Université de Montréal

Mind the rhythm: Associations between cardiac electrophysiology and cognition in healthy older adults and patients with atrial fibrillation

par

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Thèse présentée à la Faculté de médecine en vue de l'obtention du grade de doctorat (PhD)

en sciences biomédicales, option sciences du vieillissement

August 2022

Université de Montréal

Faculté des études supérieures : Faculté de médecine

Cette thèse intitulée

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Résumé

Il existe une association étroite entre la santé cardiovasculaire et la santé cognitive au cours du vieillissement. Bien que la recherche dans le domaine de la santé cardiovasculaire soit vaste, le lien entre l'électrophysiologie cardiaque et la cognition est peu étudié. La présente thèse met en évidence les liens entre l'électrophysiologie cardiaque et la cognition en examinant la régulation autonomique chez les individus sains et des marqueurs de maladie chez les patients souffrant de fibrillation auriculaire (FA ; maladie du rythme cardiaque la plus prévalente). Les résultats présentés dans le chapitre 2 démontrent pour une première fois qu'un marqueur de repolarisation cardiaque, le QTcD, est lié aux performances cognitives (fonctions globales et exécutives) chez des personnes âgées sédentaires en bonne santé. Ces observations étaient plus évidentes chez les personnes présentant des valeurs élevées de QTcD, suggérant que des altérations plus importantes du rythme cardiaque pourraient avoir une association plus forte avec les performances cognitives. Les résultats présentés au chapitre 3 montrent que chez les patients souffrant de FA, une plus grande morbidité (mesurée par le sous-type de FA) serait associée à une performance cognitive plus faible (fonctions globales et exécutives). Cette même étude démontre que le volume de l'oreillette gauche agît comme facteur modérateur de l’association entre le sous-type de FA et la performance cognitive. Ceci suggère que plus l'arythmie est sévère, plus le déficit cognitif observé est important. Le chapitre 4 présente les résultats d'une étude pilote portant sur les changements dans les performances cognitives et l'oxygénation régionale du tissu cérébral chez les patients souffrant de FA qui subissent une cardioversion électrique (une procédure visant à rétablir du rythme sinusal). Les résultats de cette étude pilote montrent qu'un tel devis est effectivement réalisable et pourrait permettre de détecter des changements cognitifs dans cet échantillon. Bien que la modification de l'oxygénation du tissu cérébral en lien avec la cardioversion n’ait pas été démontrée pour le moment, des changements au niveau de la cognition ont été observé, ce qui pourrait être partiellement expliqué par la réduction des symptômes liés à la FA post-cardioversion. Parmi toutes les capacités cognitives, la flexibilité (mesurée par le Trail-Making Test) semble être plus sensible aux détériorations du rythme cardiaque, tant chez les individus sains que chez les

patients souffrant de FA, dans toutes les études présentées. Les résultats sont discutés dans le contexte d'un continuum cœur-cerveau dans lequel les détériorations du cœur ou du cerveau peuvent avoir des impacts bidirectionnels et altérer davantage le fonctionnement de cet axe. Les orientations futures porteront sur les avantages potentiels de la prévention cognitive par l'exercice et la stimulation cognitive chez les personnes présentant des détériorations électrophysiologiques cardiaques.

Mots-clés : arythmie, rythme cardiaque, fonction autonomique, repolarisation cardiaque, cardioversion, charge de la fibrillation auriculaire, vieillissement, prévention, déclin cognitif, fonctions exécutives, MoCA

Abstract

There is a close association between cardiovascular and cognitive health in aging. While the cardiovascular health domain is vast, the link between cardiac electrophysiology and cognition is understudied. The present thesis will bring evidence linking cardiac electrophysiology and cognition by looking at autonomic regulation in healthy older individuals and disease markers in patients with atrial fibrillation (AF; most prevalent disease of heart rhythm). Chapter 2 shows for the first time that a cardiac repolarization marker, QTcD, is linked to cognitive performance (global and executive functions) in healthy sedentary older individuals. This relationship was more evident in individuals with elevated QTcD values suggesting that higher impairments in cardiac rhythm might have stronger association with cognitive performance. Results presented in Chapter 3 show that among patients with AF, higher disease burden (as measured by the subtype of AF) was associated with lower cognitive performance (global and executive functions). The study also found that the left atrial volume was a moderator of this association between AF subtype and cognitive performance. This shows that the more severe the condition is the higher the cognitive deficit observed. Chapter 4 shows the results of a pilot study investigating the changes in cognitive performance and regional cerebral tissue oxygenation in AF patients undergoing electrical cardioversion (a sinus rhythm restoration procedure). The pilot results show that such a study is indeed feasible and could detect cognitive changes in this sample. While the change in cerebral tissue oxygenation is unconclusive at this moment, the recorded change in cognition could partially be explained by the reduction in AF related symptoms. Among all cognitive abilities, switching (as measured with the Trail-Making Test) appears to be more sensitive to deteriorations in heart rhythm both in healthy individuals and patients with AF across all studies presented. The results are discussed in the context of a heart-brain continuum in which deteriorations from either the heart or the brain can have bidirectional impacts and further impair the functioning of this axis. Future directions will address the potential benefit of cognitive prevention through exercise and cognitive stimulation in older individuals with cardiac electrophysiological deteriorations.

Keywords: arrythmia, heart rhythm, autonomic function, cardiac repolarization, cardioversion, atrial fibrillation burden, aging, prevention, cognitive decline, executive functions, MoCA

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List of acronyms and abbreviations

AD	Alzheimer's Disease
AET	Aerobic training group
AF	Atrial Fibrillation
ANS	Autonomic nervous system
AV	Atrioventricular
BMI	Body mass index
BOLD	Blood oxygen level dependent
BP	Blood pressure
BPM	Beats per minute
COG	Cognitive training group
CT	Cognitive training
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
DBP	Diastolic blood pressure
DM	Dual mixed (as part of the dual-task)
DSST	Digit Symbol Substitution Test
DT	Dual-task
DTC	Dual task cost (as part of the dual-task)

ECG	Electrocardiogram
ECV	Electrical cardioversion
ES	Effect size
ET	Exercise training
GDS	Geriatric Depression Scale
GMA	Gross motor abilities training group
HF	Heart failure
HR	Heart rate
HRV	Heart rate variability
HVLT	Hopkins verbal learning test
LA	Left atrium
LAAPD	Left atrial anterior-posterior diameter
LAE	Left atrial enlargement
LAV	Left atrial volume
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NIRS	Near-infrared spectroscopy

PSNS	Parasympathetic nervous system
QTc	ECG QT interval, corrected for heart rate
QTcD	ECG QT dispersion, corrected for heart rate
rSO_2	Regional cerebral tissue oxygen saturation
RT	Reaction time
SA	Sinoatrial
SD	Standard deviation
SE	Standard error
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SM	Single mixed (as part of the dual-task)
SP	Single pure (as part of the dual-task)
TIA	Transient ischemic attack
TMT	Trail Making Test
TSC	Task set cost (as part of the dual-task)

Acknowledgments

I would like to take this opportunity to acknowledge the guidance and support I received throughout the past few years without which this PhD thesis would not have been possible. First, I would like to thank Dr Louis Bherer for his invaluable mentorship, and for giving me the opportunity to pursue my research interests as part of his team. His support has given me the freedom to put in practice original ideas and his knowledge and hard work have been a source of inspiration. The work presented here was also made possible by the considerable help I received in the past years from all the LESCA lab members, in particular Sarah Clavet, Brittany Intzandt, Dr Christine Gagnon, Dr Thomas Vincent, Dr Nicolas Berryman, Dr Kristell Pothier, and Dr Maxime Lussier. Their help, critical insight, and friendship have been essential in shaping my work.

I would also like to acknowledge the financial resources that I received during my studies from Le Fonds de Recherche du Québec – Santé (FRQS), Réseau Québécois de Recherche sur le Vieillissement (RQRV), Canadian Institutes of Health Research (CIHR), and Université de Montréal, Faculty of Graduate and Postdoctoral Studies. This made it possible for me to fully dedicate my time to my research work and complete this thesis.

Finally, I would like to thank my family for their love and valued encouragement: my parents (Beatris and Iordache Vrinceanu) for their sacrifices and support without which I would not have been here today; my brother (Stefan Vrinceanu) for his energy, and positivity; and to my partner (Sophie Beland) for loving, believing, and encouraging me even during difficult times.

Chapter 1 – Theoretical background

In North America cardiovascular diseases have a prevalence of close to 50% in individuals over the age of 20 (Tsao et al., 2022), and they are also the second cause of death in Canada, and the first cause of death in the USA (Statistics-Canada, 2022; Tsao et al., 2022). Heart diseases and modifiable cardiovascular risk factors explain the majority (87%) of the risk for stroke (Diseases & Injuries, 2020; Tsao et al., 2022), and have been closely linked to cognitive impairment (Abete et al., 2014). Cardiovascular health has been shown to be a major player in cognitive health, and the functioning of the heart could be indicative of brain health. In fact, **c**ardiac functioning has been linked to cognitive deficiencies, cognitive decline, and higher rates of dementia (Abete et al., 2014; Hammond et al., 2018; Nonogaki, Umegaki, Makino, Suzuki, & Kuzuya, 2017; Stenfors, Hanson, Theorell, & Osika, 2016). This association is the strongest in individuals with cardiovascular disease, but it is also evident in individuals with cardiovascular risk factors, or even in apparently healthy individuals. As a result, a better understanding of the association between cardiac functioning and cognitive health would help uncover the mechanisms involved, identify people at risk, and potentially work towards finding prevention targets. While the cardiovascular health domain is vast, the link between cardiac electrophysiology and cognition is understudied, although the number of new studies has increased in the past few years.

Human cognitive abilities can refer to an ensemble of tasks involving primarily the acquisition, processing, storing, manipulating and recall of mental information (Carroll, 1993; Lezak, Howieson, Bigler, & Tranel, 2012; Reed, 1982). Most of the cognitive functions are known to plateau in midlife and slightly decline over the life span (Salthouse, 2012). Among those functions, psychomotor abilities, processing speed, executive functions and memory are the most affected (Harada, Natelson Love, & Triebel, 2013). Those functions are needed for the well-functioning of an individual, and slight declines associated with aging might not be significant enough to impair functioning. However, abnormally early, or faster than expected declines could be indicative of neurodegenerative disorders like dementia.

When assessing the overall cognitive abilities of individuals in the clinical setting, tests like the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) are administered (Bleecker, Bolla-Wilson, Kawas, & Agnew, 1988; Rossetti, Lacritz, Cullum, & Weiner, 2011). Those short interview-based tests survey most of the cognitive abilities in order to identify if individuals show abnormally low scores that could indicate a cognitive disorder. For a more in-depth evaluation, researchers can use a variety of tests targeting specific cognitive abilities. The executive functions (inhibition, switching, working memory, and dual tasking) are an important set of abilities that are involved in reasoning, planning, organizing, self-monitoring, and problem-solving (Diamond, 2013; Jurado & Rosselli, 2007; Miyake & Friedman, 2012; Miyake et al., 2000). They are one of the earliest functions to decline, in average 3 to 7 years before memory, and this decline can predict global cognitive decline and even onset of dementia (M. C. Carlson, Xue, Zhou, & Fried, 2009; Kirova, Bays, & Lagalwar, 2015). The decline in those cognitive abilities is also closely linked to brain deteriorations.

