enfance à l'âge adulte, un niveau élevé d'activité physique aura un impact positif sur la santé cérébrale. Plus spécifiquement, les performances executives semblent être affectées de manière préférentielle par le niveau de condition physique. Cela tient en partie au fait que le cortex préfrontal, qui régit ces fonctions, semble être très sensible aux niveaux d'activité physique. Aujourd'hui, de nombreux mécanismes neurophysiologiques expliquant l'amélioration des performances cognitives sont relativement bien identifiés. Une question se pose alors de savoir quelle est la dose optimale d'activité physique pour observer ces effets sur notre cerveau. Un exemple de vieillissement réussi est l'exemple des « master athletes ». Cette catégorie de personnes qui se sont entraînées et qui ont participé à des compétitions tout au long de leur vie font preuve d'une bonne condition physique induite par un niveau élevé d'activité physique. Certaines études semblent confirmer que les master athlètes ont de meilleures performances cognitives que les sujets sédentaires ou moins actifs. Le but de cette revue est de rapporter les études évaluant les performances cognitives des master athlètes et de rapporter les mécanismes neurophysiologiques probables qui expliquent les bénéfices cognitifs dans cette population.

Mots clés : Master Athlètes, cognition, cerveau, neurophysiologie, mécanismes

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1 Introduction

The aging process is associated with structural and functional changes in the brain such as atrophy of both white and grey matter (Colcombe, *et al.*, 2003) and impairment of vascular function (Lucas, *et al.*, 2012; Murrell, *et al.*, 2011a, b). These alterations in cerebrovascular functions and structural changes are associated with cognitive decline, increased risk of stroke and neurodegenerative diseases like Alzheimer's (de la Torre, 2010a, b) and Parkinson's disease (Wan, *et al.*, 2019). One brain region that demonstrates a more rapid atrophy than other brain regions is the prefrontal cortex (PFC) (Yuki, *et al.*, 2012), a region that has been associated with executive functions (planning, switching, coordinating; [Miyake, *et al.*, 2000]). Cognitive aging is more associated to a decline in executive function than crystallized function in cognitive domain (Drag & Bieliauskas, 2010; Salthouse, 2010), in part due to these rapid changes in the PFC.

However, the cognitive decline during "normal" aging (non-pathological) seems to be slowed down by positive health factors, such as regular physical activity and cardiorespiratory fitness (CRF) (Bherer, 2015; Bherer, Erickson, & Liu-Ambrose, 2013). Physical activity can be defined as any body movement produced by skeletal muscles, which is responsible for an increase in energy expenditure (Saunders, Chaput, & Tremblay, 2014). In this line, highly active older adults have been found to display better cognitive performance than less active older adults. On the other side, CRF is defined as the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity and is classically measured by maximum oxygen uptake (VO_{2max}). The benefit that CRF brings to cognitive performance seems to preferentially affect executive functions. Colcombe *et al.*, in their two meta-analysis on this topic (Colcombe & Kramer, 2003; Kramer & Colcombe, 2018), reported that cardiorespiratory fitness has large positive benefits on executive function that are greater than the effect on other cognitive processes (*i.e.*, visuospatial, speed, etc.). These results suggest that CRF can have a direct impact on cognitive health and the level of fitness seems to play a major role.

The clinical benefits of CRF on cognitive function appears in the form of enhanced brain functioning, as suggested by some neuroimaging studies, which report better brain activity in physically active older subjects when compared to less active (Voelcker-Rehage & Niemann, 2013). Many underlying neurophysiologic structural changes seem to explain this improved brain functioning (Hillman, Erickson, & Kramer, 2008; Plough- man, 2008). Structural brain changes after physical training, such as both the improvement of the density and integrity of grey and white matter (Sexton, *et al.*, 2016; Voelcker-Rehage & Niemann, 2013), as well as a better brain vascularization, is due to the release and synthesis of several growth factors related to better cognitive functioning, neurogenesis, synaptogenesis and angiogenesis (Stillman & Erickson, 2018).

One particular group of older adults that is representative of individuals who maintain a high level of physical activity and have a high CRF are Master Athletes. Masters Athletes are a category of older adults who have participated in life-long exercise training and may benefit from the physiological and neurophysiological benefits of such training (Aengevaeren, Claassen, Levine, & Zhang, 2013; Tseng, *et al.*, 2013a, b). Previous research has reported cardiovascular benefits accredited to life-long aerobic training compared to less active older adults. Indeed, Master Athletes demonstrate higher VO_{2max}, often comparable to younger populations. Interestingly, high level of CRF has a positive impact on mortality (Antero-Jacquemin, *et al.*, 2015; Marijon, *et al.*, 2013). Considering all these health benefits, Master Athletes could be considered as exemplars of successful aging (Geard, Reaburn, Rebar, & Dionigi, 2017).

Based on the evidence that physical activity and CRF have an impact on cognition and brain functioning, we can hypothesize that Master Athletes would have better cognitive functioning than less active populations at the same age. However, the dose-response relationship between fitness level and cognitive function benefits in older adults is unclear. To date, the cardiorespiratory level that induces the greatest improvements in cognition and the impact of life-long aerobic training on brain structure and function remains unclear. The aim of this review was to examine the link between physical activity, CRF, and the neurophysiological mechanisms that could explain the better cognitive performance of Master Athletes.

2 Cognitive performance in Master Athletes

Few studies have assessed cognitive function in Master Athletes. These cross-sectional studies have compared cognitive performance of Masters Athletes with sedentary or less fit people. In the first study, Tseng *et al.* (2013a) recruited 12 Master Athletes (72.4 ± 5.6 years) and compared their cognitive performance with age-matched older adults and also with younger adults (27.2 ± 3.6 years). For the cognitive assessment, the authors conducted several cognitive tests. Global intelligence was assessed using the Wechsler Test of Adult Reading. Executive function was assessed using the Delis-Kaplan Executive Function System, Trail Making Tests (Trails-A and B), and Stroop Color-Word Test. The California Verbal Learning Test-II was also administered to measure declarative memory. Finally, working memory, processing speed, and reaction time were measured using the Automated Neuropsychological Assessment Metrics battery. The major findings of this study were that Master Athletes displayed better letter fluency and category fluency (executive and memory domain) and better scores on the Wechsler Test of Adult Reading than sedentary subjects. Interestingly, Master Athletes also performed better than younger adults on the letter fluency test. In line with these findings, Tarumi *et al.* (2013, 2015) have also assessed cognitive performance on middle-aged adults with endurance training who demonstrate a VO_{2max}

similar to Master Athletes. They reported better cognitive performance in those that were trained *versus* untrained participants. These participants displayed higher scores in measures of executive, attention and memory functions. Similarly, these results align with Taran, Taivassalo, & Sabiston (2013) who reported better performances on verbal learning and memory tasks (Rey Auditory Verbal Learning Test) as well as faster processing speed (Trail Making Test) in Master Athletes compared to sedentary controls. Also, Zhao *et al.* (2016) showed significantly better performance on a verbal memory task and a reaction time test (Immediate Post-concussion Assessment and Cognitive Testing (ImPACT)). More recently, Schott & Krull (2019) reported that Master Athletes displayed better cognitive performance in both working memory performance (n-back task) as well as inhibitory control (Flanker task) compared to sedentary controls. Although these studies are very interesting and support the proposal that lifelong physical training promotes improved cognitive functioning, these results do not permit to identify the dose-response relationship between cardiorespiratory fitness and brain function in the absence of experimental less active group.

This raises an important question: *Are Masters Athletes better cognitively than their less fit counterparts?* A recent study aimed to answer this question and compare within a sample Master Athletes, the influence of fitness level on cognitive performance. (Dupuy, Bosquet, Fraser, Labelle, & Bherer, 2018) recruited 39 Athletes (aged between 49 and 70 years) and split the sample into two groups (higher/lower fit) based on their CRF (*i.e.*, VO_{2max}). In this study, the participants completed neuropsychological tests including the Stroop Test, the Trail A and B Test, and the Digit Symbol Substitution Test. In addition, the participants completed a computerized cognitive dual-task (Bherer, *et al.*, 2008). This task includes an auditory task (discrimination between two sounds: low: 440 Hz; high: 990 Hz), and a visual task (identification of three geometric forms: triangle, circle or square). In the single pure trials, participants had to respond to trials of each task alone. The participant completed 20 single task trials in the auditory task, by pressing one of two keys on a response box using the major (high sound) or index (low sound) finger of the left hand and 30 single task trials of the visual task by answering with the index (triangle), the major (circle) or the ring (square) finger of the right hand on the same response box. The dual-mixed condition consisted of single mixed and dual-mixed trials. Participants had to be prepared to answer to both trial types (visual and auditory) at all times but only had to perform the two tasks concurrently in the dual-mixed trials. Similar to Tseng *et al.* (2013a), the findings of Dupuy *et al.* (2018) confirm that higher fit Master Athletes are no better at Stroop, Trail or Digit Symbol tests than those that are lower fit. However, the higher fit Master Athletes did display fewer errors in the most difficult (executive condition) of the computerized dual-task. Also, bivariate correlations of the entire sample help elucidate the dose-response relationship since the findings demonstrate a negative correlation between CRF level and reaction times and errors produced in this task respectively. This correlation supports the proposal that a higher fitness level (even among Master Athletes) is associated with faster reaction times and lower error rates. Although all these results are encouraging and corroborate the dose response relationship between CRF and brain functioning in older adults, the limited number of studies available makes it difficult to draw definitive conclusions.

3 Neurophysiological mechanisms

3.1 Structural changes

Several studies suggest that greater CRF and higher level of physical activity may be related to greater grey matter density and integrity in several brain regions. The following section discusses this point presenting cross sectional and longitudinal studies in healthy older adults.

3.1.1 Gray matter

3.1.1.1 Cross-sectional studies (CRF and gray matter)

Based on the evidence that gray volume matter in several brain regions is related to cognitive performance (Ruscheweyh, *et al.*, 2013; Taki, *et al.*, 2011), several researchers have put forth the hypothesis that regular physical activity and/or better CRF could have a positive impact on brain structures. Using magnetic resonance imagery techniques, Colcombe *et al.* (2003) were among the first to establish the link between the CRF with gray matter volume. These authors reported in 55 older adults (age between 55 and 79 years old), that the subjects with higher CRF displayed a greater gray matter volume in the prefrontal, temporal and parietal cortices than the subjects with lower CRF. These associations were more recently confirmed by several authors (Erickson, *et al.*, 2007; Gordon, *et al.*, 2008; Weinstein, *et al.*, 2012) using voxel based methods which confirmed that CRF, measured by VO_{2max}, was associated to greater gray matter volume in frontal and temporal lobes in older adults. More recently, Williams *et al.* (2017) found a positive association between CRF and cortical thickness among older adults, more specifically, in left parahippocampal, paracentral, precuneus, and supramarginal cortices, as well as right middle temporal and lateral orbitofrontal areas.

Other studies have replicated the associations with CRF and others larger brain regions. One of other brain region of interest is the hippocampus since this region is implicated to memory function. To test the hypothesis in which the CRF could have a positive impact on volume of hippocampus, Erickson *et al.* (2009) assessed the CRF (VO_{2max}) on 165 older adults and the size of their hippocampus. The authors reported that higher CRF was associated to larger size of hippocampus as well as to better memory performance. These results were more recently supported by Bugg, Shah, Villareal & Head (2012) and Szabo *et al.* (2011). Finally, Verstynen *et al.* (2012) examined the impact of CFR (VO_{2max}) on the size

of the basal ganglia. Similar to the prefrontal and hippocampus regions, basal ganglia was found to be related to CRF, which was also associated with better performances in a switching task.

3.1.1.2 Cross-sectional studies (physical activity level and gray matter)

The results from cross-sectional studies of physical activity level on gray matter are less consistent than studies assessing the impact of CRF on gray matter. Using questionnaire on physical activity level Benedict *et al.* (2013) and Arenaza-Urquijo *et al.* (2017) found that higher physical activity score was strongly correlated with greater gray matter volume. Also, Erickson *et al.* (2010) found convincing evidence of a link between self reported physical activity and brain volume. Meanwhile, several other studies have reported that physical activity is not significantly correlated with either gray matter volume or gray matter network. Davis, Nagamatsu, Hsu, Beattie & Liu-Ambrose (2012) using the Physical Activities Scale for the Elderly (PASE) questionnaire, and Seider *et al.* (2016) the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, reported no association between physical activity and gray matter volume. More recently, Masouleh *et al.* (2018) utilized the international physical activity questionnaire (IPAQ) and also found no association between physical activity and gray matter network. The difference in the question- naire used and the subjective nature of the physical activity questionnaires may influence the inconsistency on the association of physical activity and gray matter between studies in older adults. The utilization of accelerometer as the objective measurement of physical activity should help to clarify the relationship between physical activity and gray matter.

3.1.1.3 Longitudinal and randomized trials studies

As described previously in cross-sectional studies, the association between self-reported physical activity and gray matter in older adults has resulted in inconsistent results particularly in associations with gray matter volume. Such heterogeneity in the findings could indicate that cross-sectional assessments of physical activity are confounded by potential inaccuracies in self-reported assessments of physical activity. Longitudinal studies that follow individuals over an extended period, or randomized controlled trials that examine whether randomly assigning individuals to receive monitored and structured exercise for an extended period, provide greater control over several of these potential problems with cross-sectional investigations.

Longitudinal and randomized trials studies using magnetic resonance imaging (MRI) to assess structural changes due to physical activity level or CRF have reported increases in gray matter in frontal brain regions (Colcombe, *et al.*, 2006) and in the hippocampus (Erickson, *et al.*, 2011; Pajonk, *et al.*, 2010) in humans.