Age-related declines in the overall brain volume, grey matter volume and the white matter integrity have been documented across the brain with the frontal and parietal cortices being the most affected (Fjell & Walhovd, 2010; Madden, Bennett, & Song, 2009; Raz et al., 1997). Those changes are gradual and will eventually result in slight declines in executive functions and memory since those functions rely heavily on those brain areas. The higher order abilities like the executive functions are often associated with the dorsolateral prefrontal cortex (Szameitat, Schubert, Muller, & Von Cramon, 2002; Wang et al., 2011), while the medial temporal lobe (including the hippocampal region) is known to be a key area for memory (Guerrero et al., 2021; Squire, Stark, & Clark, 2004). In the context of aging studies have shown an association between better cognitive abilities and larger brain volume, greater cortical thickness, and overall better brain structural health markers in their associated areas (Lye et al., 2004; Yuan & Raz, 2014). Brain functional networks are also vital in the well-functioning of the executive functions and memory since those complex cognitive abilities rely on multiple brain areas. Evidently, aging is also associated with functional changes, mostly due to decreases in resting blood flow, changes in oxygen consumption rate, vascular changes, and deteriorations in white matter (Drag & Bieliauskas, 2010; Gazzaley & D'Esposito, 2004). Ischemic lesions have been

reported to be common as part of the normal aging process in imaging studies investigating white matter hyperintensities in healthy individuals, and have been suggested to be one of the causes for the brain functional changes observed in aging (d'Arbeloff et al., 2019; Gunning-Dixon & Raz, 2000). However, cardiovascular risk factor and cardiovascular diseases (in particular atrial fibrillation) are also known to exacerbate them, highlighting that brain aging is closely linked to cardiac functioning (Moroni et al., 2018).

The present literature on the association between cardiovascular health and cognition is moving towards a global perspective in which both the heart and the brain are on a continuum and impairments at any level on this axis can result in impairments in both cognition and cardiovascular health. One example for this shift is reflected in our current understanding of dementia. Alzheimer's Disease (AD), a neurodegenerative disease that is the most prevalent type of dementia, was thought to have vascular causes in the early research years, but with advanced imaging tools unique biomarkers were identified, suggesting that AD is separate from vascular dementia (Iadecola, 2013). Today however, new research shows that most cases of dementia are in fact mixed dementias with both vascular and AD etiology (Iadecola, 2013; Rosa et al., 2020). Not only cardiovascular diseases (CVD) are known to increase the risk of dementia (for example there is a well-established strong association between arrhythmia and increased risks for stroke and AD), but the opposite is also true: brain damage has been reported to result in cardiovascular problems (for example stroke induced arrythmias). This shows that the brain and the cardiovascular system can't be studied independently even when certain conditions have unique independent presentations (i.e., AD vs. vascular dementia). Moreover, research suggests that the cognitive decline observed in dementia is the result of a slow process that starts much earlier. A better understanding of the cognitive changes and cardiovascular health before the onset of clinical cognitive decline would make it possible to better understand the mechanisms influencing the heart-brain axis.

It is well established that CVD are closely linked to an increased risk of cognitive decline and dementia. For example, multiple review studies have identified extensive evidence linking hypertension, atrial fibrillation, coronary artery disease, and heart failure to cognitive

deficiencies and decline (Abete et al., 2014; Eriksson, Bennet, Gatz, Dickman, & Pedersen, 2010; Stampfer, 2006; Stefanidis, Askew, Greaves, & Summers, 2018). Some authors have also suggested that the degree of cognitive deficiency is dependent on how far the vascular damage is on a CVD continuum, with longer exposure and more intense cardiovascular damage being linked to more severe cognitive impairment (Abete et al., 2014; Gagnon et al., 2022). This type of association is also supported by studies linking cardiovascular risk factors (CVRF) to increased rates of dementia and lower cognitive functions later in the life of clinically healthy individuals (DeRight, Jorgensen, & Cabral, 2015; Dregan, Stewart, & Gulliford, 2013; Gupta et al., 2015; Nishtala et al., 2014). The direct mechanisms involved in causing cognitive decline are thought to be similar for both CVD and CVRF, and are mainly vascular in nature involving stroke (clinical or subclinical) and cerebral hypoperfusion (Kalaria, 2012). More specifically, studies show that individuals with CVD or CVRF are more likely to have a reduction in cerebral perfusion, cerebral glucose utilization, increased white matter lesions, decreased connectivity, and cerebral atrophy (Appelman et al., 2009; J. J. Chen, Rosas, & Salat, 2013; Haight et al., 2013; Lawrence et al., 2013; Tullberg et al., 2004). Those changes can be observed globally in the brain but are even more pronounced in the frontal lobe and hippocampal region.

On the other hand, few studies support that psychological and cognitive changes (reflecting central nervous system deteriorations) can impact cardiovascular health (Manea, Comsa, Minca, Dragos, & Popa, 2015; Samuels, 2007; Tahsili-Fahadan & Geocadin, 2017; Yang, Li, Zhang, & Ren, 2020). For example, Yang et al. (2020) reported that in multiple neurological diseases like Parkinson's disease, Huntington's disease, and Alzheimer's disease, there seems to be an increased risk of developing cardiac hypertrophy, and autonomic dysfunction (often resulting in cardiac electrical remodeling and arrhythmias). In fact, many neurological diseases are known to show electrocardiographic changes which can be grouped as either arrythmias or cardiac repolarization abnormalities (Samuels, 2007). Some studies have even reported that severe psychological stress can result in cardiac lesions, which can initiate arrythmias (Bybee & Prasad, 2008; Milinis & Fisher, 2012; Wittstein et al., 2005). In addition, there seems to be significant evidence supporting an increased rate of developing cardiac complications (in particular arrhythmias) post stroke, further supporting the bidirectional relationship between

the central nervous system and the cardiovascular system (Carrarini et al., 2022; Sposato et al., 2015; Sposato et al., 2020). In most of those situations in which the cardiac complications appear following central nervous system deteriorations, the common mechanism involves changes in the autonomic nervous system (Tahsili-Fahadan & Geocadin, 2017). Moreover, recent studies have brought evidence in support of the role of the frontal lobe and the limbic system in regulating the cardiac autonomic control even in healthy individuals that do not suffer from any cardiac or cognitive disorder (Thayer & Lane, 2009). Due to this direct bidirectional relationship, it is possible that deteriorations along the heart-brain axis can initiate a vicious circle that will lead to both cardiovascular disease and cognitive decline, potentially even dementia. However, the available information on this is limited.

Significant impairments on the heart-brain axis can also be observed on a continuum from healthy individuals with minor health deteriorations up to clinical cases (involving either vascular or cerebral deteriorations). Moreover, the cardiac electrophysiology seems to be a key component on this axis and the current understanding of its role is limited. To better understand the relationships between the heart and brain it is important to identify markers in both healthy and patients with cardiac electrophysiological impairments and study them before the onset of clinical cognitive decline. The present thesis will bring evidence linking cardiac electrophysiology and cognition by looking at autonomic regulation in healthy individuals and disease markers in AF patients. For the autonomic nervous system, we show in Chapter 2 for the first time that a cardiac repolarization marker, QTcD, is linked to cognition in healthy individuals. In AF, results presented in Chapter 3 suggest that the degree of cognitive decline is dependent on AF burden, and the length of exposure to AF. Consequently, an in-depth investigation of how terminating AF can impact cognition is needed. However, the very few studies addressing this rely on interventions that are accompanied by side effects (in the case of drugs) or potential complications (in the case of surgical medical interventions) that can also have detrimental impacts on brain health and cognition. Therefore, the pilot study included in Chapter 4 will assess the potential immediate change in a brain marker (regional cerebral tissue oxygenation) and cognitive performance following an efficient procedure known to have limited complications or side effects that terminates AF (electrical cardioversion). The present

results will be discussed in the theoretical context of a heart-brain continuum. Future directions will address the potential benefit of cognitive prevention through exercise and cognitive stimulation in individuals with cardiac electrophysiological deteriorations.

1.1. Cardiac electrophysiology

Cardiac electrophysiology refers to the study of the electrical phenomena underlying the functioning of the heart. The synchronized contractions of the heart muscle and its rate of contraction is impacted by the initiation and the propagation of the electric impulse between the cardiac cells across the heart. This electrical activity of the cardiac cells is initiated and maintained through the automaticity of the pacemaker cells, located mostly in the sinoatrial (SA) node, atrioventricular (AV) node and the ventricular conducting system (the bundle of His, the bundle branches, and the Purkinje fibers) (Lilly, 2016). The SA node, located in the right atrium, is where the electrical impulse that sets the heart rate (HR) is initiated (modulated by the autonomic nervous system), triggering the adjacent cells towards the AV node causing the contraction of the atria. The electrical signal moves then through the ventricular conducting system and ends with the contraction of the ventricles. At the cellular level, this electrical conduction process (action potential) is modulated by a transfer of ions across the cellular membrane (generally speaking an influx of Ca^{2+} and Na^{+} causing depolarization, and output of K^{+} being responsible for the repolarization). Normally, after the action potential takes place, the membrane reaches and maintains a resting potential, until an external stimulus (usually an impulse from a neighboring cell) will initiate the transfer of ions and will result in another action potential. However, pacemaker cells in the SA node can depolarize spontaneously, in a cyclic manner, without the need to have an external trigger. After repolarization, those cells have a continuous slow inward current, which will cause the cell to reach their threshold of excitation and generate another action potential automatically. Through this process the heart can maintain a continuous and automatic heartbeat. Despite this, the autonomic nervous system as well as physiological impairments in the cardiac cells can cause variations in HR or rhythm. Some of those variations are observed in perfectly healthy individuals (i.e., heart rate

variability, respiratory sinus arrhythmia), while others are clinical in nature (i.e., atrial fibrillation).

An electrocardiogram (ECG) is used to record the electrical activity of the heart. The small electrical current transmitted between cardiac cells radiates around the surrounding tissue and it can be detected by electrodes positioned on the skin around this area. This current is amplified and transformed into a waveform, which can illustrate the depolarization and repolarization cycles of the heart. To easily identify the components that make up an ECG complex, each waveform was labeled with a letter: P, Q, R, S, and T. The P wave reflects the atrial depolarization and is immediately followed by the QRS complex which reflects the ventricular depolarization. Finally, the ST segment represents the ventricular repolarization. Another important component of the ECG is the QT interval which measures the ventricular depolarization and repolarization. An abnormal duration in the QT interval might reflect cardiac problems and is used to identify individuals that are at risk of certain arrhythmias. When all the ECG components are present in the right order and with the expected duration, it can be said that the individual is in normal sinus rhythm. This usually refers to the fact that the HR is regular, between 60 and 100 beats per minute (bpm), and that the electrical signal starts from the SA node and is normally conducted to the ventricles. A deviation from this sinus rhythm which can be observed by clinicians on an ECG is often termed an arrhythmia, and it can be indicative of cardiac problems. From now on when referring to a disease of heart rhythm the term “clinical arrhythmia” will be used.

The ECG can also show variations that are considered to be within healthy normal ranges (i.e., beet to beat variations, or changes in specific segment durations). Since those measures reflect variation in heart rhythm, they can also be named arrhythmias, as is the case of respiratory sinus arrhythmia. However, those heart rhythm variations are observed in healthy individuals, and they do not reflect disease but are indicative of autonomic regulation. Despite this, those variations have been linked to health outcomes, suggesting that certain heart rhythm patterns might reflect optimal health.

1.1.1. The autonomic nervous system and cardiac electrophysiology

Some of the cardiac electrophysiological variations observed on the ECG reflect autonomic nervous system (ANS) activity. The ANS is responsible for many automatic functions of the body (i.e., breathing, HR control, sweating, pupil dilation, etc.) and its role is to keep the state of the organism constant, or make the required changes when the environment causes a change in this equilibrium (Jänig, 1989). The ANS can be divided in the Sympathetic Nervous System (SNS) responsible for stress management (flight-or-fight response) and the Parasympathetic Nervous System (PSNS) responsible for relaxation. One of the most evident impacts of the ANS is the control of the heart rate through the baroreflex. For example, when blood pressure increases, the baroreceptors are stimulated, and HR is decreased through a stimulation of the PSNS and an inhibition of the SNS. Since the ANS is responsible for many of the "vegetative state" functions of the body, it is primarily controlled by the most primordial parts of the central nervous system, notably the spinal cord and the brain steam (Kapa, Venkatachalam, & Asirvatham, 2010).

Despite the fact that the heart has innervation from both SNS and PSNS in the cardiac plexus, the parasympathetic system is the most dominant regulator of HR (Karemaker, 2017). In fact, the automaticity of the SA node, when left on its own, will initiate a contraction (a heartbeat) at a rate of around 100 bpm. However, the vagus nerve (part of the PSNS) inhibits this activity, resulting in a resting HR of around 60 to 100 bpm in adults. In addition to lowering HR by reducing the impulse formation in the atria, the PSNS can also decrease contractility by lowering the conduction speed in the AV node, and across the atria and ventricles (Lewis et al., 2001). On the other hand, the SNS can increase HR and contractility in the same target locations, with an increased metabolic demand. This change in HR by the ANS can be acutely triggered (i.e., in case of stress or a threat), but it can also be observed at rest. In fact, a sustained high sympathetic activity (or inhibited parasympathetic activity) at rest across the lifespan is associated with poorer health outcomes, and a well-functioning PSNS has been associated with better health outcomes (Curtis & O'Keefe, 2002). Based on how the ANS

impacts the heart rate and rhythm, it comes as no surprise that a well-functioning PSNS is reflected through a lower resting HR and a higher variability in HR both in relation to stress and at rest (in response to the body's own internal variation in beat-to-beat duration: respiratory sinus arrythmia, which will be explained later).

The variability in consecutive heartbeats, also known as heart rate variability (HRV), has been recorded since early 1970's and it has been suggested to reflect the interaction between the SNS and PSNS, with a lower variability being considered as a poor health marker (Hyndman, Kitney, & Sayers, 1971; Karemaker, 2017; Sayers, 1971). Early on, the HRV was measured by averaging each RR interval on the ECG (a proxy to HR), by calculating the standard deviation between those intervals, or slight variations of those approaches. Fourier transformations were also often used, in which the cyclic variation between each R point on the ECG was divided into low-frequency oscillations thought to reflect sympathetic activity (related to the baroreflex) and high-frequency oscillations though to reflect parasympathetic activity (related to respiratory sinus arrythmia) (deBoer, Karemaker, & Strackee, 1987). However, over the past 20 years the validity of those approaches used in measuring HRV has been challenged (Draghici & Taylor, 2016). The main argument is that no variable is capable to purely measure the unique parasympathetic vs. sympathetic impact on cardiac function, and that large recordings are needed to get accurate scores. Despite this, amongst all of them, the high frequency component of the power spectrum of the HRV is thought to be one of the more reliable measures reflecting predominantly parasympathetic activity due to its strong link with the respiratory sinus arrythmia (Draghici & Taylor, 2016).

The respiratory sinus arrythmia refers to the change in the heart rhythm in relation to the cyclic processes of inspiration and expiration. The respiration is in fact closely coupled with the central nervous system, and it has a bidirectional influence on the cardiovascular system (Karemaker, 2017). Briefly, during inspiration the left atrial pressure drops, which causes a decrease in left ventricular output, and a brief drop in blood pressure, causing a slight increase in HR. Conversely, during expiration the left ventricular output increases, resulting in an increase in blood pressure causing a slight decrease in HR. As a result, the underlying electrical

activity causing this variation in HR is captured on the ECG. However, this process is most obvious when the respiration takes place automatically and it is not actively controlled (Galletly & Larsen, 1999), further emphasizing the limited validity of this measure.

The autonomic cardiac control can also be observed on other ECG markers reflecting electrical conduction speed across the heart, like the dispersion of the QT interval. The QT interval on the ECG shows the electrical activity representing the ventricular depolarization and repolarization. The duration of this interval is mostly influenced by different pharmacological agents, the autonomic system as well as myocardial health (i.e., ventricular hypertrophy, or ventricular ischemia) (Bednar, Harrigan, Anziano, Camm, & Ruskin, 2001). Normally, the duration of the QT interval is dependent on HR. That is when the HR is low, each RR interval will be longer, resulting in a longer QT interval. To control for this, some formulas have been proposed, with Bazett's being one of the most widely used ones (Bazett, 1920), which allows to look at the QT interval independent of HR (QTc). The QT interval partially reflects autonomic function, since the PSNS and SNS are known to impact the conduction speed across the ventricles (Lewis et al., 2001). Research has shown that a long QT interval is a marker associated with negative health outcomes, as well as a predictor for future clinical arrhythmias, in particular ventricular arrythmias. In addition to the QT interval duration, the dispersion (or difference) between the longest and the shortest QT interval on different leads of a continuous ECG recording has also been studied. It has been proposed that a higher QT dispersion (QTcD) reflects higher instability or asynchronization of cardiac repolarization due to the autonomic regulation of the heart (in the absence of cardiac problems or drugs known to interact with the QT interval). Previous studies have shown that QTcD increases with increased sympathetic activity or decreased parasympathetic activity in experimental designs, and that it correlates with HRV measures (Nakagawa et al., 1999). Like the HRV measures mentioned above, the use of the QTcD as an autonomic function marker is equally critiqued due to its limited validity and uncertain clinical value (Rautaharju et al., 2009). Even though multiple studies have linked higher QTcD values to higher mortality rates, higher ventricular arrythmia rates, or overall higher cardiovascular complications, some methodological limitations have been highlighted questioning its clinical use (Malik et al., 2000; Rautaharju, 2002). Specifically, when QT intervals are within expected

normal values, measurement error can impact the values, and therefore result in unreliable QTcD scores. Moreover, it has been suggested that due to surface ECG methodological limitations, the QTcD might not accurately reflect the ventricular depolarization and repolarization from different angles (Malik et al., 2000). Despite this, the use of QTcD in research is still recommended as abnormally large values (e.g., 100 ms) might still reflect meaningful autonomic dysregulation even in healthy individuals (Malik et al., 2000; Malik & Batchvarov, 2000; Rautaharju et al., 2009).

Overall, cardiac autonomic control as measured with HRV and QTcD is associated with health but due to the limited current understanding of those measures, and their validity, their clinical use is not yet recommended. Despite this, a very large number of studies have reported consistent findings between those markers reflecting autonomic dysregulation and current health status, the presence of risk factors, future health prognosis and even mortality (Bazoukis et al., 2020; Pecanha, Silva-Junior, & Forjaz, 2014; Tsuji et al., 1994; Zhang et al., 2011). Autonomic dysregulation can either directly impact health or be used as a marker revealing a common underlying condition that impacts health. Possible mechanisms proposed to explain the link between poor autonomic cardiac control and health usually suggest that impaired autonomic function reflects subclinical cardiovascular disease, it acts as a catalyst for underlying cardiovascular disease, or it simply is another risk factor for future development of cardiovascular disease (Verrier & Tan, 2009). In individuals with preexistent cardiovascular disease or cardiovascular risk factors, the association between poor autonomic cardiac control and health is often associated with an increased risk of clinical arrythmias (Bigger et al., 1992; Shen & Zipes, 2014; Verrier & Tan, 2009).

1.1.2. Atrial fibrillation and cardiac electrophysiology

Deviations from the expected cardiac electrophysiology observed on the ECG can also reflect serious cardiac diseases known as clinical arrythmias. One such example is atrial fibrillation (AF), the most prevalent type of clinical arrhythmia. AF is characterized by a fast and irregular heartbeat, and a chaotic electrical activity in the P-wave of the ECG. This happens when the electrical signal that guides the contractions of the atria is no longer synchronized, leading to a

deterioration of the mechanical properties of the atria. This results in the inability of the heart to pump out the blood efficiently. In addition, since the blood does not circulate well within the heart, a high chance of emboli formation has been observed (Yamanouchi, 1998). After they form in the heart, the emboli have a high chance of blocking small capillaries and causing strokes. In fact, AF is involved in approximately 20% of all stroke cases and most of the AF management is designed to minimize the risk of stroke (Cotter et al., 2013).

In patients with AF the normal electrical rhythm is disturbed, often from a combination of focal ectopic activity and reentry circuits in the atria (Andrade, Khairy, Dobrev, & Nattel, 2014). A focal ectopic activity refers to the process in which certain perturbations cause the cells to spontaneously depolarize earlier than they should have, breaking the normal rhythm in which electrical depolarization takes place in the heart. This often takes place around the pulmonary veins, an area that is ablated in an effort to terminate AF. Reentry circuits form when conduction blocks prevent the electrical activity to follow a synchronized unidirectional path. As a result, this facilitates the reentry of the electrical impulse back in the original cells, causing a disorganized electrical activity. Once initiated, this dysregulation is maintained by the rapid firing of the cells causing fibrillatory waves.

The focal ectopic activity and reentry circuits are thought to be caused by four general dysfunctions that impact cardiac cells: Ca^{2+}-handling abnormalities, ion channel dysfunction, altered autonomic function, and cardiac structural remodeling (Andrade et al., 2014). The first two mechanisms affect the membrane potential by impairing the normal transfer of Ca^{2+}, K^{+}, and Na^{+} ions across the cell membrane. This impairs the normal action potential propagation through a delay or an early afterdepolarization, which creates the ideal setting for the formation of ectopic beats or reentry circuits. Altered autonomic activity can also cause AF through an increased sympathetic stimulation which can lead to focal ectopic activity. Moreover, altered autonomic activity (in particular sympathoadrenal discharge) has been linked to a dysregulation of the Ca^{2+} ions, as well as ion channels dysfunctions, further enhancing the initiation and maintenance of AF. Finally, structural remodeling usually refers to the formation of atrial fibrosis, or the excessive increase in extracellular matrix formations that will ultimately

impair or slow down electrical conduction, favoring reentry circuits. Fibrosis has also been shown to alter the electrophysiological behavior of cardiomyocytes, making it difficult to revert to normal electrical activity (Yue, Xie, & Nattel, 2011). AF-induced cardiac remodeling has also been associated with an increase in the dysfunction of the four mechanisms listed above, showing that being exposed to AF creates an environment that further facilitates the maintenance of AF (Schotten, Verheule, Kirchhof, & Goette, 2011; Sohns & Marrouche, 2020).

AF has been classified in three major clinical categories based on the duration of the arrhythmic episode (Fuster et al., 2011). Paroxysmal AF refers to patients that have AF episodes that last less than 7 days (with most episodes lasting less than 24 – 48 hours) which are often self-terminating. Persistent AF is also an episodic event but lasts more than 7 days and often requires the administration of a treatment for termination. If the AF episode does not respond to any treatment and lasts more than 1 year, than it is classified as permanent. If an individual experiences more than two AF episodes, the condition is labeled recurrent. While persistent and permanent AF can be assessed in the hospital, some paroxysmal AF patients might remain undetected due to the short duration of the arrhythmic episodes. Because of this, it is hard to objectively assess the frequency, or the intensity of the episodes. Sustained AF (either from multiple short recurrent episodes or from few episodes of long duration) can cause electrophysiological changes in the heart (atrial remodeling) that make it more likely to develop persistent AF, and less likely to effectively terminate the arrhythmic episode (Fuster et al., 2011). Therefore, the impact of AF on the health of an individual might start earlier than when the disease is discovered, and as the disease progresses it becomes harder to manage due to its insidious nature.

Patients with AF have a significant decrease in the quality of life in the remaining years, an increase in disease comorbidity, and have an increase in mortality rates (Bhatt & Fischer, 2015). Patients with incident AF have an age adjusted 1-year mortality rate of 23-27% higher than patients without AF (Andrade et al., 2014). At the same time patients with AF show significant impairments in their cognitive abilities, vitality, and their ability to exercise (Dorian et al., 2000;

Thrall, Lane, Carroll, & Lip, 2006). Even in the absence of symptoms, patients report to have a decreased life satisfaction (Dorian et al., 2000).

The chance of developing AF increases with age, with 1 in 25 people being diagnosed after the age of 60, and 1 in 10 people after the age of 80 (Go et al., 2001). The total lifetime risk of developing AF in people that are between 40 and 55 years of age is thought to be between 22% to 26% (Go et al., 2001; Heeringa et al., 2006). However, those numbers are conservative as AF in the early stages can be transient and asymptomatic and therefore undetected and undiagnosed. Overall, it is thought that up to two thirds of the AF population have a transient form, and between 5% and 35% of the AF population are asymptomatic (Andrade et al., 2014). Within those individuals, AF is usually detected by chance during a regular medical checkup or while investigating another medical condition.

While age is one of the highest risk factors for AF (Laredo, Waldmann, Khairy, & Nattel, 2018), other factors include hypertension, valvular heart disease, heart failure, congenital heart disease, coronary artery disease, obesity, sleep apnea, chronic kidney disease, high alcohol consumption, smoking, diabetes, thyroid dysfunction, genetic predispositions, and even intense or excessive endurance physical activity (Andrade et al., 2014). This shows that AF can often be the result of multiple chronic conditions that deteriorate the heart. Despite this, there are cases in which AF is present in the absence of any other cardiac abnormality (or other cardiac comorbidities), and it has been found that those individuals tend to be older, highlighting the important role of advanced age as an independent risk factor (Falk, 1998).