In a longitudinal study in healthy older adults, Lee *et al.* (2019) followed 767 community-dwelling participants (50 years or older) for 4 years. The results of this study suggest that older adults with higher physical activity scores demonstrated greater hippocampal volumes, total gray matter, parietal gray matter, and temporal gray matter compared to older adults with a lower physical activity scores. Similar results have also been reported from longitudinal studies that examined populations with health risks. Raji *et al.* (2016) analyzed the gray matter of 876 participants in a multisite population-based longitudinal study in persons aged 65 and older recruited for the Cardiovascular Health Study. Regardless of cognitive status, higher CRF was associated with larger gray matter volumes in frontal, temporal, and parietal lobes, as well as hippocampus, thalamus, and basal ganglia. Smith *et al.* (2014) analyzed the effect of physical activity and risk of Alzheimer's disease (AD) by following 97 participants between 71–74 years old for 18 months. Participants were classified as high active or low active based on a self-report questionnaire of frequency and intensity of exercise and risk status for AD was defined by the presence or absence of the apolipoprotein E-epsilon 4 (APOE-e4) allele. The results suggest that physical activity may help to preserve hippocampal volume in individuals at increased genetic risk for AD (those with the APOE-e4 allele).

From the controlled intervention of physical activity study, Tamura *et al.* (2015) randomized 110 healthy older adults over 65 years old. A mild-intensity aerobic training for 2 years was employed as the intervention for the exercise group. Neuroimaging analysis revealed the significant preservation of bilateral prefrontal gray matter volume in the exercise group that was not seen in the control group. Tao *et al.* (2017) also reported the benefit of the intervention of physical activity as having a significant increase of gray matter volume in 12-week Tai-Chi Chuan and Baduanjin groups compared to a control group. Both of those interventional studies highlight the beneficial effect of physical activity program in healthy older adults. Furthermore, the benefits of physical exercise program were also reported in an overweight population. Prehn *et al.* (2019) randomized 29 overweight older subjects took either part in a moderate aerobic exercise program over 6 months or control condition of non-aerobic stretching and toning. The aerobic exercise group showed an increase of gray matter volume in the middle cingulate cortex, the middle/superior temporal gyrus, and the temporal pole compared to the non-aerobic group. Taken together, longitudinal studies in older adults suggest gray matter benefits of physical activity/CRF healthy older adults and at-risk populations.

However, more recently, Matura *et al.* (2017) reported that 12-week of aerobic exercise did not lead to increased or greater total grey matter volume compared to control group. As opposed from the previous study by Tao *et al.* (2017) which also proposed a 12-week interventional aerobic exercise program, negative finding for physical activity effect on gray matter volume could be due to the dose of the training. Even though both studies have the

same duration but the participant in exercise group of Tao *et al.* (2017) received a greater amount of exercise training at a frequency of 5 days per week for 60 minutes per day compared to 3 days per week for 30 minutes per day in Matura *et al.* (2017).

Overall, longitudinal and interventional studies examining physical activity/CRF/exercise program and gray matter volume have shown that physical activity level and exercise program give beneficial effect to gray matter volume (see Matura, *et al.*, 2017 for exception). All longitudinal studies have shown that physical activity positively associated with gray matter volume either healthy older adults or older adults with the risk of Alzheimer's disease. This association is independent from cognitive status of the participants. From interventional studies, the conclusions indicate that at least 12 weeks of aerobic exercise program are required for giving advantageous effect compared to control.

The positive association of physical activity with cortical gray matter volume was found when comparing low to high spectrum of physical activity and this association still appeared when comparing on a very high level of physical activity in older adults. Master Athletes, which have a higher score in physical activity, have shown a greater cortical gray matter compared to healthy active older adults (Tseng, *et al.*, 2013a; Wood, Nikolov, & Shoemaker, 2016), suggesting a possibility of dose-response association on the relationship between physical activity and gray matter in older adults. Tseng *et al.* (2013a) reported that compared to inactive elderly controls Master Athletes displayed greater posterior cortical thickness in the cuneus and precuneus. Similarly, these results align with Wood *et al.* (2016) who reported that Master Athletes demonstrated greater whole-brain cortical thickness and more specifically in the medial prefrontal cortex, pre and postcentral gyri, and insula compared to sedentary couterparts. These results suggest that cortical areas that are associated with higher cognitive functions (*i.e.*; executive functions) may be most sensitive to variation in CRF.

3.1.2 White matter

Several studies suggest that greater CRF may be related to greater white matter (WM) density and integrity in several brain regions. The following section discusses this point presenting cross sectional and longitudinal studies in healthy older adults.

3.1.2.1 Cross-sectional study

3.1.2.1.1 White matter volume

Studies examining the effect of physical activity (PA) on white matter volume have reported inconsistent results in older adults. Davis *et al.* (2012) used the Physical Activities Scale for the Elderly (PASE) questionnaire to 79 healthy females and found that physical activity levels were not associated with white matter volume. A similar result has also been reported by Seider *et al.* (2016) which reported no significant associations observed between the white matter volumes and engagement in physical activity recorded on the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire. In contrast to these findings, Benedict *et al.* (2013) used self-reported light and hard physical activities for at least 30 minutes per week and found that physical activity (PA) was positively correlated with white matter volume. Unlike in the studies of Davis *et al.* (2012) and Seider *et al.* (2016) that included only healthy older adults in their studies, Benedict *et al.* (2013) also included participants with diabetes mellitus. The deteriorating effect of diabetes to brain structure might accentuate the benefit of physical activity on white matter volume in this sample of older adults.

3.1.2.1.2 White matter hyperintensities/hypointensities

White matter hyperintensities in the brain can be detected on MRI. The underlying pathology of these hyperintensities mostly reflects demyelination and axonal loss as a consequence of chronic ischemia caused by cerebral small vessel disease (microangiopathy). Research has shown that the presence and extent of white matter hyperintensities in MRI scans are essential for clinical assessments of cognitive and functional impairment. Also white-matter hypointensities provide an index of cerebrovascular disease and cognitive decline, as people with greater hypointensities demonstrating the greatest decline (Debette & Markus, 2010).

Some studies included in this review that examined the association between cardiovascular fitness or physical activity level in older adults and white matter hyperintensities have given consistent results. Vesperman *et al.* (2018) reported that higher cardiovascular fitness attenuates the adverse effect of age on white matter hyperintensities (WMH). Also, Tseng *et al.* (2013b) reported an 83% reduction in deep WMH volume in Master Athletes relative to their sedentary counterparts. In a study by Fleischman *et al.* (2015) using of actigraphy to calculate physical activity, higher levels of physical activity may reduce the effect of WMH on motor function in healthy older adults. Only one study about physical activity and white matter hypointensity was reported since 2012. Wood *et al.* (2016) reported no differences in white matter hypointensities between Master Athlete and healthy older adult. Nevertheless, other studies comparing cardiovascular fitness and physical activity with white matter structure supported the association between physical activity and white matter hyperintensities in older adults.

3.1.2.1.3 White matter integrity

Diffusion tensor imaging is a relatively new MRI technique that identifies changes in the white matter microstructure by quantifying directional diffusion. Diffusion tensor imaging has become one of the imaging tools available to understand the pathophysiological

mechanisms of cerebrovascular diseases on brain structure. Diffusion tensor imaging is based on the theory that water molecules follow a physiological perpendicular path through the long axis of neural fibers and bundles, formed by the integrity of the axons and the thick myelin membrane surrounding them. Any alteration in the integrity of the white matter fibers will result in changes in the water diffusion and consequently in the diffusion tensor imaging parameters. Fractional anisotropy is the main diffusion tensor imaging parameters used to identify alterations in white matter integrity. These imaging parameters provide information about the density of the white matter fiber, the diameter of the axon and degree of myelination based on a quantitative measure of the diffusion anisotropy.

Some studies in older adults that examined the association between CRF and physical activity with white matter integrity, gave consistent results. Oberlin *et al.* (2016) reported that higher VO_{2max} was associated with higher fractional anisotropy that suggests better white matter microstructural organization in higher fit older adults. Johnson, Kim, Clasey, Bailey & Gold (2012) reported a positive correlation between VO_2peak and fractional anisotropy. These studies showed that either higher CRF is associated with greater white matter integrity in healthy older adults.

Only three studies that have explored the effect of physical activity on white matter integrity have been published since 2012. The first study was Tseng *et al.* (2013b) which reported that Master Athletes showed higher fractional anisotropy values when compared to sedentary older adults. Also, Gow *et al.* (2012) reported that a higher level of physical activity was associated with higher fractional anisotrophy. Lastly, Burzynska *et al.* (2014), using accelerometer to quantify physical activity for 7 days, reported a positive association between physical activity and white matter integrity and also found that sedentary behaviour was associated with lower white matter integrity in healthy low-fit older adults. All of these studies displayed a great range of physical activity level in their participants, suggesting the advantage of physical activity on white matter integrity can be gained by participants with various physical activity levels from low levels to Master Athletes level and this is not limited to a certain level of physical activity.

Overall, cross-sectional studies of the relationship between physical activities on white matter integrity have consistent results. Cardiovascular fitness or physical activity showed a promising effect on brain structure health, primarily to prevent or reduce white matter hyperintensities and maintain white matter integrity. The only inconsistent result is the relationship between physical activity and white matter volume. Again, as discussed earlier, the subjective nature of self-reported physical activity questionnaires may influence the results. In addition, the characteristics of participants should be evaluated as this also may influence the relationship between physical activity and white matter volume.

3.1.2.2 Longitudinal study

Smith *et al.* (2014) did a longitudinal study in 97 older adults to analyze the effect of physical activity and risk of Alzheimer's disease on white matter volume. Participants were classified as high active or low active based on a self-report questionnaire of frequency and intensity of exercise and risk status was defined by the presence or absence of the apolipoprotein E-epsilon 4 (APOE-e4) allele. The results suggest that no significant main effects or interactions were observed between genetic risk and PA on cortical white matter volume. Furthermore, another study from Smith *et al.* (2016) with similar classification of participants' group, reported greater levels of physical activity were associated with greater fractional anisotropy in healthy older adults who did not possess the APOE-e4 allele. These results support that existing cross-sectional study results in healthy older adults demonstrate the beneficial effect of physical activity on white matter integrity but not white matter volume.

In interventional studies, Voss *et al.* (2013) random- ized 70 sedentary healthy older adults into aerobic walking group or a flexibility, toning and balance control group. Both the walking and control programs were one year in duration and consisted of three structured forty-minute exercise sessions per week led by a trained exercise leader. The results showed that greater aerobic fitness after the walking program was associated with greater change in white matter integrity compared to the flexibility, toning and balance control group. In another study, 174 healthy but low-active older participants were randomized into 4 groups (dance, walking, walking + nutrition, and control) and were followed for 6 months. Diffusion tensor imaging showed white matter integrity declined over 6 months in all groups but increased in the dance group. These studies suggested that aging of the brain is detectable on the scale of 6-months and more physically active lifestyle is associated with better white matter integrity in healthy sedentary older adults.

Taken together, cross-sectional as well as longitudi- nal studies have provided results in favour of beneficial effects of physical activity or CRF on cognitive on grey and white matter density and thickness. To date, very few studies corroborate brain plasticity in Master Athletes. Tseng *et al.* (2013a, b) and Wood *et al.* (2016) reported that Master Athletes demonstrated greater density in grey matter and white matter integrity in several brain regions and could explain their improved cognitive performance.

3.2 Cerebrovascular changes

Aerobic exercise might induce beneficial effects on brain functions by changes in blood flow and vascularizа- tion, which could lead to an overall better energy and oxygen supply to the brain. The following section discusses this point presenting cross sectional and longitudinal studies in healthy older adults.

3.2.1 Cerebral blood flow and cerebral oxygenation

Sedentary lifestyle has recently been associated with reduced cerebral blood flow (CBF), which increases the risk of a more rapid decline in aging or a higher risk of stroke or neurodegenerative disorders (Carter *et al.*, 2018). However, the increase of walking time every day could counteract this sedentary effect (Carter, *et al.*, 2018). Furthermore, several cross sectional studies, which compared higher active people to less active or sedentary people, confirm the positive impact of CRF on cerebral blood supply. Higher fit people have higher CBF during rest or during tilt test or during exercise than lower fit people (Murrell, *et al.*, 2011a, b). This improved cerebral perfusion was measured using transcranial Echo-Doppler or functional MRI techniques, either at the carotid arteries, at the median cerebral arteries, or at the level of the hippocampus. Using functional near-infrared spectroscopy techniques, several studies have also reported that cardiorespiratory fitness has positive effect on cerebral oxygenation, and higher fit people displayed greater cerebral oxygenation responses during exercise (Rooks, Thom, McCully, & Dishman, 2010) or during cognitive task (Agbangla, Audiffren, Pylouster, & Albinet, 2019; Albinet, Mandrick, Bernard, Perrey, & Blain, 2014; Dupuy, *et al.*, 2015).
In a randomized controlled trial, (Chapman *et al.*, 2013) demonstrated that a 12-week aerobic exercise intervention significantly increased regional cerebral blood flow in the anterior cingulate cortex of sedentary older adults (Chapman, *et al.*, 2013). Murrell *et al.* (2013) also observed a similar increase of middle cerebral artery blood velocity after 12 weeks of aerobic training in young and older adults. Likewise, a cross-sectional study by Thomas *et al.* (2013) showed that Master Athletes had significantly greater regional CBF in the posterior cingulate cortex than age-matched sedentary controls (Thomas, *et al.*, 2013).
The increase in cerebral perfusion improving the oxygen and nutrient supply would partly explain the improvement in cognitive status after exercise training. Davenport, Hogan, Eskes, Longman & Poulin (2012) hypothesized that the larger the cerebrovascular reserve, the better the participants' cognitive performance were. This hypothesis was confirmed by several studies in healthy and non-healthy subjects (Gayda, *et al.*, 2017). These authors reported that better cognitive performance was associated with the amplitude of cerebral oxygenation during exercise.
Beyond the increase in CBF, this cerebrovascular reserve is also under the influence of vascular mechanisms such as the regulation, the vasoreactivity and the arterial stiffness.

3.2.2 Arterial stiffness

Several studies support the hypothesis that cognitive performance in aging is linked to vascular health (Barnes & Corkery, 2018). Indeed, one of the main mechanisms that explain cognitive decline during the aging process is the increase in blood pressure. Hypertension is one of major vascular risk factors for cognitive decline. Several studies have reported that hypertensive subjects have poorer cognitive performance than their counterpart with normal blood pressure (Hajjar, *et al.*, 2011; Iadecola, *et al.*, 2016; Novak & Hajjar, 2010). Even in the absence of hypertension, higher blood pressure is associated to cognitive impairment (Tsivgoulis, *et al.*, 2009). The relationship between blood pressure and cognition seems to be mediated by the state of the vasculature. Indeed, higher blood pressure may reduce CBF (Deverdun, *et al.*, 2016), increase cerebral bleeds and white matter hyperintintesities (Tsivgoulis, *et al.*, 2009). Also, the high blood pressure may cause the rigidity of arteries. Several cross sectional studies have reported that higher carotid stiffness (Tarumi, *et al.*, 2013) and higher aortic pulse wave velocity are associated to poorer cognitive performance (Gauthier, *et al.*, 2015) possibly mediated by a lower cerebral oxygenation. Nevertheless, CRF appears to improve arterial stiffness thus preserving cognitive decline in the elderly. All these studies support the hypothesis that preservation or the improvement of vessel elasticity may be one of the key mechanisms by which CRF attenuates cognitive aging. Regarding Masters Athletes, it has been reported that this population has a very good vascular health, which could explain their better cognitive performance (Tarumi, *et al.*, 2013).

3.2.3 Cerebro-reactivity/regulation

Cerebral blood flow decreases approximately 5% per decade (Grolimund & Seiler, 1988). This results in a decrease of 25 to 30% between the ages of 20 and 80 years (Ainslie, *et al.*, 2008; Krejza, *et al.*, 1999). The reduction of CBF and the impairment of his regulation are risk factors for cerebrovascular disease. Reduced CBF can lead to a cerebrovascular accident such as stroke (Markus, 2004) and may be a risk factor for dementia and neurodegenerative disorder such as Alzheimer's disease (de la Torre, 2010a, b). Since, the CBF is largely controlled by the partial pressure of arterial carbon dioxide ($PaCO_2$), impaired ability of the cerebrovascular system to respond to changes in $PaCO_2$ (called cerebrovascular responsiveness) is a risk factor for cerebrovascular disease (Markus & Cullinane, 2001).
Several cross sectional studies have been shown that higher fit subject displayed better vascular reactivity and regulation (Barnes, Taylor, Kluck, Johnson, & Joyner, 2013) than lower fit counterpart. Longitudinal studies have also found the similar pattern. Murrell *et al.* (2013) and Tyndall *et al.* (2013) found an increase of vasoreactivity and regulation after 3 months and 6 months of training. Also, Ivey *et al.* (2011) demon- strated an elevation in cerebrovascular reactivity to CO_2 following 6 months of exercise training in stroke survivors.

3.3 Neurotropin Release

Using magnetic resonance spectroscopy, Erickson *et al.* (2012a, b) measured N-acetylaspartate (NAA) levels in the frontal cortex of older adults. N-acetylaspartate is only found in neuronal tissue and has been recognized as a marker of neuronal health (Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007). Erickson *et al.* (2012a, b) reported a positive correlation between NAA levels, cardiovascular fitness and working memory. Gonzales *et al.* (2013) supported these findings and found higher NAA levels in middle-aged endurance athletes compare to sedentary controls. These results highlight the potential contribution of growth factors that allow for the maintenance and renewal of neuronal health. Growing evidence suggests that acute and chronic exercise influence the brain through circulating growth factors like neurotrophins, modulated several mechanisms for cognition. Among these factors, brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) have been designated as the main factors that produce cerebral plasticity.

3.3.1 BDNF

Evidence on the effect of BDNF on neurogenesis and synaptic plasticity comes from animal studies (Marie, *et al.*, 2018). In humans, it's well documented that acute bouts of exercise increase the plasmatic concentration of BDNF (Ferris, Williams, & Shen, 2007; Hakansson, *et al.*, 2017; Schmolesky, Webb, & Hansen, 2013). Moreover, Winter *et al.* (2007) reported an increase in BDNF in humans running at a high intensity and that this BDNF release accelerated learning. Furthermore, several studies have reported changes in the BDNF level after chronic exercise (Leckie, *et al.*, 2014; Seifert, *et al.*, 2010). More recently, Szuhany, Bugatti & Otto (2015) performed a meta-analysis and supported elevations in plasmatic BDNF levels in humans after chronic exercise. This elevation seems to be responsible for cognitive performance improvement and increased hippocampal volume (Erickson *et al.*, 2012a, b). In addition, Engeroff *et al.* (2018) found that BDNF was negatively associated with sedentary time but beneficially related to total activity counts (*via* accelerometer) and moderate to vigorous physical activity.

Beyond its crucial role in neuroplasticity, BDNF upregulates the production of insulin-like growth factor 1 (IGF-1) and works in conjunction with it, to promote both neurogenesis and angiogenesis (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). Also, although lactate has been incorrectly considered as a factor of fatigue, it appears, based on the recent work, to be an important metabolic derivate for the brain. It can be considered as a source of energy for the brain and also as a growth factor for BDNF and VEGF (E, Lu, Selfridge, Burns, & Swerdlow, 2013; El Hayek, *et al.*, 2019; Schiffer, *et al.*, 2011).

3.3.2 IGF-1

IGF-1 is also considered a growth factor for the brain and involved in neurogenesis and synaptogenesis (Aleman & Torres-Aleman, 2009). In studies with older adults, high plasmatic IGF-1 concentrations are associated with improved cognitive performance while for older adults with cognitive impairment, low IGF-1 concentrations were associated with poorer cognitive performance (Stein, *et al.*, 2018). In response to acute exercise, plasmatic IGF-1 concentrations are increased (Schwarz, Brasel, Hintz, Mohan, & Cooper, 1996). This finding was supported by a recent systematic review, which reported a positive relationship between physical exercise and increased IGF plasmatic concentrations (Arwert, Deijen, & Drent, 2005). This increase seems to be related to higher cognitive status in healthy older adults and play an essential role for neurogenesis. Chronic exercise, particularly resistance training, has been found to increase the plasmatic IGF-1 concentrations (Cassilhas, *et al.*, 2007; Koziris, *et al.*, 1999). Recently, Maass *et al.* (2016) reported that changes in IGF- I levels were positively correlated with hippocampal volume changes and delayed verbal recall performance.

3.3.3 VEGF

More physically active older adults have been found to display a higher number of small cerebral vessels than less physically active older adults (Bullitt, *et al.*, 2009). It's well known that VEGF regulates endothelial cell proliferation and angiogenesis (Cotman & Berchtold, 2002). Exercise increases the production of plasmatic VEGF which is the main growth factor associated with capillary formation in the brain (Cotman & Berchtold, 2002; Duman, 2005). Along this line, Pereira *et al.* (2007) observed an *in vivo* neurogenesis and angiogenesis in the adult dentate gyrus that was induced by exercise and an increase of cerebral blood volume in this specific area. Furthermore, acute aerobic exercise elevates plasmatic and hippocampal VEGF (Tang, Xia, Wagner, & Breen, 2010), and promotes endothelial nitric oxide synthase (eNOS) (Gertz, *et al.*, 2006). The production of eNOS supports the maintenance of the vascular endothelium (Forstermann & Munzel, 2006) and contributes to angiogenesis (Gertz, *et al.*, 2006). Cerebral angiogenesis increases cerebral circulation (Pereira, *et al.*, 2007) and cerebral oxygenation (Dupuy, *et al.*, 2015). This is associated with transiently increased permeability of the blood brain barrier (Bailey, *et al.*, 2011) which may facilitate the proliferation of these growth factors. All of these mechanisms are likely responsible for more efficient bloodstream delivery of neurotrophins influencing brain plasticity during or following exercise. Currently, no data are available to confirm these neurotrophic hypotheses in the Master Athletes. Future studies will be necessary to support these hypotheses.

All these neurophysiological mechanisms are represented in the Figure 1.

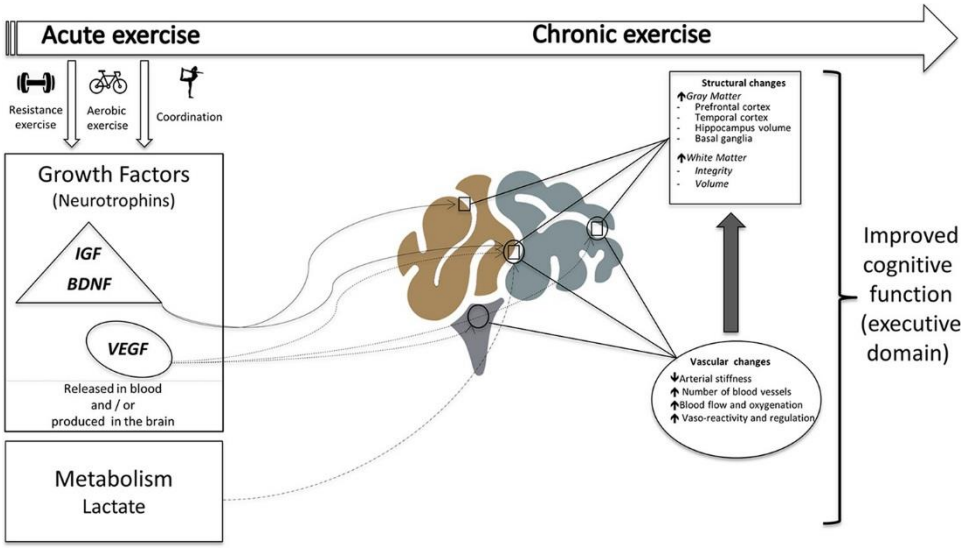

Fig. 1. Summary of the possible neurophysiological mechanisms underlines cognitive improvement after long life intense training.

4 Conclusion

This review highlighted the possible neurophysiological mechanisms that could explain the better cognitive performance observed in Masters Athletes. Several studies have indeed observed that this population has better cognitive performance than sedentary subjects or even active subjects of low CRF level. It has also been shown that the Master Athletes possessed brain volumes of gray and white matter larger than sedentary subjects. Also, cerebro-vascular health seems to be improved in these athletes. Although all these results are encouraging and corroborate the dose response relationship between CRF and brain functioning in older adults, the limited number of studies available makes it difficult to draw definitive conclusions. Future studies seem necessary to confirm that Masters Athletes have higher cognitive and brain abilities than their lower-level counterparts.

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4 Study 4

4.1 Resume

The Relationship between Cardiorespiratory Fitness and Prefrontal Oxygenation during a Stroop Task in Healthy Older Males.

Description of Study 4

Healthy lifestyle factors are increasingly being recognized to play a critical role in the maintenance of cognitive and brain functioning through the adult lifespan (Hertzog et al. 2008). The recognition of a positive association between fitness and several aspects of cognitive functioning in older adults has led to an escalation in the focus of exercise-cognition as a topic of research in the last decade (Kramer and Colcombe 2018; Erickson et al. 2009; Voss et al. 2011). Cardiorespiratory fitness (CRF) has been reported being associated with increased volumes in the frontal and temporal lobes and also in the hippocampus (Stanley J. Colcombe et al. 2006; Erickson et al. 2009). Moreover, increased fitness levels and participation in aerobic exercise training is associated with greater neural recruitment of regions involved in executive function including the prefrontal and the parietal lobes and increased functional connectivity between many regions of the brain network (Voss et al. 2011; Stanley J. Colcombe et al. 2004). Extending this work, we are now interested in examining the neurophysiological changes in neural recruitment that may accompany higher levels of fitness and also the influence of age on that interaction.

In this study, we aimed to examine whether higher levels of cardiorespiratory fitness are associated with a prefrontal (PFC) oxygenation during a Stroop task performance in healthy older adults. Twenty-four healthy older males (62.0 ± 6.4 yrs) were classified as higher-fit (n = 10) or lower-fit (n = 14) according according to their $\dot{V}O_2peak$. To evaluate the effect of age on cognitive performance and PFC oxygenation, we also grouped participants according to their age as 55-60 years old group (n = 14) or 61-69 years old group (n = 10). Bilateral PFC oxygenation was assessed using functional near infra-red spectroscopy (fNIRS) during a computerized Stroop task (which included naming, inhibition, and switching conditions). Accuracy (% of correct responses) and reaction times (ms) were used as indicators of cognitive performances. Two-way ANOVA (CRF level x Stroop conditions) was performed to test the null hypothesis of an absence of interaction between CRF level and executive performance and prefrontal oxygenation.

The main results of this study are:

- CRF is not related to Stroop task performance nor PFC oxygenation in overall older males.

- After grouped by age, greater CRF is related to better performance in naming (p = .006) and flexibility conditions (p = .04) in 61-69 years old group.
- After grouped by age, greater CRF is related with greater right ΔHHb change in inhibition condition (p = .02) and flexibility conditions (p = .03) of Stroop task in 61-69 years old group.
- Greater benefits of CRF on executive function performance to PFC oxygenation observed in 61-69 years old group than in 55-60 years old.
- Age-group classification is essential to evaluate the effect of CRF on executive function in older male subjects.