A second strong predictor for AF, in addition to age, is sex (Odening et al., 2019). Men generally have a 1.5 times higher risk of developing AF (Andrade et al., 2014). However, women with AF often show worse symptoms, lower quality of life and higher risk of adverse effects like stroke (Odening et al., 2019). Women diagnosed with AF were also found to be older, have a higher comorbidity burden, and potentially have different risk factors (Magnussen et al., 2017; Noubiap et al., 2021), Moreover, a recent study showed that women with AF were less likely to receive an electric cardioversion or catheter ablation for AF management (Noubiap et al., 2021). However, it is not clear if this is due to the different health profile between the two

sexes which might result in a higher number of patients with counterindications for those procedures.

Most often, the deviation from the sinus rhythm in AF is mostly caused by myocardial problems (i.e., cardiac hypertrophy or ion dysfunctions) that impair the normal electrical conduction. However, deviations in autonomic activity can also facilitate the onset and maintenance of AF, in particular when those cardiac predispositions are present (Hammerle et al., 2020; Kapa et al., 2010; Olshansky, 2005). In fact, impaired autonomic cardiac control in AF patients has been linked to higher cardiovascular mortality (Hammerle et al., 2020). Moreover, sustained AF is associated with an increased rate of damage in the central nervous system (most notably strokes, but also subclinical brain damage), which has further been independently linked to autonomic dysfunction (Dorrance & Fink, 2015). Past researchers have already suggested a global reciprocity between the central nervous system and the heart (Schnabel et al., 2021), but new evidence suggests that there might be a heart-brain continuum even when looking at cardiac electrophysiology alone. As a result, this interaction could also play a role in how cognitive abilities change with age in certain populations. Maintaining cognitive abilities in aging is dependent on brain health, and neurodegenerative disorders form a growing concern already exacerbated by the presence of cardiovascular disease.

1.2. Cardiac electrophysiology and cognition

1.2.1. Autonomic function and cognition

There is a well-established association between cardiac autonomic regulation and cognitive performance. To date, there are numerous reports that individuals with dementia also show autonomic dysfunction (da Silva et al., 2018; Idiaquez & Roman, 2011). Although the direction of this relationship is still investigated, authors often attribute most of the autonomic dysfunction in this population to degeneration of key brain areas like the anterior cingulate cortex, insular cortex, amygdala, hypothalamus and the brainstem (Cheshire, 2014; Idiaquez & Roman, 2011). Patients with dementia can show autonomic dysfunction in multiple domains including urinary incontinence, dysphagia, constipation, hyperhidrosis, but also changes in

cardiac autonomic control which can be observed in cardiac electrophysiological changes (Allan et al., 2007; da Silva et al., 2018; Idiaquez & Roman, 2011). More specifically there is evidence that individuals with AD or vascular dementia show worse HRV, and poorer markers of cardiac repolarization. Among the HRV markers a meta-analysis showed that there is stronger evidence for a reduction of parasympathetic activity in AD (with lower values for the standard deviation of mean interval RR and the square root of the mean squared differences of successive RR intervals) relative to healthy controls (da Silva et al., 2018). The authors, however, were not able to find a significant difference within the frequency domain of the HRV data. Moreover, they mention that despite that some of those studies control for other comorbidities, some patients included still had conditions that are considered as risk factors for both dementia and autonomic dysfunction (i.e., hypertension, diabetes, advanced age) making it hard to identify the direction and cause of this association.

There is also evidence that individuals suffering from vascular dementia might be more likely to show a prolonged QT interval than healthy controls (Matei, Corciova, Matei, Constantinescu, & Cuciureanu, 2015). Although not significant, one study found that the QT values of individuals with vascular dementia were also higher than those with AD (Matei et al., 2015). This could suggest that cardiac electrophysiological functioning might be linked to a higher degree to vascular dementia than AD. In this case, it looks like cardiac repolarization markers might show some sensitivity to cognitive decline that has cerebral vascular damage origins. On the other hand, some studies were able to show higher QT dispersion values (reflecting autonomic function) in people suffering from AD and mild cognitive impairment (Coppola et al., 2013; Zulli et al., 2005). Although debated, it has been even suggested that the higher QTcD values might predict the progression from mild cognitive impairment to dementia (Coppola et al., 2013). The authors were also able to show that individuals with AD had higher QTD and QTcD values than individuals with mild cognitive impairment, which were significantly higher than healthy controls, and those values were corroborated with HRV data (Zulli et al., 2005). A similar linear relationship between autonomic function and cognitive performance was also found in AD using HRV spectral frequency data. In one study including 78 AD patients it was found that global cognitive function was negatively associated with increased cardiac sympathetic

modulation, while memory performance was negatively associated with sympathetic modulation and positively associated with parasympathetic cardiac modulation (Nonogaki et al., 2017). When putting together the available data it looks like the individuals suffering from dementia are likely to show an impairment in the reactivity of the ANS (with decreased PSNS and increased SNS activity), and a decrease in cardiac repolarization, with a potential linear association between the extent of the cognitive impairment and those autonomic markers. Since those results are recorded in individuals with dementia that also show central nervous system deteriorations it is possible that the autonomic impairment is caused by disease related brain degeneration. However, similar findings were also reported in cognitively healthy individuals suggesting that the association is more complex, and that it cannot be fully attributed to the brain deterioration following dementia pathophysiology.

The current literature investigating the association between autonomic function and cognition in healthy individuals mostly uses HRV markers which have been suggested to potentially be early biomarkers for future cognitive decline (Forte, Favieri, & Casagrande, 2019). A study investigating the autonomic activity during an acute cognitive task showed that healthy young adults with higher baseline parasympathetic activity had better cognitive abilities and showed a better autonomic reactivity to the cognitive task measuring processing speed and discrimination (Duschek, Muckenthaler, Werner, & del Paso, 2009). Moreover, those that showed better autonomic reactivity during the cognitive task also performed better. A strength of this study was the fact that they characterized the cardiac autonomic activity in their sample using multiple parameters, namely spectral frequency HRV values (reflecting respiratory sinus arrythmia), the cardiac baroreflex, and the R-wave to pulse interval. More general, a recent systematic review shows that higher resting HRV is associated with better global cognition as well as better performance in specific cognitive domains (Forte et al., 2019). Specifically, poor resting parasympathetic activity was associated with lower performance in global, verbal reasoning, inhibition, and other executive functions. Other HRV markers which are impacted by both SNS and PSNS (low- and mid-frequency spectral values of HRV) were associated with memory, language, verbal reasoning, and spatial tasks (Forte et al., 2019).

Studies show that higher resting HRV is associated with a better functioning of the inhibitory circuits of the pre-frontal cortex which are used in specific cognitive abilities that require flexibility, and adaptation to environmental demands (Colzato, Jongkees, de Wit, van der Molen, & Steenbergen, 2018; Forte et al., 2019). The neurovisceral integration model is a theory that suggests how the autonomic functions, the cognitive abilities and the emotional functionality are linked through common brain areas (Thayer & Lane, 2009). This model suggests that the association between vagally mediated autonomic cardiac control and executive functions is modulated by the prefrontal cortex. As a result, it is suggested that cardiac autonomic markers can be used as proxies reflecting the integrity of the central nervous system, in particular the frontal cortex. Similarly, Forte et al. (2019) suggest that the brain localization of autonomic functions and that of specific cognitive functions might be the reason there is a differential association between certain cognitive functions and autonomic markers reflecting PSNS activity vs. SNS activity. The vagally mediated PSNS activity is closely linked to prefrontal cortex which is also heavily involved in higher order cognitive abilities (Forte et al., 2019; Melis & van Boxtel, 2001). On the other hand, sympathetic activity has been linked more with the occipital, parietal, and motor cortices (which corroborates the association of HRV markers impacted by the SNS and the verbal and visual cognitive abilities).

Within healthy samples, cardiac repolarization markers are not as studied as HRV in relation to cognition (Imahori, Vetrano, Ljungman, & Qiu, 2021). As a result, the literature is limited, with few mostly recent studies reporting a significant association between QT interval or QT variability index and global or executive abilities (Stenfors et al., 2016; Zonneveld et al., 2020). However, it must be noted that an almost equal number of studies failed to detect an association between cardiac repolarization markers and cognition (Imahori et al., 2021; Lucas, Mendes de Leon, Prineas, Bienias, & Evans, 2010; Suemoto et al., 2020).

To date it is still not clear what causes this autonomic dysfunction in healthy individuals and how it is related to cognition. There is evidence that brain damage preceding neurodegenerative disorders can lead to autonomic dysfunction and cardiac disease like arrythmia. On the other hand, cardiac diseases or risk factors can result in autonomic

dysfunction, as well as brain damage. It is not clear if one pathway is more dominant than the other, or how all those components interact with each other to result in cognitive deficits. Most likely, there is a bidirectional interaction of both the heart and the brain impacting the functioning of the autonomic system, with deteriorations at any stage in this pathway resulting in cognitive decline.

Despite this link, the markers of cardiac autonomic control are very dependent on individual and environmental factors, making it hard to obtain standardized values (de Geus, Gianaros, Brindle, Jennings, & Berntson, 2019). Moreover, all of the above studies use multiple parameters of cardiac autonomic control, and they obtain significant findings with only some of them (the other ones being non-significant). Amongst all of the markers, there doesn't seem to be one strong marker that is consistently sensitive to cognitive variation. This, combined with the critiqued validity and reliability of those markers mentioned in section 1.1.1 make it hard to create normative data that can be used for clinical guidelines (Billman, Huikuri, Sacha, & Trimmel, 2015). As a result, those autonomic markers of cardiac control cannot be used in the clinical setting to predict individuals that are at risk of significant cognitive decline. However, expanding the knowledge in this field will allow for a better understanding on how cardiac electrophysiology can be informative about cognitive health. In addition, clinical impairments in cardiac electrophysiology (e.g., atrial fibrillation) can offer a different insight on how the heart-brain continuum works and impacts cognitive functioning.

1.2.2. Atrial fibrillation and cognition

Atrial fibrillation has been repeatedly associated with a higher incidence of dementia, but also with lower cognitive abilities, and higher rates of cognitive decline in non-demented individuals (L. Y. Chen et al., 2018; Chopard et al., 2018; Diener, Hart, Koudstaal, Lane, & Lip, 2019; O'Connell, Gray, French, & Robertson, 1998; Rivard & Khairy, 2017). Multiple longitudinal cohort studies have identified an association between AF and an increased chance of developing dementia (de Bruijn et al., 2015; Liao et al., 2015; Singh-Manoux et al., 2017). Moreover, the Rotterdam cohort study found this relationship to be more evident within the individuals developing dementia at a younger age (de Bruijn et al., 2015). Meta-analyses looking

at the studies investigating the risk of developing dementia following AF have also confirmed the same pattern of results (Kalantarian, Stern, Mansour, & Ruskin, 2013; Kwok, Loke, Hale, Potter, & Myint, 2011; Liu, Chen, Jian, Zhang, & Liu, 2019). The general conclusion from those studies is that patients with AF who had a stroke had the highest chance of developing dementia, and anticoagulants were found to be efficient at preventing future strokes and cognitive decline. In addition, Kalantarian et al. (2013) found that the association between AF and dementia could also be present independent of strokes.

Early research has shown that AF is linked to vascular dementia and AD, two of the most prevalent subtypes of dementia (Di Nisio et al., 2015; Habeych & Castilla-Puentes, 2015). Out of the two subtypes it looks like AF has a stronger association with AD rather than vascular dementia (Ott et al., 1997). Indeed, in the Rotterdam study approximately 80% of the individuals with either prevalent or incidental AF were diagnosed with AD (de Bruijn et al., 2015). However, newer studies show a growing association between AF and vascular dementia, suggesting there might have been an over diagnosis of AD, or an underdiagnosis of mixed dementias in older studies (Papanastasiou et al., 2021; Skoog, 1998).