4.2 Article

The relation between cardiorespiratory fitness, executive performance, and prefrontal cortex oxygenation during Stroop task in older males: The importance of age-grouping

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INTRODUCTION

Several reviews suggest that cardiorespiratory fitness (CRF) may protect the brain against the typical effects of aging as well as the cumulative effects of age-associated health problems (McAuley, Kramer, and Colcombe 2004; Kramer et al. 2005; Bherer, Erickson, and Liu-Ambrose 2013). Interventional studies support the fact that cardiorespiratory training reduces cognitive decline and may eventually lead to cognitive improvement in older adults (Bherer, Erickson, and Liu-Ambrose 2013). These benefits appears to be specific to a specific subset of cognitive functions: executive functions (S. Colcombe and Kramer 2003). Executive function refers to a collection of cognitive abilities such as planning, inhibition control, working memory, and attentional control (Roberts and Pennington 1996). The Stroop task is a frequently used paradigm to examine executive function, as certain components of this task require executive control (Dupuy 2015; Lague-Beauvais 2013; Scarpina and Tagini 2017). In an interventional study, Predovan et al. (2012) observed that in comparison to wait-list controls, individuals who completed a three-month aerobic training showed significant improvements in the executive condition of the Stroop task (Predovan et al. 2012). Also, only the trained group demonstrated a significant correlation between this executive measure and aerobic fitness level.

Several underlying mechanisms, involving both the structure and the function of the brain, have been proposed to explain this beneficial effect of exercise on executive functions (Hillman, Erickson, and Kramer 2008; S. J. Colcombe et al. 2004; Hayes et al. 2013; Kramer and Colcombe 2018). From a functional point of view, oxygen availability appears to play a major role in cerebral functioning (Obrig and Villringer 2003). Cerebral oxygen availability is determined in part by the interaction between cerebral vasculature and the regulation of cerebral blood flow (CBF) but also by the availability of oxygen in the environment, as suggested by studies showing cognitive performance impairments during hypoxia (Ando, Yamada, and Kokubu 2010; Ainslie et al. 2008; Novak and Hajjar 2010). Since high-fit older adults display higher cerebral oxygenation during a cognitive task, differences in CRF seem to play a vital role in cerebral oxygenation (Olivier Dupuy et al. 2015; Agbangla et al. 2019; Albinet et al. 2014).

Contrasting from the young adults, CRF is widely recognized to decline with age in older adults (Fleg et al. 2005). Moreover, the longitudinal rate of decline in the peak oxygen uptake ($\dot{V}O_2peak$) in healthy adults is not constant across the age span, and accelerates with each successive decade, especially in men, regardless of physical activity habits (Fleg et al. 2005). This specific kinetics may have substantial implications for functional cerebrovascular regulation and cerebral oxygenation in healthy older adults. Indeed, some studies reported that a higher CRF predicted better cerebral oxygenation in healthy older adults (Guiney et al. 2015; Olivier Dupuy et al. 2015; Albinet et al. 2014). However, no studies have specifically examined the implication of age-related decline in CRF on cerebral oxygenation during executive function tasks in older adults.

Therefore, the purpose of this study was to determine the interactions between CRF, executive function, and PFC

oxygenation during a Stroop task in two different age groups of healthy older males. Considering the literature and previous studies, we expected that a higher CRF level would be associated with a better Stroop task performance in healthy older males, especially in condition that is more complex. Secondly, we expected that a higher CRF level would also be associated with a greater change in ΔHbO_2 and ΔHHb during a Stroop task. Thirdly, we expected that a higher CRF level would associate with greater benefit in Stroop task performance and change of ΔHbO_2 and ΔHHb in the older group compared to the younger group. Consequently we hypothesized that: 1) Stroop task assessed in dual-task would be better in higher-fit older males compared to lower-fit ones, 2) PFC oxygenation would be greater in higher-fit older males, and 3) Greater benefit of CRF on Stroop task performance and PFC oxygenation would be shown in older group of healthy older males compared to the younger ones.

METHOD

PARTICIPANTS

Healthy men aged between 18 and 35 years old were considered for inclusion in this study. Women were not included in order to avoid the potential influence of varying sex hormone levels on PFC functions (Keenan et al. 2001; Jacobs and D'Esposito 2011; Hausmann 2017). Twenty four healthy older males were recruited in this study. They were non-smokers, did not undergo major surgery in the 6 months prior to the experiment, did not report any neurological or psychiatric disorders, and were not taking medication known to affect cognition. Moreover, given the physical implications of the study, participants were also screened and excluded for cardiovascular disease, and moderate to severe hypertension based on self-report. The protocol was reviewed and approved by a national ethics committee for non-interventional research (CERSTAPS # 2017-23-11-17) and was conducted in accordance with recognized ethical standards and national/international laws.

STUDY DESIGN

Once included, participants had to complete to testing sessions. Participants were investigated on two study sessions. During the first session, participants completed the informed consent form, a Beck's Depression Inventory-II questionnaire and a Montreal Cognitive Assessment (MoCA) test. Then, participants completed anthropometry measurements to obtain height, weight and body composition (Tanita BC418, Tanita Corp., Tokyo, Japan) and performed the cognitive assessment using computerized Modified Stroop task. At the end of the first session, all participants were given a 24-h ambulatory blood pressure measurement device. The arm cuff was attached and instructions were provided so that 24-h blood pressure monitoring could be started. During the second session, participants completed the maximal continuous graded exercise test. To avoid any residual fatigue induced by recent workout, participants were asked to refrain from strenuous exercise the day before each session. They were also asked to abstain from alcohol and caffeine-containing beverages 24 hours before the test in order to avoid any influence of these beverages on the regulation of the cardiovascular system. Both sessions were administered between 8:00 a.m. to 4:00 p.m., with at least 48h between each.

Once the experimental sessions were completed, participants were ranked

according to their peak oxygen uptake ($\dot{V}O_2peak$). A median split was performed to generate two groups of different CRF (higher- and lower-fit). In parallel we conducted an age grouping by clustering the participant into two different groups (55-60 years old and 61-69 years old). Once again, we performed a median split on $\dot{V}O_2peak$ in each group in order to generate two subgroups with different CRF level (higher and lower-fit).

CARDIORESPIRATORY FITNESS ASSESSMENT

This test was performed on a motorized treadmill (Valiant 2 sport, Lode B.V., Groningen, Netherlands). A modified Balke walking protocol was used to determine peak oxygen uptake ($\dot{V}O_2peak$). This test is well suited to evaluate aerobic fitness in heterogeneous populations that vary in terms of fitness level, age, adiposity or health status in general (Fletcher et al. 2013). The velocity was set at 5.6 km/h throughout the test, with an initial 0% grade. The inclination was increased by 6% after the first minute, and then by 2% every minute until voluntary exhaustion. Verbal encouragement was given every minute throughout the test (Andreacci et al. 2010). Oxygen uptake ($\dot{V}O_2$, in $ml.kg^{-1}.min^{-1}$) was determined continuously on a 30-s basis using a portable cardiopulmonary exercise testing system (MetaMax Cortex 3B, CORTEX Biophysik GmbH, Germany). Gas analyzers were calibrated before each test using ambient air and a gas mixture of known concentration (15% O_2 and 5% CO_2). The turbine was calibrated before each test using a 3-l syringe at several flow rates. The highest $\dot{V}O_2$ over a 30-s period during the test was considered as the peak oxygen uptake ($\dot{V}O_2peak$, in $ml.kg^{-1}.min^{-1}$). Perceived exertion (RPE) was assessed at the end of the test with the ~~15-point~~ Borg scale (in which higher scores represent higher perceived exertion) (Borg 1982).

COGNITIVE ASSESSMENT

The computerized Modified Stroop task used in this study is based on the Modified Stroop Color Test and included three experimental conditions: naming, inhibiting, and switching (Bohnen, Jolles, and Twijnstra 1992). Each block lasted between 2-4 minutes and was interspersed with 60-s resting blocks. Overall, there were three experimental task blocks (one naming, one inhibiting, and one switching) and two resting blocks, for a total length between 8-14 min. In total, there were sixty naming trials, sixty inhibiting trials, and sixty switching trials. All trials began with a fixation cross (or square for switching condition) for 1.5 s, and all visual stimuli appeared in the center of the computer screen for 2.5 s. Participants provided their responses with two fingers (index and major finger) from each of their hands on an AZERTY keyboard. In the Naming block, participants were presented with a visual stimulus of the name of colors (RED/BLUE/GREEN/YELLOW) in French presented in congruent color with the word and participants were asked to identify the color of the ink with a button press. In the Inhibition block, each stimulus consisted of a color-word (RED/BLUE/GREEN/YELLOW) printed in the incongruent ink color (i.e., the word RED was presented in blue ink). Participants were asked to identify the color of the ink (i.e., blue). In the Switching block, in 25% of the trials, a square in place of the fixation cross appeared before the word. When this occurred, participants were instructed to read the word instead of identifying the color of the ink (i.e., RED). As such, within the Switching block, there were both inhibition trials in which the participant

had to inhibit their reading of the word and correctly identify the color of the ink, and there were switch trials in which the participant had to switch their response mode to read the word instead of identifying the color of the ink when a square appeared before the word presented. Visual feedback on performance was presented after each trial. A practice session was completed before the acquisition run to ensure the participants understood the task. The practice consisted of a shorter version of the task. Dependent variables were reaction times (ms) and the number of errors committed (%).

The computerized Modified Stroop task has been used successfully in previous studies (Olivier Dupuy et al. 2015; O. Dupuy et al. 2010). The Stroop task is frequently used to examine executive function, as certain components of this task require extensive executive control (Olivier Dupuy et al. 2015; Laguë-Beauvais et al. 2013; Scarpina and Tagini 2017). The relationship between physical activity and executive function has been confirmed in systematic review studies, including the one measured by the Stroop task (Verburgh et al. 2014; Cox et al. 2016). Those studies indicate that the Stroop task can be used to observe the relationship between PA and executive function.

PFC OXYGENATION MEASUREMENT

The concentration changes of HbO_2 (ΔHbO_2) and HHb (ΔHHb) were measured with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands). This system utilizes near-infrared lights, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in the cortical layer. The lights were transmitted with two different wavelengths, 760 and 850 nm. Based on different Hb absorption spectra, concentration changes of HbO_2 and HHb in the PFC area are calculated from the changes in detected light intensity. The calculation was done using the modified Lambert-Beer law, assuming constant light scattering [48]. A probe of PortaLite has three transmitters and one receiver, with transmitter-receiver distances of 30, 35, and 40 mm. The differential pathlength factor (DPF) was specified for DPF807, which is determined using the formula: $DPF807 = 4.99 + (0.067 \times Age^{0.814})$ [49], and data were sampled with a frequency of 10 Hz.

Two probes were placed on the forehead of the participants, at a height corresponding to 10 % of the nasion-inion distance from nasion, and the middle of the device was placed at 5 % of the head circumference to the left and right from midline, corresponding to the Fp1 and Fp2 according to the international EEG 10–20 system. These locations roughly target left and right Brodmann's areas 9 and 10, which represent the dorsolateral and anterior PFC. Probes were shielded from ambient light with a black cloth fixed by an elastic strap. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection.

Measurement started with a measure of resting PFC oxygenation in a sitting condition for 2 minutes. During the practice phase, no PFC oxygenation data was acquired. During the 2-back task conditions, the last 30 s of each block was used as a measurement of PFC oxygenation. In the dual-task condition, the PFC oxygenation values from the self-selected pace walking block were subtracted to isolate the dual-task condition. The PortaLite uses wireless technology (Bluetooth), gives a possibility to measure the cerebral oxygenation during walking without restriction of wires. During the

experimentation, tight fitting band and no long wires pulling on optode were applied in order to minimize noise in the hemodynamic signals. For the same objective, our participants were asked to always facing forward during the test, avoid making a sudden head movement, clenching their jaw, frowning, and other facial expressions.

NIRS data analysis was performed on unfiltered data. The artifacts in the signal were identified by visual inspection and replaced by interpolation of adjacent data. Conversion of optical density to HbO_2 and HHb signals occurred in the oxysoft software with the modified Beer-Lambert law. The change in prefrontal oxygenation was calculated as the average of the three channels of NIRS in the same side of prefrontal cortex. As in all fNIRS calculations the experimental condition activity was subtracted from the baseline activity in order to have a change in cerebral oxygenation for each condition.

STATISTICAL ANALYSIS

Standard statistical methods were used for the calculation of means and standard deviations. Normal Gaussian distribution of the data was verified by the Shapiro–Wilks test and homoscedasticity by a modified Levene Test. The compound symmetry, or sphericity, was checked by the Mauchley's test. T-tests for independent samples were used to compare the baseline characteristics of groups and subgroups. A two-way ANOVA with Bonferroni post-hoc tests was conducted to test the absence of interaction between CRF level (higher-fit or lower-fit), PFC oxygenation, and Stroop's performance (naming, inhibition, switching). The magnitude of the difference was assessed by the Cohen's d (d). The magnitude of the difference was considered either small ($0.2 < d < 0.5$), moderate ($0.5 < d < 0.8$), or large ($d > 0.8$) (Cohen, 1988). The significance level was set at $p < .05$ for all analyses. All calculations were made with Statistica 7.0 (StatSoft, Tulsa, USA).

RESULTS

Characteristics of our participants are presented in Table 1. As expected, we found a large difference in ~~the~~ $\dot{V}O_2$peak between higher-fit and lower-fit participants ($p < .01$, $d = 2.2$). When classified by age, we also observed a large difference between higher-fit and lower-fit participants, whatever the age-group ($p < .01$, $d > 2.0$). There were no other differences between groups.

COGNITIVE ASSESSMENT

Results obtained during the computerized modified Stroop task are presented in Table 2. The ANOVA assessing differences in accuracy revealed a main effect of Stroop condition ($p < .001$). Participants completed naming and inhibition conditions with a better accuracy than switching condition (97.4% ± 2.7, 96.7% ± 4.6, and 73.1% ± 22.9, respectively, $0.19 < d <, 1.49$). There was no effect of CRF on accuracy and no interaction between conditions.

Regarding reaction times, the ANOVA showed a main effect of age ($p < .001$). The 55-60 years old individuals had faster overall reaction times than the 61-69 years old individuals (1012.6 ± 284.9 ms and 1289.3 ± 460.6 ms, respectively, $d = 0.8$). We also found a significant CRF by age interaction ($p = .001$), in which higher fitness levels related to faster reaction times in the 61-69 years old group but not in the 55-60 years old group. There was also a main effect of Stroop condition ($F_{(2, 40)} = 113.31$, $p < .001$).

Participants completed the naming condition faster than inhibition, and inhibition conditions faster than switching. Moreover, there was a significant age by Stroop's condition interaction (p = .03). Bonferroni post-hoc analysis revealed a large difference in reaction time in which participants of the 55-60 years old group were faster than the 61-69 years old group, whatever the condition.

PFC OXYGENATION MEASUREMENT

PFC oxygenation changes during the computerized modified Stroop task are presented in Table 3. For ΔHbO_2, the ANOVA indicated a main effect of Stroop condition in the right PFC ($p < .001$) and the left PFC ($p < .001$), in which the ΔHbO_2 in switching condition was greater than in naming and inhibition conditions. We found no interaction between CRF and Stroop condition whatever the side of the PFC.

Regarding ΔHHb, the ANOVA revealed a main effect of CRF in the right PFC (p = .04), in which higher-fit participants had a greater ΔHHb than the lower-fit. We also found a fitness by age interaction for ΔHHb in the right PFC (p = .04).

We also found a main effect of Stroop condition on ΔHHb in the right PFC (p = .01) and the left PFC ($p < .03$), in which the ΔHHb in switching condition was greater than in naming and inhibition conditions.

DISCUSSION

The study investigated the interactions between CRF, Stroop task performance, and PFC oxygenation in two age-groups of healthy older males, a 55-60 years old group and 61-69 years old group. Based on the literature, we hypothesized that individuals with higher-CRF would have better Stroop task performance and greater PFC oxygenation than individuals with lower-CRF. We also hypothesized that the benefits of higher-CRF on Stroop task performance and PFC oxygenation would be greater in 61-69 years old group of healthy older males compared to the 55-60 years old group. Our main findings were that 1) Higher CRF did not relate to a better performance in the Stroop task in overall healthy older males. 2) PFC oxygenation change during the Stroop task, specifically the ΔHHb in the right PFC, was greater in higher-fit participants compared to lower-fit. 3) After age grouping, CRF is related to greater beneficial effects in Stroop task reaction time and right PFC ΔHHb in the 61-69 years old group compared to the 55-60 years old group.

In the Stroop task performance, overall, participants responded with faster reaction time and higher accuracy to the naming condition than the inhibition and the switching condition. This effect supports our complexity manipulation in that participants are slower to respond and less accurate in the more complex conditions, such as inhibition and switching. Regarding Stroop task reaction time, 55-60 years old participants were faster overall than 61-69 years old participants. The increased complexity between conditions resulted in slower reaction time for the 61-69 years olds than the 55-60 years olds, suggesting that the complexity manipulation had a greater effect on the older participants compared to the younger ones. This results in agreement with Zaninotto (2017), which reported a progressive age-related decline in executive function in males after fifty years old (Zaninotto et al. 2018). No effect of CRF on reaction time was found in overall healthy older males. This ambiguous finding might be attributed to the differences in $\dot{V}O_2$peak level

across the older age spectrum, as mentioned in the study of Fleg (2015), that the rate of decline in CRF accelerated from 10% every 10 years in the 40s to greater than 20% every 10 years in the 70s and beyond (Fleg et al. 2005). This difference in CRF level between age group might influence the relation of CRF and executive function performance in older males. Interestingly, after age grouping, higher-fit participants were faster than the lower-fit in the 61-69 years old group but not in the 55-60 years old group. Counting that both age groups have the same mean $\dot{V}O_2$peak for their higher-fit and lower-fit, these results were suggesting that CRF gives greater benefit on Stroop task reaction time performance to the 61-69 years old group compared to the 55-60 years old group.

It has long been suggested that the increase in regional CBF during neural activation is driven by a need for increased delivery of oxygen or glucose (Ances et al., 2001b; Gjedde et al., 2002; Dunn et al., 2005). Increased oxygen metabolism and regional cerebral blood flow alteration not only counteracting effects on tissue oxygenation but also on hemoglobin oxygenation. On the one hand, increased oxygen metabolism drives the conversion of oxygenated (oxy-Hb) to deoxygenated hemoglobin (deoxy-Hb). On the other hand, a disproportionately large increase in regional CBF leads to a washout of deoxy-Hb from the activation area, resulting in a decrease of deoxy-Hb and an increase of oxy-Hb (Obrig and Villringer 2003; Lindauer 2010).

In this study, regarding the changes in PFC oxygenation during Stroop task, both higher-fit and lower-fit participants responded with greater ΔHbO_2 and ΔHHb to the switching condition than the inhibition and naming condition on both sides of PFC. These results support the study of Dupuy (2015) and Vermeij (2012) that higher complexity of the task or condition is responded by greater oxygenation change in PFC in older adults (Olivier Dupuy et al. 2015). In our study, concerning the changes in PFC oxygenation, we found that higher-fit individuals had a greater decrease in ΔHHb, but not change in ΔHbO_2, than lower-fit individuals in the right PFC. Once again, after age grouping, we found an interaction between CRF and age group on ΔHHb, suggesting that the decrease of ΔHHb had a greater effect in the 61-69 years old group than in the 55-60 years old group. In left PFC or, no effects of CRF nor age group on the ΔHHb nor ΔHbO_2. Altogether, these results showed that healthy older males with greater CRF displayed a greater decrease of ΔHHb in the right hemispheres of PFC during a Stroop task and also emphasized the importance of age-grouping in CRF-related association in older males. Moreover, this relation supports the CRF hypothesis that PFC hemodynamic is influenced by the regulation of the cardiovascular system (Dustman et al. 1984) According to this hypothesis, high-fit individuals have a greater regional cerebral blood flow and therefore suggesting a greater PFC activation, which might contribute to their better executive performances (Ainslie et al. 2008).

Using the fNIRS technique, this study confirms that higher-fit older males displayed a greater hemodynamic change in PFC during executive function task (Voelcker-Rehage and Niemann 2013). Furthermore, in contrast to a recent study that reported a greater ΔHbO_2 during Stroop task in higher-fit older women compared to their lower-fit counterpart (Olivier Dupuy et al. 2015), our study reports no difference in ΔHbO_2 between fitness groups in all conditions.

CONCLUSION

This study supports the positive effect of higher CRF on PFC oxygenation and Stroop performance in healthy older males. The results indicated that the high-fit individuals performed better than low-fit individuals only in the 61-69 years old group but not in 55-60 years old group. Moreover, in 61-69 years old group, greater PFC oxygenation change in the ΔHHb measure was also demonstrated in the higher CRF group. Consequently, healthy older males with high CRF might enable healthy older males, more specifically between 61-69 years old, to have a greater PFC oxygenation and a better performance in the executive functions, and also put emphasis on the importance of age-grouping in the study about CRF in older adults.

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Table 1: Characteristics of Study Participants. Data are presented as mean (SD)

	Overall (n = 24)		Higher-fit (n = 13)		Lower-fit (n = 11)		Cohen's d	55-60 Years Old (n = 14)				Cohen's d	61-69 Years Old (n = 10)				Cohen's d
								Higher-fit (n = 8)		Lower-fit (n = 6)			Higher-fit (n = 5)		Lower-fit (n = 5)		
Age (yrs)	60.4	(4.3)	61.9	(4.6)	59.5	(4.3)	0.5	57.9	(1.6)	57.3	(2.0)	0.3	64.8	(3.6)	65.7	(2.9)	0.3
Height (cm)	174.7	(6.6)	175.7	(7.3)	173.9	(6.2)	0.3	178.0	(6.7)	173.7	(2.9)	0.8	174.6	(8.2)	170.6	(7.1)	0.5
Weight (kg)	80.9	(12.4)	79.9	(12.7)	81.9	(12.6)	0.1	80.4	(15.2)	88.3	(10.9)	0.6	79.3	(9.1)	74.1	(10.4)	0.5
$\dot{V}O_2peak$ ($ml.kg^{-1}.min^{-1}$)	32.8	(5.1)	36.2	(3.2)	28.7	(3.6) *	2.2	35.8	(3.8)	28.2	(3.8) *	2.0	36.8	(2.4)	29.4	(3.8) *	2.3

*different from Higher-fit (p<0.05)

Table 2. Accuracy and reaction time during Stroop tasks. Data are presented as mean (SD)

	Overall (n = 24)		Higher-fit (n = 13)		Lower-fit (n = 11)		Cohen 's d	55-60 Years Old (n = 14) Higher-fit (n = 8)		55-60 Years Old (n = 14) Lower-fit (n = 6)		Cohen 's d	61-69 Years Old (n = 10) Higher-fit (n = 5)		61-69 Years Old (n = 10) Lower-fit (n = 5)		Cohen 's d
Accuracy (% of correct responses)																	
Naming	97.4	(2.7)	97.4	(3.2)	97.3	(2.1)	0.1	96.3	(3.7)	97.5	(1.8)	0.4	99.3	(0.9)	97.0	(2.7)	1.1
Inhibition	96.7	(4.6)	98.2	(2.4)	94.9	(5.8)	0.8	98.3	(1.5)	94.7	(7.2)	0.8	98.0	(3.6)	95.0	(4.6)	0.7
Switching	73.1	(22.9)	81.2	(15.7)	63.5	(26.9)	0.8	80.0	(15.4)	71.4	(21.9)	0.5	83.0	(17.7)	54.0	(31.8)	1.1
Reaction time (ms)																	
Naming	861.3	(132.3)	846.3	(68.9)	879.1	(184.1)	0.2	841.7	(89.2)	744.3	(99.6)	1.0	853.7	(13.6)	1040.8	(111.4) *	2.3
Inhibition	1009.9	(206.5)	990.4	(136.8)	1032.8	(273.1)	0.2	930.7	(106.6)	840.0	(160.9)	0.7	1085.9	(132.9)	1264.1	(177.4)	1.1
Switching	1512.6	(408.9)	1433.3	(229.1)	1606.2	(551.2)	0.4	1437.7	(171.9)	1223.9	(197.4)	1.2	1426.4	(324.9)	2064.9	(478.3) *	1.6

*different from Higher-fit ($p < .05$)

Table 3. Cerebral oxygenation changes from baseline during computerized Stroop tasks. Data are presented as mean (SD).

	Overall (n = 24)		Higher-fit (n = 13)		Lower-fit (n = 11)		Cohen 's d	55-60 Years Old (n = 14)				Cohen 's d	61-69 Years Old (n = 10)				Cohen 's d
								Higher-fit (n = 8)		Lower-fit (n = 6)			Higher-fit (n = 5)		Lower-fit (n = 5)		
Naming																	
Right PFC																	
ΔHbO_2 (umol.L-1)	2.00	(1.39)	2.17	(1.22)	1.80	(1.60)	0.3	2.57	(1.37)	1.84	(1.46)	0.5	1.54	(0.60)	1.74	(1.93)	0.1
ΔHHb (umol.L^{-1})	-0.23	(0.67)	-0.36	(0.64)	-0.07	(0.70)	0.4	-0.18	(0.65)	-0.39	(0.54)	0.3	-0.65	(0.56)	0.30	(0.73)	1.5
Left PFC																	
ΔHbO_2 (umol.L-1)	2.42	(1.74)	2.49	(1.22)	2.32	(2.27)	0.1	2.93	(1.26)	1.71	(0.85)	1.1	1.80	(0.83)	3.07	(3.27)	0.5
ΔHHb (umol.L^{-1})	-0.12	(1.18)	-0.11	(0.54)	-0.14	(1.15)	0.03	-0.16	(0.53)	-0.52	(0.59)	0.6	-0.03	(0.47)	0.31	(2.54)	0.2
Inhibition																	
Right PFC																	
ΔHbO_2 (umol.L-1)	2.38	(1.39)	2.57	(1.23)	2.16	(1.59)	0.3	2.71	(1.36)	2.43	(1.45)	0.2	2.35	(1.12)	1.83	(1.85)	0.3
ΔHHb (umol.L^{-1})	-0.48	(0.57)	-0.65	(0.56)	-0.29	(0.53)	0.6	-0.63	(0.70)	-0.52	(0.56)	0.2	-0.68	(0.30)	-0.02	(0.38) *	1.9
Left PFC																	
ΔHbO_2 (umol.L-1)	2.93	(1.93)	2.88	(1.40)	2.99	(2.50)	0.06	3.18	(1.57)	2.63	(1.89)	0.3	2.39	(1.05)	3.42	(3.27)	0.4
ΔHHb (umol.L^{-1})	-0.34	(1.15)	-0.37	(0.59)	-0.30	(1.62)	0.06	-0.43	(0.61)	-0.72	(0.46)	0.5	-0.28	(0.61)	0.21	(2.39)	0.2
Switching																	
Right PFC																	
ΔHbO_2 (umol.L-1)	3.17	(1.74)	3.40	(1.58)	2.90	(1.95)	0.3	3.85	(1.81)	3.42	(1.87)	0.2	2.67	(0.86)	2.27	(2.07)	0.3
ΔHHb (umol.L^{-1})	-0.69	(0.75)	-0.93	(0.70)	-0.40	(0.81)	0.8	-0.82	(0.75)	-0.65	(0.76)	0.2	-1.12	(0.64)	-0.09	(0.61) *	1.6
Left PFC																	
ΔHbO_2 (umol.L-1)	3.58	(1.92)	3.66	(1.67)	3.47	(2.26)	0.1	4.23	(1.69)	3.37	(1.81)	0.5	2.76	(1.30)	3.59	(2.93)	0.6
ΔHHb (umol.L^{-1})	-0.54	(1.18)	-0.65	(0.96)	-0.40	(1.44)	0.2	-0.63	(1.02)	-0.54	(1.12)	0.1	-0.68	(0.99)	-0.24	(1.88)	0.3

PFC, Pre-frontal cortex; ΔHbO_2, changes in oxyhemoglobin concentrations; ΔHHb, changes in deoxyhemoglobin concentrations

*different from higher-fit group ($p < .05$)

5 Study 5

5.1 Resume

The Correlation between Vascular Parameters and Stroop Task Performance in Young and Older Males

Description of Study 5

Aging is associated with a reduction of performance in multiple areas of cognition, such as executive function and processing speed (Murman, Editor, and Jorgensen 2015; Bucur and Madden 2010). The cumulative research of the past decade indicates that aging is not affected exclusively to chronological age but is also influenced and modified by many factors associated with aging (Levine and Crimmins 2018). One of the most significant modifiers of cognitive aging is vascular disease (Levine and Crimmins 2018). Multiple studies have indicated that cardiovascular risk factors become more prominent with age and exacerbate age-related cognitive declines (Dahle, Jacobs, and Raz 2009; M. F. Elias et al. 2005). Moreover, early life elevated blood pressure has been reported to correlate with midlife cognitive decline, showing that young adults are also susceptible to blood pressure-associated decline in cognitive performance as the older adults and that the decline starts in young adulthood (P. K. Elias et al. 2004). However, gender difference has been stated to influence age-related vascular health (Merz and Cheng 2016); Therefore, the relation between vascular parameters and executive function performance across the adults' age span is still an ongoing discussion.