Although not as studied, research has also shown that the link between AF and cognitive impairment can also be observed in the absence of a dementia diagnosis (Kalantarian et al., 2013). Studies have shown that AF can increase the risk of having cognitive decline without stroke by approximately 34% even after controlling for common risk factors (Kalantarian & Ruskin, 2016; Kalantarian et al., 2013). More precisely, Knecht et al. (2008) found that individuals with AF had lower scores for learning memory, attention, and executive functions than non-AF participants in a stroke-free, non-demented sample. Although not significant, they also observed a trend towards worse memory performance in patients with chronic AF as opposed to paroxysmal AF. Other studies too suggest that persistent AF might be associated with worse cognitive functions than paroxysmal AF (L. Y. Chen et al., 2016; Gaita et al., 2013). This implies that the longer the individuals are exposed to arrhythmia the more significant the cognitive decline. If this is the case, then AF should not be considered as a binary risk factor for cognitive decline, and other information about the AF burden should be taken into account.

However, the evidence is not yet clear if the different types of AF have different impacts on cognition due to the small number of studies, which are underpowered and confounded by different treatments (Dagres et al., 2018). Another reason why those studies are harder to conduct is because paroxysmal AF is hard to assess due to the short duration of each episode. Considering this, it is still possible that AF impacts cognition early on, before either AF or cognitive decline can be felt by the patient or diagnosed by the health professional. As such, more studies including patients across all levels of AF exposure are needed to better understand the impact that AF has on health.

One of the main reasons why AF has been thought to cause dementia is due to the presence of strokes common in both conditions. AF has been shown to increase the chance of having strokes four to five times, and the presence of strokes doubles the chance of developing dementia (Ivan et al., 2004; Mozaffarian et al., 2015). Initially this was thought to be the main mechanism linking AF to cognitive decline. However, as mentioned already, AF was associated with dementia and cognitive decline even in the absence of clinical strokes, suggesting that there must be other mechanisms at play as well. Another possibility is that the silent cerebral infarcts common in AF patients lead to lower cognitive abilities (Dagres et al., 2018; Kalantarian et al., 2014). Indeed, imaging studies were able to identify micro-infarcts mostly in the frontal cortex, in patients with AF (Gaita et al., 2013). The authors were also able to find a higher number of micro-infarcts in individuals with persistent AF than paroxysmal AF. Moreover, persistent AF was also associated with a higher concentration of the micro-infarcts in the frontal lobe. This again, suggests that there might be higher damage the longer an individual is exposed to arrhythmia. Since those deteriorations are not large enough to translate into behavioral or significant cognitive decline, the brain damage remains undetected early on. However, the accumulation of those micro-infarcts has been shown to be associated with cognitive decline (L. Y. Chen et al., 2014; Gaita et al., 2013). Similarly, microbleeds are thought to have a similar impact, with more impairment as they accumulate over time (Poels et al., 2012). This is particularly relevant for this population since microbleeds can be caused by the use of anticoagulants in patients with AF (Akoudad et al., 2014).

Another potential mechanism linking AF to cognitive decline could be through common risk factors. In fact, both AF and dementia have multiple common risk factors, like hypertension, congestive heart failure, and diabetes (Kalantarian et al., 2013). Therefore, it is possible that those risk factors increase the chance of developing both conditions in parallel. However, research has shown AF to be linked to cognitive decline even after controlling for those common risk factors (Elias et al., 2006; Marzona et al., 2012). Nonetheless, it would be recommended to measure those variables in order to control for their impact in all studies looking at AF and cognition.

Inflammation, too, could play a significant role in linking AF to cognitive decline. Although it is not yet clear if inflammation predates or is initiated by AF, the evidence available suggests that AF is associated with higher levels of inflammatory biomarkers, and an increase in inflammatory responses (Guo, Lip, & Apostolakis, 2012). Those biomarkers are known to play a role in the formation of thrombi and to increase the coagulability of the blood, which can result in strokes (Choudhury & Lip, 2003). At the same time, some studies have shown inflammation to also be related to dementia (Simone & Tan, 2011; Stefaniak & O'Brien, 2016). A study has shown that individuals who had AF and developed dementia in the 3-year follow-up of the study also had higher levels of inflammatory biomarkers at baseline, than the individuals who did not develop dementia (Barber et al., 2004). In a different study, patients with AF were randomized in an anti-inflammatory treatment or placebo group for one year (Lappegard et al., 2013). The authors found that the treatment group resulted in decreased inflammatory biomarkers, and this decrease was associated with cognitive improvements. Although the causality relationship cannot be fully analyzed with the available data, it looks like inflammation plays a role in the link between AF and cognitive decline.

Another plausible mechanism linking AF to lower cognition is through cerebral hypoperfusion caused by the decreased cardiac output present in AF patents (Lavy et al., 1980). Since AF impairs the ability of the heart to pump the blood, the cardiac output is lowered resulting in an inconsistent and possibly insufficient blood reaching all areas of the brain. Alosco et al. (2015) found that among a heart failure population, patients with AF had lower cognitive abilities as

well as lower cerebral blood flow compared to those without AF. Moreover, the cerebral blood flow level was able to significantly predict the decrease in cognitive functions even after controlling for common risk factors. Similar results were also reported in the Rotterdam study where they found an increase in the chance of developing dementia and AD in individuals with a lower cardiac index (Jefferson et al., 2015). However, some authors doubt that cerebral hypoperfusion is the primary link between AF and cognitive deficits or increased dementia rates, since cerebral autoregulation should prevent major impairments in blood flow (Dietzel et al., 2018; Ding & Qiu, 2018). So far is not yet clear if this mechanism has a high impact on the relationship between AF and cognition, but if this is the case, managing AF through resynchronization to the sinus rhythm would be recommended since anticoagulation treatments don't improve the brain hypoperfusion (Diener et al., 2019; Gardarsdottir et al., 2020). Finally, few studies have reported an improved cerebral tissue oxygenation and microvascular blood flow after the restoration of the sinus rhythm in AF patients (Elbers et al., 2012; Wutzler et al., 2014). Since the majority of the brain's energy comes from oxidation of glucose (Raichle & Mintun, 2006), a decreased cerebral oxygenation will also be associated with decreased cognitive abilities (B. W. Carlson, Neelon, Carlson, Hartman, & Bliwise, 2011; Davranche et al., 2016). However, this relationship was not replicated in AF patients.

Poor cardiac autonomic control can also play a role in the link between AF and cognition, although not much is known about the exact pathway. A recent publication form the SWISS-AF trial has shown that poor autonomic cardiac control (HRV) in over 700 AF patients is associated with worse cognitive performance for the first time (Hammerle et al., 2022). This is important because often AF patients are excluded from HRV studies because of the difficulty with which those indexes are calculated. Considering this, those results must be taken with a grain of salt, because the irregular electrophysiological activity in the AF population makes it difficult to know if the variability in HR is indeed caused by the ANS or maybe by other AF pathophysiology.

Overall, this shows that the presence of AF impacts the brain through a multitude of avenues and put together the risk of cognitive decline can be significant. Due to the insidious nature of

the mechanism involved between AF and cognitive decline it is expected that longer exposure to AF (or increased AF burden) could result in a continuous deterioration of the cognitive abilities. Conversely, terminating the AF should have a positive impact on cognition, by improving brain functioning. Despite this, the evidence for this is very limited and more research is needed before formulating any conclusions.

1.3. The present thesis

The present thesis will start by investigating the link between a cardiac repolarization marker reflecting cardiac autonomic control (QTcD) and cognition in healthy older individuals (Chapter 2). This autonomic marker has been found to be closely associated with cognitive disease severity in individuals with dementia and mild cognitive impairment, and this is the first study to investigate if there is a similar association recorded in healthy individuals. Results show that higher QTcD scores are linked to lower cognitive performance (global and executive functions) and this association is more obvious in individuals with very high QTcD values. This suggests that individuals with higher electrophysiological impairment might also show higher cognitive impairment, and to better understand this association Chapters 3 and 4 investigate a population with AF. In Chapter 3 we investigate if AF patients with higher disease severity also show worse cognitive performance. The results show that subtypes of AF reflecting longer arrythmia exposure indeed show lower cognitive performance (global and executive functions). Moreover, a cardiac health marker (left atrial volume) known to be affected by longer AF exposure significantly moderates the association between AF type and cognition. Since sustained cardiac electrophysiological impairments resulting in longer AF exposure are indeed associated with progressively worse cognitive performance, it would be important to investigate the immediate impact that sinus rhythm restoration might have in individuals with AF. Chapter 4 shows the results of a pilot study investigating the changes in cognitive performance and regional cerebral tissue oxygenation in AF patients undergoing electrical cardioversion (a sinus rhythm restoration procedure). The pilot results show that such a study is indeed feasible and could detect cognitive changes in this sample. While the change in cerebral tissue oxygenation is unconclusive at this moment, the change in cognition could partially be

explained by the reduction in AF related symptoms. The results from all those studies will be discussed in the context of a heart-brain continuum in which deteriorations from either the heart or the brain can have bidirectional impacts and further impair the functioning of this axis. Cognitive prevention strategies will also be proposed.

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Chapter 2 – Article 1

Mind the rhythm: ECG QT dispersion and cognition in healthy older adults

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Journal: Frontiers in Psychology

Publication date: September 2021

2.1. Abstract

Background: Autonomic function has been linked to cognitive abilities in aging. Even in non-clinical states, a certain variability in heart rhythm regulation can be measured with QT dispersion (QTcD), an ECG marker of ventricular repolarization which has been linked to autonomic function and cardiovascular health. QTcD has been shown to be higher in individuals with mild cognitive impairment, and the highest in individuals with Alzheimer's disease. The goal of this study was to see if QTcD is associated with cognitive performance in healthy individuals.

Methods: Sixty-three healthy inactive older adults (> 60 years) completed an extensive cognitive assessment (including inhibition, divided attention, updating, working memory, and processing speed), a physical fitness assessment, and underwent a resting ECG.

Results: After controlling for age, sex, and education, QTcD significantly predicted global cognition (MoCA) scores (R^2 = .17, $F_{(4.58)}$ = 3.00, p < .03, β = -.36). Exploratory analysis on the MoCA subcomponents revealed a significant association between the visual/executive subcomponent and QTcD (R^2 = .12, $F_{(1.61)}$ = 7.99, p < .01, β = -.34). In individuals with high QTcD, QTcD values were linked to executive functions (R^2 = .37), processing speed (R^2 = .34), and dual-task performances (R^2 = .47). No significant associations were found within the low QTcD group.

Conclusion: This study shows an association between ventricular repolarization (QTcD) and cognitive performance, in particular speed and executive functions, in healthy older adults. The results provide further support for linking autonomic heart regulation and age-related cognitive changes, and suggest that deviations on ECG, even within-normal range, could help detect early cognitive deficits.

Keywords: cognition, ventricular repolarization, aging, cardiovascular health, autonomic function

2.2. Introduction

Studies have shown an association between variability of specific cardiac ECG parameters and cognition in older adults (Frewen et al., 2013), suggesting a link between autonomic regulation and brain health (Obara et al., 2018). This relationship is thought to be even more evident in individuals suffering from cardiovascular or neurodegenerative diseases, further emphasizing a potential bidirectional link between heart and brain (Keary et al., 2012; Toledo & Junqueira, 2010). Few recent studies have suggested ventricular repolarization ECG measures as one potential marker linking autonomic cardiovascular regulation and cognition (Lucas, Mendes de Leon, Prineas, Bienias, & Evans, 2010; Mahinrad et al., 2019). A better understanding of the association between specific ECG parameters and different cognitive functions would allow a better characterization of the heart-brain continuum and help identify better indices or proxies of early subtle cognitive decline. This study investigated whether QTcD, a measure of ventricular repolarization reflecting autonomic cardiovascular regulation, is related to cognitive performance in healthy inactive older adults.

The autonomic nervous system (ANS) comprised of two independent branches, sympathetic and parasympathetic, is thought to have a direct impact on the heart through the vagus nerve (parasympathetic influence). With increased age, most studies have reported a loss of the balance between the sympathetic and parasympathetic tone (Abhishekh et al., 2013). More precisely, it has been shown that advanced age is marked by a gradual loss of the vagal tone, and a relative increase in sympathetic activity (Abhishekh et al., 2013). Those changes are multidetermined often involving a gradual degradation of neuronal structures responsible for autonomic control, and a decrease in the body's sensitivity to ANS triggers (Hotta & Uchida, 2010). Those age-related changes in autonomic function have also been associated with other lifestyle risk factors (such as lack of physical activity, poor diet, smoking), with other age related health deteriorations (higher blood pressure, dyslipidemia, cognitive decline), and it has been shown to even predict the incidence of cardiovascular disease in longitudinal studies (Forte, Favieri, & Casagrande, 2019; Liao et al., 1996; Liao et al., 1997).