To observe the relation between vascular health parameters and Stroop task performance in young and older males, we recruited 29 young males and 24 older males. Participants asked to attend a two-day visit to the laboratory. On the first day, the protocol started with giving a written informed consent form to the participants. After written informed consent was obtained, anthropometric data were taken to acquire the characteristics of the participants. Subsequently, vascular parameters were measured with a continuous non-invasive blood pressure monitoring (FINAPRES), a central arterial pressure waveform analysis, and a 24-hour blood pressure monitoring (ABPM). In the second visit, the cognitive assessments were obtained with the computerized modified Stroop task in several conditions (naming, inhibition, and flexibility). Then, they were asked to prepare for the cardiovascular test and were explained about the protocol of the cardiovascular test. The cardiovascular test was performed using the modified Balke walking protocol on a motorized treadmill to measure peak oxygen consumption ($\dot{V}O_2peak$).

The main results of this study are:

- In young males, reaction time in the Stroop task has no correlation with vascular parameters.

- In older males, reaction time in the Stroop task was found to have a moderate to strong correlation with 24h-systolic arterial pressure, 24h-diastolic arterial pressure, 24h-mean arterial pressure, day-systolic arterial pressure, day-diastolic arterial pressure, systolic dip, and diastolic dip. In general, those vascular parameters have a stronger correlation in the most complex condition of the Stroop tasks
- In young males, vascular health negatively correlated to HbO_2 change during Stroop task, while inversed correlation observed in older males
- Young males have different cerebral hemodynamics response to cognitive load compared to older males. Limited cerebrovascular and cognitive reserve in older males, especially the ones with poorer vascular parameters, is suspect to be the cause of this difference relationship in young and older males.

5.2 Article

The correlation between vascular parameters, prefrontal cortex oxygenation during stroop task, and stroop task performance in young and older males

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INTRODUCTION

Cognitive impairment affecting more than 25% of people over 65 years old and the number of cases are trending upward rapidly in the last 20 years [1]. Cardiovascular risk factors have been known to play a role in the development of cognitive decline. Blood pressure and arterial stiffness, particularly, have been frequently observed in previous studies since those are easily measured, have had a consensus standard, and need relatively inexpensive equipment. Aortic PWV is related to the intrinsic material stiffness of the aorta and is a major determinant of the pressure load on the heart both through the compliance of the aorta itself and the transmission of the forward and reflected pressure wave [9]. The negative effect of high blood pressure and arterial stiffness on cognition is reported not only in older adults but also in younger age and seems to accumulate over time [2], [3].

The previous studies in the link between vascular and cognition have been focused on vascular parameters as factors that impaired cognitive function, but the physiological mechanism in the brain that underlie this relationship remains to be explained [3], [4]. Given that high blood pressure and arterial stiffness related to microvascular injury, vascular remodeling, then decreased brain perfusion [5], it is understandable that cerebral oxygenation takes part in the relationship between vascular health and cognitive performance. Previous studies investigating the relationship between vascular health and cognitive function have not been observed the profile of functional cerebral oxygenation and focused more on one age-group and included both genders. Hence, in this study, we aimed to assess the association between vascular parameters, executive performance in a computerized modified stroop task and prefrontal cortex oxygenation during the task in young and older males. We hypothesized that (1) vascular parameters would be associated with executive performance in older males but not in young males; (2) better vascular parameters would be associated with greater prefrontal cortex (PFC) oxygenation change during the Stroop task in young and older males; (3) greater PFC oxygenation change during a Stroop task would associate with better executive function performance in young and older males.

MATERIAL AND METHODS

Participants. Considering the influence of female sex hormones on cardiovascular function and prefrontal cortex, we decided to focus specifically on males [6]. Young males aged between 18 and 35 years old and older males aged between 55 and 70 years old were considered for inclusion in this study. A communication campaign in the University and in local media allowed us to recruit 30 young males and 26 older males. They were non-smokers, did not undergo major surgery in the 6 months prior to the experiment, did not report any neurological or psychiatric disorders, did not suffer from cardiovascular disease and were not taking medication known to affect cognition or the cardiovascular system. Data from one young participant were deleted because of technical difficulties in measuring baroreflex sensitivity, as well as data from two older participants who did not complete the full protocol. The final sample size was 29 young males and 24 older males. The protocol was reviewed and approved by a national ethics committee for non-interventional research (CERSTAPS # 2017-231117) and was

conducted in accordance with recognized ethical standards and national/international laws.

Experimental design. Once included, participants had to complete to testing sessions. During the first session, participants completed the informed consent form, a Beck's Depression Inventory-II questionnaire and a Montreal Cognitive Assessment (MoCA) test. Then, participants completed anthropometry measurements to obtain height, weight and body composition (Tanita BC418, Tanita Corp., Tokyo, Japan) and performed the computerized modified Stroop task combined with a measure of prefrontal oxygenation. At the end of the first session, all participants were given a 24-h ambulatory blood pressure measurement device to obtain measures of 24h-, daytime- and nighttime-systolic and diastolic blood pressure. During the second session, participants were assessed for the carotid-femoral pulse wave velocity (PWV) and baroreflex sensitivity (BRS). To avoid any residual fatigue induced by recent workout, participants were asked to refrain from strenuous exercise the day before each session. They were also asked to abstain from alcohol and caffeine-containing beverages 24 hours before the test in order to avoid any influence of these beverages on the regulation of the cardiovascular system. Both sessions were administered between 8:00 a.m. to 4:00 p.m., with at least 48h between each.

Measurement of cognitive performance. The Computerized Modified Stroop task used in this study is based on the Modified Stroop Color Test [11] and included three experimental conditions: naming, inhibiting, and switching. Each block lasted between 2-4 minutes and was interspersed with sixty-second resting blocks. Overall, there were three experimental task blocks (one naming, one inhibiting, and one switching) and two resting blocks, for a total length between 8-14 min. In total, there were sixty naming trials, sixty inhibiting trials, and sixty switching trials. All trials began with a fixation cross (or square for switching condition) for 1.5 s, and all visual stimuli appeared in the center of the computer screen for 2.5 s. Participants provided their responses with two fingers (index and major finger) from each of their hands on an AZERTY keyboard. In the Naming block, participants were presented with a visual stimulus of the name of colors (RED/BLUE/GREEN/YELLOW) in French presented in congruent color with the word and participants were asked to identify the color of the ink with a button press. In the Inhibition block, each stimulus consisted of a color-word (RED/BLUE/GREEN/YELLOW) printed in the incongruent ink color (i.e., the word RED was presented in blue ink). Participants were asked to identify the color of the ink (i.e., blue). In the Switching block, in 25% of the trials, a square in place of the fixation cross appeared before the word. When this occurred, participants were instructed to read the word instead of identifying the color of the ink (i.e., RED). As such, within the Switching block, there were both inhibition trials in which the participant had to inhibit their reading of the word and correctly identify the color of the ink, and there were switch trials in which the participant had to switch their response mode to read the word instead of identifying the color of the ink when a square appeared before the word presented. Visual feedback on performance was presented after each trial. A practice session was completed before the acquisition run to ensure the participants understood the task. The practice consisted of a shorter version of the task. Dependent variables were reaction times (ms) and the number of errors committed (%). This task

and procedure have been used successfully in previous studies [12], [13].

Measurement of prefrontal cortex oxygenation. The concentration changes of HbO_2 (ΔHbO_2) were acquired with the PortaLite fNIRS system (Artinis Medical Systems, Elst, Netherlands). This system utilizes near-infrared light, which penetrates the skull and brain but is absorbed by hemoglobin (Hb) chromophores in capillary, arteriolar, and venular beds [7]. The light was transmitted with two wavelengths, 760 and 850 nm, and data were sampled with a frequency of 10 Hz. The PortaLite uses wireless technology (Bluetooth), which allows participants to walk and move without the restriction of wires. Two sensors were placed on the forehead of the participants, one on the right and one on the left side. According to the modified international EEG 10–20 system, both devices were positioned at the height of 10% of the nasion-inion distance from nasion, and the middle of the device was placed at 5% of the head circumference to the left and right from midline, to avoid measuring the midline sinus. These locations target left and right Brodmann's areas 9 and 10, which roughly represent the dorsolateral and anterior prefrontal cortex (PFC). The sensors were shielded from ambient light with a black cloth. Oxysoft version 3.0 (Artinis Medical Systems, Elst, Netherlands) was used for data collection. This protocol for optode positioning was used successfully in a recent study [8].

Measurement of blood pressure. Blood pressure parameters were measured with an ambulatory blood pressure measurement device (Mobil-O-Graph, I.E.M GmbH, Stolberg, Germany). Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP; MAP = 1/3 SBP + 2/3 DBP) were measured every 20 minutes during a 24-h period and were divided into daytime (8 am to 10 pm) and night-time (from 10 pm to 8 am) periods.

Measurement of carotid-femoral pulse wave velocity. Pulse wave velocity was evaluated between the carotid and femoral artery, with the participant lying in the supine position. Pulse measurements were performed non-invasively using the SphygmoCor probe (AtCor Medical, USA) over the carotid and femoral artery while an ECG recording was performed simultaneously. A minimum of 11 sec of signal were recorded after a strong, accurate, and reproducible pulse wave signal was obtained. The transit time from the R-wave of the simultaneously acquired electrocardiogram to the foot of the carotid and femoral pulse is measured. The difference between these two transit times is divided by distances measured from the body surface to estimate the arterial path length in order to calculate the carotid-femoral PWV.

Measurement of baroreflex sensitivity. Baroreflex sensitivity data were obtained by a non-invasive continuous blood pressure monitor (Finapres NOVA, FMS Company, the Netherlands) that continuously monitor and collect hemodynamic data. Arterial blood pressure was obtained continuously and noninvasively from a finger cuff by using the system with the volume-clamp technique maintaining the diameter of the artery under an inflated finger cuff at a set point, thereby determining arterial pressure with time changes. Diodes were located in the finger cuff, on either sides of the finger, to detect changes in artery diameter and change the inflation of the cuff to remain the diameter at the set point. The cuff was inflated or deflated via an air bladder connected to an air hose and pump. The software, using a mathematical

model, generates an aortic pulse waveform from the finger arterial pressure wave. This computation takes into account changes in the pulse pressure and waveform shape as the pressure pulse is transmitted down the brachial arteries to the finger arteries. With the Finapres finger cuff, left ventricular stroke volume was calculated and together with heart rate and BRS were calculated. The BRS was calculated at rest and in a supine position. The measured index was derived from a mean of 3–6 cardiac cycles and parameters, such as age, sex, body height and weight, were also included in the computation for each individual subject.[10]

Statistical Analysis. Standard statistical methods were used for the calculation of means and standard deviations. Normal Gaussian distribution of the data was verified by the Shapiro–Wilks test and homoscedasticity by a modified Levene Test. A t-test for independent samples was used to test the null hypothesis of an absence of difference between groups. The test of Mann-Whitney was used when at least one of the two underlying assumptions for a parametric procedure was not verified. The magnitude of the difference was assessed by the Cohen's d (d). The magnitude of the difference was considered either small ($0.2 < d < 0.5$), moderate ($0.5 < d < 0.8$), or large ($d > 0.8$) (Cohen, 1988). The product moment correlation of Pearson was used to test the null hypothesis of the absence of association between relevant variables. The non-parametric rank-order correlation of Spearman was preferred when at least one of the two underlying assumptions for a parametric procedure was not verified. The significance level was set at $p < .05$ for all analyses. All calculations were made with Statistica 7.0 (StatSoft, Tulsa, USA).

RESULTS

The characteristics of participants are presented in Table 1. In addition to a very important difference in age ($p < .01$, $d = 8.74$), both groups were also characterized by a moderate difference in body weight ($p < .05$, $d = 0.58$). Vascular parameters as well as performance during the modified computerized Stroop task and the associated PFC oxygenation are shown in Table 2. Older males presented higher PWV, heart rate and blood pressures than young males ($p < .05$, $0.54 < d < 1.51$), and lower BRS ($p < .05$, $d = 1.12$). They were also slower during the computerized modified Stroop task, whatever the condition (i.e. naming, inhibition and switching; $p < .05$, $1.7 < d < 1.9$). However, we did not find any difference in PFC oxygenation, whatever the condition of the test or the side of the PFC.

Association between cognitive performance and vascular parameters. These variables were not associated in young participants. In older participants, we found an association between reaction time in the naming condition and daytime systolic blood pressure ($r = 0.42$, $p = .04$), between reaction time in the inhibition condition and 24-h systolic blood pressure ($r = 0.47$, $p = .02$), daytime systolic blood pressure ($r = 0.58$, $p = .01$) and 24-h mean arterial blood pressure ($r = 0.41$, $p = .04$), and between reaction time in the switching condition and 24-h systolic blood pressure ($r = 0.41$, $p = .04$), daytime systolic blood pressure ($r = 0.52$, $p = .01$), 24-h diastolic blood pressure ($r = 0.42$, $p = .04$) and 24-h mean arterial blood pressure ($r = 0.46$, $p = .02$).

Association between cognitive performance and PFC oxygenation. These variables were not associated in young participants. In older participants, reaction time in the switching condition was negatively associated with ΔHbO_2 in the right PFC (r = -0.49, p = .01)

Association between vascular parameters and PFC oxygenation. Young participants presented an association between ΔHbO_2 in the right PFC during the switching condition and PWV (r = 0.41; p = 0.03) or 24-h mean arterial pressure (r = .41; p = .03). Regarding the left PFC, ΔHbO_2 during the naming condition was associated with nighttime systolic blood pressure (r = .50; p < .01), while ΔHbO_2 during the switching condition was associated with heart rate (r = .42; p = .02), and daytime diastolic blood pressure (r = .40; p = .03). We found a negative association between ΔHbO_2 in the right PFC of older participants and PWV both in the naming (r = -0.45; p = 0.03) and in the switching conditions (r = - 0.48; p = 0.02). Regarding the left side of PFC, ΔHbO_2 was positively associated with baroreflex sensitivity, either in the naming (r = 0.51; p = 0.01) or in the inhibition condition (r = 0.50; p = .01).

DISCUSSION

The aim of this study was to compare the association between vascular parameters, cerebral oxygenation, and executive function performance in healthy young males and older males. Based on the existing literature, we hypothesized that the vascular parameters would associate with executive function in a computerized Stroop task in older males but not in young males. Secondly, we hypothesized that better vascular parameters would be associated with greater PFC oxygenation change during a Stroop task. Thirdly, we hypothesized that greater PFC oxygenation change during a Stroop task would associate with better executive function performance. The results of this study supported our first hypothesis, as we found several vascular parameters were associated with reaction time on the Stroop task, especially in inhibition and switching conditions, in older males but not in young males. For the second hypothesis, we found that better vascular parameters were associated with greater PFC oxygenation change during a Stroop task in older males. However, different from our hypothesis, a positive association was found between vascular parameters (specifically: PWV and 24-h MAP) and PFC oxygenation in young males. Regarding our third hypothesis, we observed that a greater PFC oxygenation change during a Stroop task was associated with better Stroop task performance in switching condition only in older males but not in young males.

Concerning the impact of vascular parameters on executive function, we found an association between Stroop task performance and several vascular parameters in older males. In this result, we observed that the associations were stronger with increasing the complexity of the tasks' condition. This finding is in accordance with a previous study of Mitchell et al. (2011) which assessed using Stroop task and other tasks in 668 older adults between 69-93 years old and found that PWV and pulse pressure was associated with slower processing speed and executive function performances [14]. Our findings are consistent with the hypothesis that marked poorer vascular health, such as arterial hypertension and aortic stiffness, facilitates transmission of excessive pressure and flow pulsatility into the carotid circulation where these abnormal physical forces trigger microvascular damage and remodeling that

limits flow or flow reserve, leading to microvascular ischemia, quantifiable tissue damage and reduced cognitive performance [15], [16]. On the other side, we found no association between Stroop task performance and several vascular parameters in young males. Similarly, Pase et al. (2016) from the Framingham cohort study also found that even though aortic stiffness was associated with subtle brain injury but it was not associated with cognitive deficits in young adults (between 30-45 years old) [17]. All of this shows that vascular health is associated with vascular risk factors not only in older adults but also in young adults. However, the manifestation of the brain tissue injury into cognitive deficits seems to depend on the length of exposure of the vascular risk factors.

Hypertension and aortic stiffness are associated with not only accelerated cognitive decline but also increased the incidence of small vascular disease [3]. These conditions could decrease the vascular wall compliance, which leads to excessive pulsatile force output in the microcirculation [14], increased microvascular injury, impaired perfusion and oxygen transport [18]. End organs with high-flow characteristics, such as the brain, are particularly vulnerable by those conditions. Consequently, increased blood pressure or aortic stiffness could manifest into reduced cerebral perfusion and brain injury. In our study, older males are higher blood pressure parameters and PWV are associated with greater PFC oxygenation change during a Stroop task. Interestingly, a negative association between vascular parameters and ΔHbO_2 change during Stroop task was observed in young male participants. Comparing with the results in older males, it showed older and young males might have a different neurovascular response to cognitive load. The negative association between PWV and ΔHbO_2 change during Stroop task in young males may be related to the compensation and dedifferentiation of brain resources recruitment. According to Cabeza (2002), compensation is an additional increase of neuronal activity to counteract neural deficits that aim to preserve task or cognitive performance, while dedifferentiation relates to the inefficiency of neuronal processes that impaired task or cognitive performance [19]. Back to our results, it seems that in young adults, poorer vascular parameters related to a greater neural deficit and less efficient of neural processing. Therefore, increase cerebral hemodynamics is regarded as a compensation for the cognitive shortage to maintain cognitive performance. Young adults, have been reported to have greater cerebrovascular reserve than the older adults [20], seem able to increase their cerebral hemodynamics in response to increase cognitive challenge in Stroop task's conditions. Meanwhile, older males did not have the same capacity as young adults to increase their cerebral hemodynamics during Stroop task. This condition lead to a failed compensation mechanism and resulted as a decline in Stroop performance.

Lower availability of HbO_2 impaired cognitive performance [21]–[23]. The same association also reported using the Stroop task paradigm in young adults [12], [24] and older adults [21]. Our results in the relationship between ΔHbO_2 change during Stroop task and reaction time performance in older males are consistence with results from the mentioned studies. However, no association between ΔHbO_2 and reaction time performance predicting that, in young males, individuals with poorer vascular parameters buffered their neural deficit and inefficiency with increased PFC hemodynamics to maintain their cognitive performance. This

method of neural response has been observed in the previous study of Cabeza (2002) and Reuter-Lorenz (2008) that found increased brain activation in older subjects related to less optimal brain function than young subjects [25], [26]. One of the hypotheses that describe the situation is the Compensation-related Utilization of Neural Circuits Hypothesis (CRUNCH) proposed by Reuter-Lorenz and Cappell [27]. The main principle of the CRUNCH is that in the impaired or less optimal brain, a submaximal load of cognitive tasks would result in over-activation of the brain. The over-activation would put the brain closer to its limit. At some point, the cognitive performance would suffer due to limited available cognitive or neurovascular reserve. Therefore, according to our results, Stroop task conditions are expected to be within the capacity of cognitive or neurovascular reserve in young males, but not in older males, especially in switching condition of the Stroop task.

CONCLUSION

This study observes the association between vascular variables, PFC oxygenation, and executive functions in young and older males. Vascular health is associated with reaction time in the Stroop task in older males but not in young males. Increased cerebral oxygenation, more specifically in the right PFC, is expected to play a major factor in this neurovascular activity. In young males, poorer vascular parameters associated with greater PFC oxygenation change during a Stroop task, showing higher cognitive resource usage to maintain cognitive performance. Meanwhile, poorer vascular parameters in older males were associated with less PFC oxygenation change, supposing to some limitation in their capacity to increase oxygenation in the right PFC especially in higher cognitive load. Consequently, even though young and older males have a different neurovascular response to executive function load, better vascular parameters associated with direct and potential benefits to PFC oxygenation and cognitive function not only in older males but also in young males.

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Table 1: Characteristics of Study Participants. Data are presented as mean (SD)

	Young males (n=29)		Older males (n=24)		Cohen's d
Age (yrs)	23.5	(4.1)	60.8	(4.6) *	8.74
Height (cm)	175.3	(6.3)	175.8	(6.0)	0.08
Weight (kg)	74.6	(12.8)	81.9	(12.6) *	0.58
BMI	24.1	(4.3)	26.5	(4.6)	0.50

PWV, Pulse Wave Velocity; BRS, Baroreflex Sensitivity; MAP, Mean Arterial Pressure; ΔHbO_2, change of oxyhemoglobin during Stroop task;

*different from Young Males ($p < .05$)

Table 2: Vascular parameters, PFC oxygenation, and cognitive performance of study participants. Data are presented as mean (SD)

	Young males (n=29)		Older males (n=24)		Cohen's d
Vascular Parameters					
PWV (ms^{-1})	5.94	(1.1)	8.2	(1.8) *	1.51
BRS	13.3	(3.4)	8.9	(4.4) *	1.12
HR (beats/minute)	58.9	(8.5)	66.1	(8.8) *	0.84
24-h SBP (mmHg)	112.8	(6.7)	121.2	(6.3) *	1.28
24-h DBP (mmHg)	73.9	(9.2)	79.6	(6.8) *	0.68
24-h MAP (mmHg)	86.9	(7.0)	93.4	(5.9) *	0.99
Daytime SBP (mmHg)	117.7	(6.8)	125.5	(6.2) *	1.18
Daytime DBP (mmHg)	78.5	(10.7)	84.1	(10.4) *	0.54
Nighttime SBP (mmHg)	102.7	(9.4)	112.9	(8.2) *	1.14
Nighttime DBP (mmHg)	64.8	(7.3)	73.6	(7.1) *	1.23
PFC Oxygenation					
Right ΔHbO_2					
Naming (umol)	2.2	(1.9)	2.0	(1.4)	0.08
Inhibition (umol)	3.1	(2.0)	2.5	(1.4)	0.35
Switching (umol)	3.9	(2.0)	3.3	(1.8)	0.29
Left ΔHbO_2					
Naming (umol)	2.2	(1.6)	2.5	(1.8)	0.13
Inhibition (umol)	2.8	(1.6)	3.0	(2.0)	0.12
Switching (umol)	4.2	(1.8)	3.7	(1.9)	0.29
Reaction Time					
Naming (ms)	598.5	(101.9)	833.6	(135.8) *	1.9
Inhibition (ms)	705.6	(120.4)	998.0	(181.7) *	1.9
Switching (ms)	970.8	(188.7)	1511.8	(411.3) *	1.7

PWV, pulse wave velocity; BRS, baroreflex sensitivity; 24-h, 24-hour; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; daytime, 7 am-11 pm; nighttime, 11 pm-7 am.ΔHbO_2, change of oxyhemoglobin during Stroop task;
*different from Young males ($p < .05$)

GENERAL DISCUSSION

The aim of this section is to discuss the results obtained in this thesis. We followed two objectives. The first one was to understand the effect of age, CRF, and physical activity on cerebral oxygenation and executive function in males. The second one was to identify the influence of age on the interaction between vascular health and executive function. To obtain those objectives, five studies were conducted : (1) Prefrontal oxygenation reserve: the relationship between physical activity level and the cognitive load during a Stroop task in healthy young males; (2) CRF, blood pressure, and cerebral oxygenation during a dual-task in healthy young males; (3) Master athletes and cognitive performance: what are the potential explanatory neurophysiological mechanisms? (review article); (4) The relationship between CRF and prefrontal oxygenation during a Stroop task in healthy older males; and (5) The correlation between vascular parameters, prefrontal cortex oxygenation, and Stroop task performance in young and older males.

The hypotheses tested in those studies are : (1) Physical activity levels and CRF are related to a better executive performance in both young and older males (2) Benefits of physical activity to the brain structures, brain functions, and executive function performances in older adults could be explained by change in cerebrovascular dynamics; and last (3) Vascular parameters are related to executive function, and the age influences the association between vascular parameters and executive function.

This general discussion will be presented into three parts, starting with the relationship between physical activity and CRF and executive functions, followed by a discussion about the effect of PFC oxygenation on executive functions. Last, we will discuss the mediation effect of PFC oxygenation.

Benefits of physical activity and CRF on executive function

Regular physical activity has been recognized to influence cognitive performance throughout the lifespan (Berryman, Pothier, and Bherer 2018). This beneficial effect on cognition is more specific to executive functions, a subset of high-order cognitive functions including planning, inhibition or switching, that are mainly supported by the prefrontal regions of the cortex (Kramer et al. 1999; Miyake et al. 2000).

From the first and second studies, we identified that: (1) physical activity or CRF was related to flexibility in the Stroop task and working memory in dual-task condition but not in the single-task condition in young males. (2) Active participant displayed faster reaction time in flexibility but not inhibition compared to inactive ones (3) CRF was associated with better accuracy in 2-back dual-task condition but not in single-task condition. These results are in line with a

longitudinal study that reported a specific physical activity level effect on the switch and mixing costs in task switching in young adults (Kamijo and Takeda 2010). Further, these results are also in accordance with a cross-sectional study of younger adults and older adults using the Stroop task (Dupuy et al. 2015) and dual-task (Fraser et al. 2016). All these results suggest that fulfilling physical activity recommendations (of ≥ 150 mins/week) and having a high CRF level have a positive impact on cognition in healthy young males, specifically in the most complex executive tasks.

We conducted several studies to assess the relationship between physical activity and executive functions in older males. In our third study, the effect of physical activity on cognitive performance, specifically on executive functions, and the potential neurophysiological mechanisms that underlie those effects were studied in master athletes. Our literature review about master athletes clearly showed that physical activity benefited executive functions in several areas. In fact, master athletes have been reported with greater gray and white matter volumes than inactive subjects. Even though not yet concluded, improved cerebrovascular health seems to be the basis of those benefits. Cross-sectional experimentation in the fourth study, which was conducted in older male participants, confirmed the results from the third study that higher CRF was related to faster reaction time in the Stroop task.