Most of the studies investigating the link between the ANS and cognition have used heart rate variability (HRV) as the primary proxy to assess autonomic regulation. This method takes advantage of the autonomic control of the inter beat variability by measuring RR intervals over a longer period (usually over a few minutes). Analyses conducted in the time domain, frequency domain, or using non-linear analyses of the averaged inter-beat intervals can be used to extract specific values thought to reflect sympathetic or parasympathetic activity (Forte et al., 2019).

Poor autonomic regulation of the heart has been associated with neurovascular damages and cognitive decline. Specifically, reduced HRV in older adults has been shown to predict lower global cognitive performance beyond the expected impact of cardiovascular risk factors or other comorbidities (Mahinrad et al., 2016; Zeki Al Hazzouri, Haan, Deng, Neuhaus, & Yaffe, 2014), and it has been suggested as an early biomarker able to detect future cognitive decline (Forte et al., 2019). In addition, autonomic dysregulation (measured through a multitude of methodologies) has been found to correlate with neurodegeneration and deterioration of brain functional activity among healthy individuals and those with dementia (Allan et al., 2007; Lin et al., 2017; Obara et al., 2018). However, due to the large quantity of data required to be recorded and analyzed, the HRV is extracted from a digital ECG recording and the scores are calculated using automated software. This makes it harder to implement in the routine clinical setting.

Some studies investigating the link between autonomic cardiac control and cognition have also used other cardiac markers beyond HRV like ventricular repolarization (QT interval on the ECG). The autonomic tone is known to impact the rate of cardiac repolarization and the difference between the longest and the shortest QT intervals (QT dispersion) is thought to reflect the heterogeneity in cardiac repolarization, with higher values being linked with an impaired ANS functioning and other cardiovascular problems (Ahnve & Vallin, 1982; Guntekin et al., 2011; Marek Malik & Batchvarov, 2000; Monitillo, Leone, Rizzo, Passantino, & Iacoviello, 2016; Rosen, Jeck, & Steinberg, 1992). The advantage of this marker is that it can be easily extracted from a routine paper ECG without requiring any other software for analysis. Studies have previously linked ventricular repolarization to cognitive functioning, however, most of the studies have

focused on individuals with cognitive deficiencies or with cardiovascular problems. For example, high heterogeneity in ventricular depolarization (spatial QRS-T angle) was linked to steeper decline in processing speed, and immediate and delayed recall after a 3.2 years follow-up in individuals with cardiovascular disease or at high cardiovascular risk (Mahinrad et al., 2019). High heterogeneity in ventricular repolarization (QTcD) has also been shown to be higher in older individuals with clinical cognitive decline than in healthy individuals (Coppola et al., 2013; Zulli et al., 2005). It is worth noting that this relationship was dependent on the severity of the cognitive decline, that is, individuals with Alzheimer's disease (AD) had higher QTcD values than individuals with mild cognitive impairment (MCI). Whether high QTcD is linked to cognition in healthy asymptomatic individuals has never been explored. Moreover, it is not clear if certain cognitive functions are more likely to be associated with ventricular repolarization markers since the previous studies used clinical global cognitive tests.

Like all other markers of autonomic cardiac control, QTcD is linked to cardiovascular health (Monitillo et al., 2016). As a result, the present study included only healthy individuals without any cardiovascular disease. This would allow for the investigation of the link between QTcD and cognition independent of cardiovascular disease. Due to methodological challenges in fully understanding the mechanisms captured by QTcD, it is not yet recommend its use in the clinical setting, however, the investigation of QTcD in the experimental settings has been recommended in order to better understand its significance, and its ability to detect individuals at risk (M. Malik et al., 2000; Rautaharju et al., 2009). It has also been suggested that QTcD values might reflect measurement error within normal range (Marek Malik & Batchvarov, 2000). However, confidence in its interpretation is increased within higher values as this might reflect unusual activity beyond measurement error (Marek Malik & Batchvarov, 2000). Since there are no current recommendations for QTcD cutoff values in healthy individuals, the present study will use a median split on the QTcD value in order to identify if participants that have higher QTcD values might show a stronger association with the cognitive variables measured.

Finally, the variability in autonomic regulation of cardiovascular function has also been associated with physical fitness, which is also known to be linked to cognitive performance in older adults (Baur, Leiba, Christophi, & Kales, 2012; Bherer et al., 2019; Bjornstad, Smith, Storstein, Meen, & Hals, 1993; Bjornstad, Storstein, Meen, & Hals, 1991). It is generally accepted that higher fit individuals have a lower resting heart rate, better autonomic regulation, and better cognitive functions (Bjornstad, Storstein, Meen, & Hals, 1993; Dupuy, Bosquet, Fraser, Labelle, & Bherer, 2018). Therefore, the cardiovascular fitness level of the participants must be taken into account as a potential mediator when investigating the link between autonomic regulation of cardiovascular function and cognition. The present study sought to investigate whether higher QTcD would predict poorer cognitive performance in healthy inactive asymptomatic older adults while considering fitness level as a potential mediator.

2.3. Methods

The cross-sectional data used for the current study was part of a larger registered physical activity intervention clinical trial (clinicaltrials.gov identifier: NCT02455258) comparing the impact of a 3-months aerobic training, dance movement training and a wait-list control group on cognition and quality of life (Esmail et al., 2020; Vrinceanu et al., 2019). For a more detailed description of the procedure, and an in-depth breakdown of the composite scores used please see Esmail et al. (2020). In order to test the hypothesis of this paper the pre-intervention data from all participants was used. The study has been approved by the ethics board of the research institution, and all participants offered their informed consent before starting the study.

2.3.1. Participants

Sixty-three healthy, inactive, older adults over the age of 60 (*M* = 67.48, range = 60-86) recruited from the community agreed to participate in the study (Table 2.1.). Exclusion criteria were: cognitive impairment (Mini-Mental State Examination – MMSE score ≤ 24), engagement in an exercise program (of 150 minutes/week or more) in the last year, impaired mobility, any

surgery involving general anesthesia in the past year, diagnosis of any orthopedic, neurological, cardiovascular, respiratory, progressive neurologic, psychiatric and somatic diseases in the past 6 months, history of smoking in the past five years, drinking more than two standard drinks per day. Based on a geriatric assessment, the sample used did not suffer from any condition known to interact with the ECG QT (e.g., heart disease, diabetes, central nervous system disease, uncontrolled thyroid disease, folic acid intake, B12 deficiency). None of the participants were taking any QT-related drugs. Participants were also excluded if they were taking any other medication that could impact the variables of interest of the RCT (related to cognitive function, or ability to exercise). In the case in which they were taking any cardiovascular medication, they were included in the study if the doctor considered it did not have an interaction with the variables of interest of this paper (cognitive ability, and cardiac electrical activity) and if there was no major change in their medication in the past 6 months. This information has been assessed by the medical doctor at two points, once at the inclusion visit, and once when the data was compiled for analysis in the preparation of this paper. During the medical visit the geriatrician evaluated the presence of any of the conditions mentioned above and assessed the overall health status of the participants. Participants were considered healthy for their age if they didn't present any of the conditions listed.

Characteristic	Mean (SD)		
	Full sample (n=63)	High QTcD (n=29)	Low QTcD (n=34)
Age	67.48 (5.37)	67.75 (5.65)	67.26 (5.20)
BMI (kg/m^2)*	26.93 (4.96)	25.39 (4.88)	28.16 (4.74)
Education Level (years)	14.94 (3.40)	14.95 (2.72)	14.94 (3.90)
Women %*	77.8%	89.3%	68.6%
GDS	4.77 (5.56)	6.30 (6.57)	3.52 (4.30)

MMSE	28.08 (1.41)	28.25 (1.14)	27.94 (1.59)
MoCA	26.62 (2.42)	26.39 (2.26)	26.80 (2.55)
VO_2Peak ($ml.kg^{-1}.min^{-1}$)	21.55 (5.25)	21.95 (5.38)	21.22 (5.19)
10mW (m/s)	1.81 (.26)	1.84 (.23)	1.77 (.27)
QT (msec)	394.05 (25.64)	400.21 (27.37)	388.97 (23.30)
QTcD (msec)*	52.76 (17.63)	69.14 (12.15)	39.66 (7.19)
PR (msec)	162.38 (23.66)	165.07 (20.39)	160.23 (26.09)
QRS (msec)	83.11 (7.35)	82.21 (7.97)	83.83 (6.85)
RR (sec)	.93 (.16)	.94 (.16)	.92 (.16)
HR	66.68 (11.42)	66.18 (12.81)	67.09 (10.35)
SBP	137.73 (18.17)	134.56 (20.31)	140.41 (16.0)
DBP	79.29 (9.46)	78.41 (10.82)	80.03 (8.24)
Cardio. comorbidities	.62 (.86)	.46 (.66)	.71 (.95)

Table 2. 1. - Baseline Descriptive Data.

Abbreviations: BMI: Body Mass Index; GDS = Geriatric Depression Scale; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; 10mW: 10 meters walk test speed; QTcD: QT dispersion – controlled for heart rate; HR: resting heart rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; Cardio. comorbidities: sum of cardiovascular comorbidities based on the presence of: hypertension, diabetes, dyslipidemia, & stable ischemic heart disease.

** $p < .05$.*

2.3.2. Procedure

Participants completed all assessments over the course of three days. After the medical exam, participants underwent an extensive neuropsychological assessment, a 10-meter walk test, and a VO_2Peak to assess their mobility and physical fitness level. A resting state ECG measure was taken prior to the VO_2Peak test.

2.3.3. Assessments

ECG: A standard medical 12-lead seated resting ECG was collected for all participants for 5 minutes using Schiller Cardiovit AT-10 Plus. A trained medical doctor who did not participate in testing analyzed the paper-based ECG data and extracted manually the RR, PR, QRS, and QT according to standard medical procedure. The last 10-second paper strip (or the last 12 QRS complexes if fewer were present in the last 10 seconds) was used and the measurements were made visually, using a ruler with the smallest unit being 0.5mm corresponding to 20ms. The QT intervals were measured according to standard criteria, from the start of QRS complex to the end of the T wave. The end of the wave was defined as the point of return to the isoelectric line. If a U wave was present, the QT interval was measured to the nadir of the curve between the T and the U waves. In each participant, at least nine leads had to be clearly visible. From the QT interval the QTc was calculated using the Bazett's formula to control for heart rate (Bazett, 1920). QTc dispersion (QTcD) values were calculated as the difference between the longest and the shortest QT interval on different leads of the continuous ECG recording (Zulli et al., 2005).

Cognitive assessments: A detailed description of all cognitive variables and the detailed breakdown of the cognitive composite scores can be found in Esmail et al. (2020). All cognitive assessments were done by a neuropsychologist, or a trained psychology student. Global cognition was measured using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). The total score on the MoCA (out of 30) is obtained by adding up all the scores obtained in each subsection of the MoCA: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. Most of the MoCA subscales are scored out of 1, 2

or 3 points, except visuospatial/executive and delayed recall being scored out of 5, and orientation being scored out of 6 points. The results using the MoCA subscales should be interpreted with caution due to its restricted range and limited validity. The Digit Symbol Substitution Test was used to assess processing speed (Jaeger, 2018).