Regarding those results, the benefits of physical activity and CRF to executive functions in older males were observed in all tasks and conditions. These results are in agreement with Zaninotto (2018), who reported a progressive age-related decline in executive function in males after fifty years old (Zaninotto et al. 2018). We found no effect of CRF on reaction time in overall healthy older males. This ambiguous finding might be attributed to the differences in CRF across the older age spectrum, as mentioned in the study of Fleg (2005), which reported that the rate of decline in CRF accelerated from 10% per decade in the 40s to more than 20% per decade in the 70s and beyond (Fleg et al. 2005). Interestingly, after age sub-grouping, we found a main effect of fitness on Stroop task performance in the group of 61-69 years old males. In conclusion, as in young males, higher CRF enables older males, more specifically between 61-69 years old, to have a better performance in the executive function conditions.

Interchangeability between physical activity and CRF is an issue that needs to be addressed as they represent two different dimensions (Rennie and Wareham 1998). Physical activity is defined as any bodily movement produced by skeletal muscles and resulting in energy expenditure, while CRF is defined as the ability of the circulatory and respiratory systems to supply fuel during sustained physical activity (Caspersen, Powell, and Christenson 1985). The relation between physical activity and CRF across the adults' age span is still an ongoing debate. Nevertheless, the correlation analysis that we calculated from our participants showed that physical activity was strongly related to CRF in young males ($r = .62$; $p < .01$) and moderately related to CRF in older males ($r = .46$; $p = .03$). An age-based group fractioning increases the strength of correlation between physical activity and CRF in older males in group of 55-59 years old males ($r = .63$; $p = .05$) and in group of 60-69 years old males ($r = .69$; $p < .02$). All those correlations suggesting that physical activity and CRF can be interchangeably in our

participants and emphasized the importance of age-grouping when studying CRF in older adults.

Taken together, higher physical activity and CRF related to a better executive function performance, especially in the most complex tasks or conditions. Therefore, being physically active or having a good CRF level is beneficial to executive function performance for both young and older males and also triggered speculation whether these benefits were related to some kind of greater cognitive reserve capacities when the cognitive load is high but not at the submaximal load.

What is already known on this subject
➢ Physical activity and CRF are beneficial to executive function performance in older adults ➢ The relation between physical activity and CRF in adults is not yet concluded ➢ Aging decreases both physical activity and CRF progressively

What this study adds
➢ Physical activity and CRF are beneficial to executive function performance not only in older males but also in young males (18-35 years old), but only in high cognitive load tasks (switching condition or dual-task n-back) ➢ Physical activity and CRF are correlated in young and older adults. ➢ Age sub-grouping is important to analyze physical activity and CRF, especially in older males

Effect of PFC oxygenation on executive function

Several stimuli, such as cognitive tasks, can activate neurons leading to electrical and chemical activities. The immediate energy needs of activated neurons are met by oxidation of lactate present in the extracellular space, resulting in a transient decrease in lactate levels and oxygen concentrations (Pellerin and Magistretti 1994). As oxygen concentrations decrease, the lack of energy for ATP synthesis via oxidative phosphorylation causes an increase in the level of extracellular adenosine and lactate. These conditions resulting in larger arteriole dilation and greater blood flow at the activated brain regions, thus providing a transient increase in HbO_2 and a relative decrease in ΔHHb, due to the increased HbO_2 concentration (Magistretti and Allaman 2015). Therefore, a greater change of cerebral oxygenation should give a positive impact on cognitive performance, more specifically, oxygenation on the prefrontal cortex for executive performance (Albinet et al. 2014; Dupuy et al. 2015; Fraser et al. 2016).

The first and second studies allowed us to show that PFC oxygenation changes during a cognitive task were concurrent with a better cognitive performance in young males, but from the fifth study, we found that PFC oxygenation, especially in the right PFC, negatively correlated with cognitive performance (slower reaction time) in Stroop task in switching

condition. Therefore, we found that PFC oxygenation is not consistently related to cognitive performance in young males. On the other side, from the third study, a greater amplitude of PFC oxygenation during exercise or cognitive tasks was associated with better cognitive performance in older adults. This statement was confirmed in our fourth and fifth studies that greater ΔHHb change during executive conditions of the Stroop task in the right PFC corresponded with faster reaction time in the Stroop task in older males.

Comparing those results in young and older males, suggested that they had a different neurovascular response to cognitive load. This may be related to the compensation and dedifferentiation of brain resources recruitment. According to Cabeza (2002), compensation is an additional increase of neuronal activity to counteract neural deficits that aim to preserve task or cognitive performance, while dedifferentiation relates to the inefficiency of neuronal processes that impaired task or cognitive performance (Cabeza 2002). It seems that in young adults, poorer vascular parameters were related to a greater neural deficit and less efficient neural processing. Therefore, increase cerebral hemodynamics is regarded as compensation for the cognitive incapacity to maintain cognitive performance. Young adults have been reported to have greater cerebrovascular reserve than the older adults (Davenport et al. 2012), thus being able to increase their cerebral hemodynamics in response to an increased cognitive challenge in the Stroop task's conditions. Meanwhile, older males who did not have the same capacity as young males to increase their cerebral hemodynamics failed to use this compensation mechanism, which resulted in a decline in cognitive performance.

To sum up, the relationship between PFC oxygenation and executive performance in young and older males is still inconclusive. There are two possibilities for these conditions. First, young and older males have a different cerebral hemodynamics response to a given cognitive load. Secondly, they may have the same cerebral hemodynamics to a cognitive load, but there are other factors that influence this relationship. Therefore, in the following part, we will discuss several factors that affect PFC oxygenation to observe the relationship between PFC oxygenation and executive function more comprehensively.

What is already known on this subject

- PFC oxygenation affect cognitive performance positively, especially the executive function performance
- Increase cerebral oxygenation can be caused by a compensation action from less efficient neural processing or neural activity deficit on other brain regions

What this study adds

- PFC oxygenation is positively related to executive function performance only in older males, the results in young males are still inconclusive
- Inconsistent results in young males might occur because of the compensation mechanism which increases PFC oxygenation to maintain cognitive performance

- Observation of factors regulating PFC oxygenation is needed to clarify the link between PFC oxygenation and executive function performance

Factors that influence PFC oxygenation

As oxygen in the brain is delivered by the hemoglobin via the circulatory system, the cerebral oxygenation is closely related to the cerebral blood flow (Lucas et al. 2010). There are several determinants that regulate cerebral blood flow, such as neurovascular coupling, cerebral autoregulation, blood pressure, autonomic nervous system, and arterial blood gases. In this general discussion, we will explore three factors that influence the cerebral blood flow and cerebral oxygenation, specifically oxygenation in the PFC region: (1) Blood pressure and aortic stiffness; (2) Physical activity and CRF; and (3) Age.

a. Blood pressure and aortic stiffness

The regulation of blood pressure has been recognized as a complex mixture of neural, hormonal, and intrinsic factors involving the brain, heart, vasculature, and especially the kidneys due to its control of fluid balance (Hellsten and Nyberg 2016). Hypertension and aortic stiffness are associated with an accelerated cognitive decline and also with an increased incidence of small vascular disease (Singer et al. 2014). These conditions could decrease the vascular wall compliance, which leads to excessive pulsatile force output in the microcirculation (Mitchell et al. 2011), increased microvascular injury, impaired perfusion and oxygen transport (Mitchell 2008). End organs with high-flow characteristics, such as the brain, are particularly vulnerable by those conditions. Consequently, increased blood pressure or aortic stiffness could manifest into reduced cerebral perfusion and brain injury. In our study, older males with higher blood pressure parameters and greater aortic stiffness were associated with a lower PFC oxygenation change during a Stroop task. Interestingly, the inverse relationship between vascular parameters and ΔHbO_2 change during switching condition in a Stroop task was also observed in young male participants. When comparing our groups, it appeared that older males had a different neurovascular response to cognitive load than young males. Relating the results from the fifth study that vascular parameters were not related to Stroop performance in young males while a greater ΔHbO_2 correlated with a better executive function performance, the negative association between vascular parameters and ΔHbO_2 change during Stroop task in young males may be related to the compensation mechanism in neural activation. Increased blood pressure and greater aortic stiffness decrease neuronal activity which later stimulate more neural recruitment. This compensation mechanism is seems to be utilized to maintain cognitive performance as proposed by Cabeza (2002) (Cabeza et al. 2002).

b. Physical activity and CRF

Physical activity and CRF have been reported to be beneficial for cerebrovascular control via grey and white matter structural changes, cerebrovascular adaptations, and neurotrophins release. The exercise-induced shear stress and hypoxia seem to be the basis of physiological

stimuli for the adaptations detected after exercise training in healthy subjects (Chobanian et al. 2003; Tinken et al. 2010; Dupuy et al. 2019). From the first and second studies, we observed that physical activity and CRF were related to greater change in PFC oxygenation during executive function tasks in young males. From the fourth study, we knew that CRF also had a similar effect on PFC oxygenation change during Stroop task in older males, especially in 60-69 years old participants. It should be noted that, in those studies, an increase in PFC oxygenation change was always followed by a better executive performance. Taken together, physical activity and CRF related to increasing PFC oxygenation changes during cognitive tasks and better executive function performances, both in young males and older males.

c. Age

The age-related increase in blood pressure is accompanied by an increase in cardiovascular risk that manifests beyond BP levels of 115/75 mmHg (Lewington et al. 2002). Evidence suggests that the increase in blood pressure is preceded by an increase in arterial stiffness (Kaess et al. 2012). To some extent, the age-related increase in arterial stiffness and BP are unavoidable and are associated to lifestyle (participation in physical activity, diets, or psychological stress) (McEniery et al. 2010; Thijssen et al. 2010).

Regarding the relationship with physical activity, aging has been related to a progressive decline in physical activity and CRF (Fleg et al. 2005). Aging is also associated with poorer vascular health, including higher blood pressure, higher aortic stiffness, and lower baroreflex sensitivity, than young adults (Xing et al. 2017). Indeed, our data confirmed this trend as our older participants had a lower physical activity and CRF compared to the young participants. Moreover, they also have relatively poorer vascular health than young participants. Thus, we confirm the results from the literature.

As already discussed previously, poorer physical activity, CRF, and vascular profiles in older males lead to a smaller cognitive and cerebrovascular reserve in the older males compared to young males. Those conditions make older males more susceptible to perform poorly in cognitive tasks, especially the ones that include executive functioning.

What is already known on this subject
➢ There are several factors that regulate cerebral blood flow, such as neurovascular coupling, cerebral autoregulation, blood pressure, autonomic nervous system, and arterial blood gases ➢ Increased blood pressure or aortic stiffness decrease the vascular wall compliance and increase microvascular injury, which leads to reduced cerebral perfusion ➢ Physical activity and CRF have been reported beneficial for cerebrovascular control via grey and white matter structural changes, cerebrovascular adaptations, and neurotrophins release ➢ Aging has been related to a progressing decrease in physical activity and CRF and poorer vascular profiles

What this study adds

- Older males with high blood pressure and greater aortic stiffness display a lower PFC oxygenation change during a Stroop task. In young males, higher blood pressure and greater aortic stiffness are associated with a higher PFC oxygenation during switching condition in Stroop task
- The negative association between vascular parameters and ΔHbO_2 change during Stroop task in young males confirmed the compensation mechanism in neural activation that was proposed in the previous part of the discussion
- Physical activity and CRF are related to an increase in PFC oxygenation changes during cognitive tasks and better executive function performances in Stroop and dual-task, both In young males and older males
- Poorer executive function performance in older males seems to relate to a smaller cognitive and cerebrovascular reserve than young males

GENERAL CONCLUSION

Throughout the lifespan, regular physical activity has been recognized to give beneficial effect to cognitive performance. This beneficial effect on cognition is more specific to executive functions, a subset of high-order cognitive functions including planning, inhibition or switching, that are mainly supported by the PFC. PFC oxygenation is one of the physiological mechanisms that regulates executive performance and has been observed associated with physical activity and CRF. Therefore, understanding of how PFC oxygenation affect executive function and factors that influence it will shed a light on link between physical activity and cognition.

Through this thesis, we tried to understand the relationship between physical activity and CRF and executive functions, the effect of PFC oxygenation on executive functions, and the mediation effect of PFC oxygenation in young and older males.

In the relationship between physical activity and CRF and executive functions, we found that :

- Physical activity and CRF are beneficial to executive function performance not only in young and older males, but only in high cognitive load tasks (inhibition and switching condition in Stroop task or dual-task in n-back task).
- Physical activity and CRF are interchangeable in young and older males.
- Age-grouping is important when studying CRF in older males.

Regarding the link between PFC oxygenation and executive performance, our studies show as that :

- PFC oxygenation is positively related to executive function performance only in older males, but not in young males
- Young males might use the compensation mechanism which increases PFC oxygenation to maintain cognitive performance

We observed several factors that influence PFC oxygenation: Blood pressure, aortic stiffness, baroreflex sensitivity, physical activity, CRF, and age. Several results from this observations are :

- Older males with high blood pressure and greater aortic stiffness displayed a lower PFC oxygenation change during a Stroop task. In young males, higher blood pressure and greater aortic stiffness are associated with a higher PFC oxygenation during switching condition in Stroop task

- The negative association between vascular parameters and ΔHbO_2 change during Stroop task in young males confirmed the compensation mechanism in neural activation that was proposed in the previous part of the discussion
- Physical activity and CRF are related to an increase in PFC oxygenation changes during cognitive tasks and better executive function performances in Stroop and dual-task, both In young males and older males
- Aging seems to relate to a smaller cognitive and cerebrovascular reserve than young males

Taken together, this thesis give us an insight on the relationship between physical activity, PFC oxygenation, and executive performance in males. Results from this thesis show us that both young and older males can get advantage in executive performance by being physically active or having good cardiorespiratory fitness and this link can be explained by change in PFC oxygenation

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