Cognitive functions were further measured using three tablet tasks: N-back (adapted from Owen, McMillan, Laird, and Bullmore (2005) , Stroop (adapted from Sedo (2004); and a divided attention Dual Task (adapted from Lussier, Brouillard, and Bherer (2017), during which reaction time and accuracy were recorded (Esmail et al., 2020). During the N-back task participants had to identify if the digit present on the screen is the same or different than the digit presented N-positions before, with N gradually increasing from 1 to 2. The Digit Stroop task used was modified for tablet and it included four different conditions: reading, counting, inhibition, and switching. In the inhibition block, the participant had to identify the number of identical digits present on the screen, while inhibiting the automated action of reading the digits. For the switching block, participants were instructed to either name the number of items (inhibition trials) or, if the items were surrounded by a white border, to provide the value of the digits (reading trials). In the Dual-Task (DT), participants were asked to perform two visual discrimination tasks, alone or concurrently. The task had three conditions: Single Pure (SP), Single Mixed (SM), and Dual Mixed (DM). In the SP condition participants had to identify which one of 3 symbols (planets for one task and animals for the other task) was presented on the screen. In the SM condition, participants had to identify one stimulus among any of the stimuli of the 2 tasks. In the DM condition, participants had to identify two stimuli (one from each of the sets) presented at the same time. In addition to response speed and accuracy, two types of costs were also extracted from the DT (Esmail et al., 2020). Dual task cost was calculated by subtracting the RT during the SM condition from the RT in the DM condition. This cost reflects the ability to direct attention and answer to two different stimuli. The task set cost was calculating by subtracting the RT in the SP condition from the RT in the SM condition. This cost reflects the ability to prepare and maintain attention to all potential stimuli.

Two composite scores were created with the data obtained from the tablet tasks. An executive cognitive composite score was comprised of (1) 2-back accuracy of the N-back task, (2) average SM trials' RT from the DT, (3) average DM trials' RT from the DT, (4) average RT from the Stroop inhibition block, and (5) average RT from the Stroop switching block. A second non-executive cognitive composite score was comprised of (1) 1-back accuracy of the N-back, (2) average SP trials' RT from the DT, and (3) average RT from the Stroop reading block. All components within each composite score correlated with each other, and they showed a convincing degree of internal consistency (Cronbach's $\alpha = 0.83$ for the executive score, and $\alpha = 70$ for the non-executive score).

Physical assessments: The 10-meter walk test was used to assess participants' mobility. Starting from a standstill position, participants had to walk as fast as they could in a straight line without running over 10 meters. Time was recorded. VO_2Peak was assessed during a maximal continuous graded test performed on a stationary bicycle (Corival Recumbent, Lode B.V., Groningen, The Netherlands). For more details on the test please see Berryman et al. 2013 (Berryman et al., 2013). Initial mechanical power was set at 50 W for males and 35 W for females. Power was then increased by 15 W every 60 s, with a fixed pedaling cadence of 60 to 80 rpm. Termination criterion was the inability to maintain the required pedaling cadence. The highest VO_2peak over a 30-s period during the test was considered as VO_2peak (in $ml.kg^{-1}.min^{-1}$).

2.3.4. Statistical analysis

The study's objectives were investigated using IBM SPSS version 24.0 for Windows (IBM, Inc., Chicago, IL). In order to decrease the impact of outliers, data were winsorized at 3 SD away from the mean. Normality of data distribution was determined by following recommendations by Tabachnick and Fidell (2019) which included assessing the kurtosis and skewness of all variables. Prior to conducting any analyses, the sample was partitioned and binary coded as high (QTcD > 47 ms) vs. low (QTcD ≤ 47 ms) based on a median split. This has been considered due to the high range of QTcD values observed in the present sample (range: 20 – 105 ms). Zero-order bivariate Pearson correlations were performed between the QTcD values and the

cognitive variables before testing the hypotheses, both in the high QTcD and low QTcD subgroups and on the two subgroups combined (see Table 2.2). This was followed by a series of multiple linear regressions on the significantly correlated relationships to test the study's hypotheses. All regression analyses controlled for the effect of age, sex and education, due to their documented impact on cognitive aging.

In order to limit the role of physical fitness on the association between cardiac autonomic control (QTcD) and cognition, we limited our sample selection only to inactive older adults, as this was an inclusion criterion. We further tested if the aerobic fitness (VO2Peak) was correlated with QTcD, in order to decide if VO2 Peak can be included as a potential mediator. In order to test the hypothesis that QTcD predicts cognition, the primary analysis consisted of testing the association between QTcD and global MoCA within the low and high QTcD subgroups. Secondary exploratory analysis investigated if a specific pattern of cognitive functions emerges as being associated with QTcD. The cognitive variables used at this stage are the executive functions composite score, non-executive composite score, DSST, DTC, TSC, and the MoCA subscores.

2.4. Results

The primary outcome of this study consisted of the global MoCA score. Partitioning QTcD revealed almost an equal split between those in low (n = 34) and high (n = 29) groups. Table 2.1. provides demographic data. VO_2Peak did not significantly correlate with QTcD ($p > .05$), and therefore could not be further investigated as mediator. Table 2.2. shows bivariate correlations between QTcD and all cognitive variables. Notable correlations found QTcD to correlate with global MoCA only in the whole sample (r = -.28, $p < .05$) and in the high QTcD group (r = -.58, $p <$ .05). The primary analysis within the whole sample revealed that QTcD was a significant predictor of the global MoCA score ($F_{(4.58)} = 3.00$, $p < .05$, $R^2 = .17$, $\beta = -.36$, $p <.01$). It is important to note that within the high QTcD group, QTcD explained significantly more variance on the global MoCA score ($R^2 = .34$, $F_{(4.23)} = 2.99$, $p < .04$, $\beta = -.57$, $p < .01$; Table 2.3; Figure 2.1.), than in the whole sample. No such association was found to be significant in the low QTcD group ($p > .05$).

	QTcD[a]	QTcD[b]	QTcD[c]
MoCA	-.28*	-.58**	-0.19
Exec.	-0.04	-.40*	-0.14
Non-Exec.	-0.03	-0.25	-0.13
DSST	-0.04	-.41*	-0.17
TSC	0.2	.42*	0.13
DTC	-0.03	-0.28	-0.07
MoCA V-E.	-.34**	-.39*	-0.15
MoCA Naming	-0.24	-0.17	0.22
MoCA Attention	-0.21	-0.05	-0.06
MoCA Language	-0.13	-.62**	-0.14
MoCA Abstr.	0.01	-.44*	0.17
MoCA Mem.	0.02	-0.24	-0.08
MoCA Orien.	0.11	/	-0.15

Table 2. 2. - Pearson correlation coefficients between QTcD and the cognitive variables.

Abbreviations: MoCA = Montreal Cognitive Assessment; Exec. = executive composite score; Non-Exec. = non-executive composite score; DSST = digit symbol substitution test; MoCA V-E. = visual/executive subcomponent of MoCA; MoCA Abstr. = abstraction subcomponent of MoCA; MoCA Mem. = memory subcomponent of MoCA; MoCA Orien. = orientation subcomponent of MoCA; QTcD = ECG QT dispersion – controlled for heart rate.

Note: Pearson correlation score for MoCA Orientation in the high QTcD group could not be

calculated because everyone answered the question correctly, and the variable was constant.

[a]Whole sample; [b]High QTcD sample; [c]Low QTcD sample

** p < .05; ** p < .01*

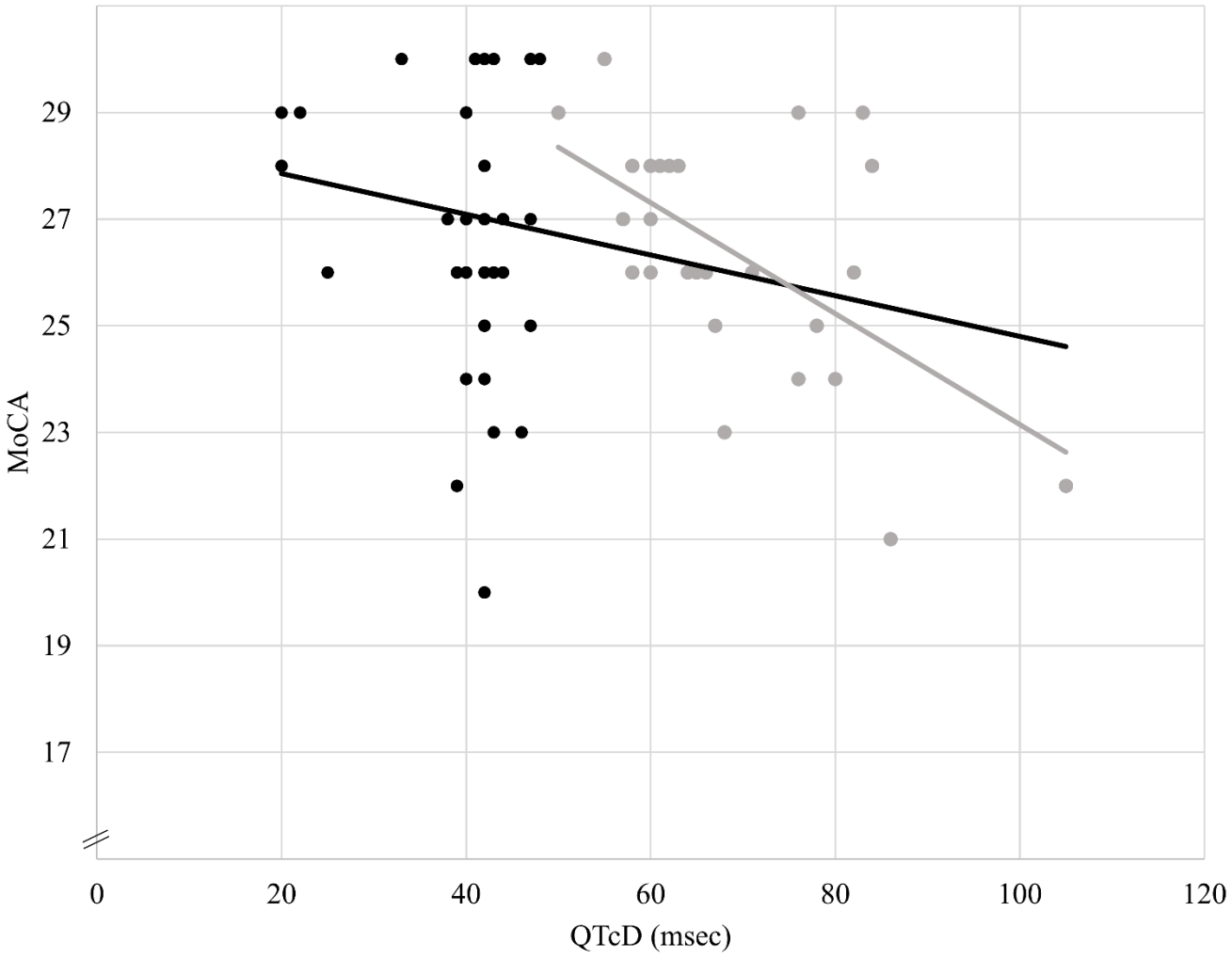

Figure 2. 1. - Association between QTcD and MoCA scores.

The darker trend line shows the association between QTcD values and MoCA scores in the whole sample (n=63, R^2 = .08, β = -.28). The lighter gray trend line shows the association between QTcD values and MoCA scores only in individuals with high QTcD values (QTcD > 47 msec, n=28, R^2 = .33, β = -.58).

Secondary exploratory analyses involved the MoCA subcomponents and the other cognitive scores recorded. All significant associations reported here were observed within the high QTcD group (Table 2.2). Analysis investigating the subcomponents of MoCA found QTcD to predict the language component (R^2 = .39, $F_{(4.23)}$ = 3.74, p < .05, β = -.60, p < .01), and the abstraction component (R^2 = .35, $F_{(4.23)}$ = 3.04, p = .04, β = -.43, p < .05; Table 2.3**)**. Results also showed that the QTcD significantly predicted the executive composite score of the tablet tasks (R^2 = .37, $F_{(4.23)}$ = 3.38, p = .03, β = -.45, p < .01), the digit symbol substitution score (R^2 = .34, $F_{(4.23)}$ = 2.93, p = .04, β = -.41, p < .05), and the task set cost in the dual-task (R^2 = .47, $F_{(4.23)}$ = 5.13, p < .01, β = .46, p < .01;(Table 2.3). No significant associations were found between QTcD and the secondary cognitive variables among individuals with low QTcD values.

Independent variable	Dependent Variable	β	SE	t	P-value
QTcD	Global MoCA	-.36	.02	-2.92	.005
QTcD§	Global MoCA	-.57	.03	-3.29	.003
QTcD§	Vis/Exec MoCA	-.34	.01	-1.90	.070
QTcD§	Language MoCA	-.60	.01	-3.60	.002
QTcD§	Abstraction MoCA	-.43	.01	-2.47	.021
QTcD§	Executive Composite Score	-.45	.01	-2.66	.014
QTcD§	DSST	-.41	.23	-2.35	.028
QTcD§	Dual Task – Task Set Cost	.46	1.77	2.98	.007

Table 2. 3. - Results of multiple linear regression models.

Abbreviations: DSST = Digit Symbol Substitution Test; MoCA = Montreal Cognitive Assessment; QTcD = ECG QT dispersion – controlled for heart rate; Vis/Exec MoCA = Visual/Executive subcomponent of MoCA;

Notes: β is the standardized beta coefficient. § = analysis done on the high QTcD subgroup.

2.5. Discussion

The current study investigated the link between QTcD and cognition in healthy inactive older adults. The results show that higher QTcD values were associated with lower global and executive cognitive scores, and this relationship was even more apparent in individuals with high QTcD values. In other words, individuals having higher heterogeneity in ventricular repolarization exhibited lower cognitive functions. This study included an extensive cognitive assessment battery which allowed the identification of specific cognitive domains that are linked to ECG parameters. Among all of them, general executive functions, processing speed, and the ability to maintain multiple response alternatives in working memory were shown to be associated with QTcD. The findings using the median split show that some results are restricted to the high QTcD group, suggesting a discontinuous relationship between QTcD and cognition. The association between QTcD and global MoCA score was stronger in the high QTcD group relative to the whole sample (High QTcD R^2= .33 vs. all sample QTcD R^2=.17), and the other secondary cognitive variables were linked to QTcD only in the high QTcD group. This might suggest that only individuals with higher values in ventricular repolarization might show a stronger association with poorer cognitive abilities. This is in accordance with previous work suggesting that higher values on QTcD have more predictive value and are less likely to be affected by measurement error (Marek Malik & Batchvarov, 2000).

Although the relationship between ventricular repolarization dispersion and cognition has been documented in dementia (Coppola et al., 2013; Zulli et al., 2005), to our knowledge, this is the first study to find a similar relationship in healthy individuals. This study further expands existing knowledge by identifying ventricular repolarization as an important marker of cognitive performance in healthy inactive older adults before the onset of a cardiovascular disease or clinical cognitive decline. The cognitive performance linked to QTcD in the present study included executive functions and processing speed. These results are consistent with previous findings that also identify executive functions (inhibition, updating and switching) and psychomotor speed as the cognitive functions most likely to be associated with a better autonomic cardiovascular regulation (measured by heart rate variability) in a population-based

sample (Stenfors, Hanson, Theorell, & Osika, 2016). This is not trivial in a prevention perspective as executive functions have been shown to predict further global cognitive decline in prospective studies (Clark et al., 2012). Low executive functions were also shown to predict future functional decline and increased mortality (Gross et al., 2016; Johnson, Lui, & Yaffe, 2007). As such, detecting subtle changes in executive functions with non-invasive ECG parameters could help identify those at greater risk of future cognitive decline and who need more aggressive preventive strategies.

One potential explanation for the link between QTcD and cognition in aging is that both the autonomic function and cognitive abilities degrade at the same time as a result of age-related deteriorations of the prefrontal cortex. Evidence suggests that both autonomic regulation and cognition (especially executive functions) in healthy older adults are controlled in part by the prefrontal cortex as part of the central autonomic network (Duschek, Muckenthaler, Werner, & del Paso, 2009; Nonogaki, Umegaki, Makino, Suzuki, & Kuzuya, 2017; Shah et al., 2011; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). The neurovisceral integration model suggests that the cognitive abilities, autonomic function and emotional regulation are supported by a common hub of neural structures that includes the prefrontal cortex (Thayer & Lane, 2009). During normal aging, the frontal cortex is affected first, and it declines faster than other structures (Drag & Bieliauskas, 2010). As a result, it is possible that the functions controlled by this area are impaired, including executive functions and autonomic regulation. This top-down explanation is also supported by a recent study showing a reduction in the inter-connectedness between the autonomic system and cognition following stroke (Beer, Soroker, Bornstein, & Leurer, 2017). In this population, the sudden brain damage was associated with lower cognitive abilities and a decreased parasympathetic activity compared to individuals without stroke. In addition, the autonomic activity of the stroke patients failed to show an association with cognitive functions, and it was less likely to adapt during a dual-task. Higher ventricular repolarization heterogeneity was also observed in older individuals immediately after stroke, and the prognosis after hospital discharge was poorer among individuals with higher variation in ventricular repolarization scores (Rahar, Pahadiya, Barupal, Mathur, & Lakhotia, 2016).

The link observed between QTcD and cognition in aging could also reflect subtle cardiovascular declines that can impact both autonomic regulation and cognitive functioning. QTcD has been shown to be higher in individuals suffering from certain conditions known to be associated with lower cognitive functions, like hypertension (Marek Malik & Batchvarov, 2000). Therefore, changes in ventricular repolarization could reflect subtle deteriorations of the cardiovascular system which can have a negative impact on brain health and eventually result in lower cognitive functions. For example, a recent study has showed that autonomic function markers predicts future white matter hyperintensities (Obara et al., 2018). In addition, the authors suggest that the white matter hyperintensities can be caused by the gradual deterioration of the cardiovascular system. As a result, it is possible that subtle, non-clinical cardiovascular declines could result in cardiac, autonomic and cognitive declines simultaneously. Similarly, other cardiovascular variables that were not measured as part of the present study should be considered to better document the relationship between cardiovascular health and cognition.

Although the use of QTcD as a clinical tool to predict the risk of mortality and sudden cardiac death has been challenged (Rautaharju et al., 2009), poor QTcD has still been linked to numerous cardiovascular conditions even beyond the increased risk of developing arrythmia. For example, QTcD was found to be higher in individuals with hypertension, coronary disease, chronic myocardial infarction, left ventricular hypertrophy, heart failure, dilated cardiomyopathy, hypertrophic cardiomyopathy, acute myocardial infarction, and long QT syndrome (Guntekin et al., 2011; Marek Malik & Batchvarov, 2000). In addition, a higher QTcD value was associated with an even higher severity of the disease (Marek Malik & Batchvarov, 2000). The current results bring further evidence to the importance of high QTcD values as those were the ones to better predict cognitive abilities in this sample. Therefore, future longitudinal studies should investigate the predictive properties of QTcD as a potential indicator of future cognitive deficits, and its ability to detect people at risk of dementia.

The electrical functioning of the heart can be influenced by exercise, various cardiovascular problems (like hypertension and arrythmias) as well as natural aging which are all known to remodel the heart over time (Devereux et al., 1983; Havmoller et al., 2007; Kang, 2006). In the

present sample the participants were inactive, and had a relatively low VO_2Peak indicating a low cardiovascular fitness. It is possible that the link between ventricular repolarization and cognition might be more evident in those individuals with low fitness or that are sedentary. Previous studies have indeed highlighted the link between sedentary behavior and lower cognitive abilities (Falck, Davis, & Liu-Ambrose, 2017). Since the present sample was recruited to be very homogeneous in terms of physical fitness and physical activity, and since the VO_2Peak values did not correlate with the variables of interest, there is not enough evidence to suggest that the association between QTcD and cognition observed in this study is mediated by physical fitness. On the other hand, future studies should investigate this in more detail by looking at the potential benefits of exercise training on cognitive abilities and autonomic regulation, and how this intervention might affect the link between QTcD and cognition. The lack of significant association between QTcD and VO_2Peak in the present study might be related to the low variance of the VO_2Peak due to the sample selection criteria. Indeed, it is already well documented that regular physical activity and exercise interventions show benefits on cognitive functioning, cardiac health, and autonomic regulation independently (Dupuy et al., 2018; Ludyga, Gerber, Puhse, Looser, & Kamijo, 2020; Rosenwinkel, Bloomfield, Arwady, & Goldsmith, 2001). The benefit of exercise on cognition could be multidetermined, having the potential to improve autonomic regulation, cardiac functioning, and promote brain neuroplasticity, all of which can independently or synergistically result in improved cognitive abilities.

Overall, the results of this study agree with the current literature linking autonomic regulation and cardiac health to cognition. The present study is important because it offers novel insight into the heart-brain connection and reveal ventricular repolarization as an important ECG parameter associated with cognition in healthy older adults. Overall, the results show that higher heterogeneity in ventricular repolarization (QTcD) can be detected before the onset of any cardiovascular disease, and this is linked to lower cognitive abilities. Future studies should investigate this further by looking at the potential benefit of improved autonomic cardiovascular regulation on cognition through various interventions such as exercise.

2.6. Funding sources

This work was supported by a grant from the Quebec Ministry of Health and Social Services to L.B. and Les Grands Ballets Canadiens de Montreal, as well as partial support from Concordia University Chair in Preventive Health Research (L.B.). T.V. was supported by a doctoral salary award from the Fonds de la recherche en sante du Quebec.

2.7. Conflict of interests

None.

2.8. Author contributions

T. Vrinceanu participated in the development of the original hypothesis, data collection, data entry, data analysis, writing of the article. All other co-authors gave their feedback on the final draft. Co-author L. Bherer developed, supervised the project and the writing of the article, and was involved in all stages of the process. Co-author G. Lagacé-Lavoie extracted and interpreted the ECG data and offered a clinical interpretation of the results. Co-authors A. Nigam & M. Vu had medical oversight over the participants, N. Berryman was involved in the study development, N. Kaushal validated the statistical approach, and A. Esmail was involved in data collection, data entry, and study development.

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Chapter 3 – Article 2

Pattern of Atrial Fibrillation and Cognitive Function in Young Patients with Atrial Fibrillation and Low CHADS2 Score: Insights from the BRAIN-AF Trial

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3.1. Abstract

Background: Atrial Fibrillation (AF) and left atrial (LA) enlargement, which frequently coincide, have both been associated with lower cognitive abilities. The purpose of this study was to investigate the association between AF subtype (paroxysmal vs. non-paroxysmal), LA volume (LAV), and cognition in young patients with lone AF.

Methods: A cross-sectional study was performed in patients with echocardiographic data who were randomized in the internal pilot of the BRAIN-AF RCT trial (ClinicalTrials.gov #NCT02387229). All patients had documented AF, were at low risk of stroke (between 30 to 62 years of age, absence of hypertension, diabetes mellitus, congestive heart failure or prior stroke or transient ischemic event) and had no major depression or dementia. Exploratory analyses were performed to assess group differences in the Montreal Cognitive Assessment (MoCA) subscores.

Results: 195 patients were included (135 with paroxysmal AF, mean age 53 years, 21.5% female). LAV moderated the association between AF subtype and MoCA score ($p<0.01$). Conditional effects revealed that LAV was a significant moderator of cognitive function in those with non-paroxysmal but not paroxysmal AF. In non-paroxysmal AF patients, a LAV one standard deviation higher than average (or 56.2 mL) predicted a lower global MoCA score by 1.29 points ($p <0.01$) than those with paroxysmal AF. Overall, non-paroxysmal AF was associated with a lower global MoCA score ($p=0.03$) and visuospatial-executive subscore ($p=0.02$) when compared to paroxysmal AF. All analyses were corrected for age, sex, BMI, education, and depressive symptoms.

Conclusions: In a young population with lone AF, higher LAV was associated with lower cognitive abilities in non-paroxysmal but not paroxysmal AF. Moreover, non-paroxysmal AF was associated with lower cognitive function scores.

Keywords: Atrial fibrillation burden, Cognitive decline, Cardiovascular health, Aging, Prevention;

3.2. Introduction

To date, much the current understanding of how atrial fibrillation (AF) is associated with cognitive performance is from studies that treat AF as a present or absent condition. However, to better understand how much cumulative impact AF has on the body, in the past few years there has been an effort to look at AF beyond its binary nature by focusing on how much time an individual is exposed to AF (Chen et al., 2018; Tiver, Quah, Lahiri, Ganesan, & McGavigan, 2021). Following this trend, it can be hypothesised that AF doesn't have an all or none effect on cognition. Rather, the AF burden, which is often defined as the amount or quantity of AF that a person is exposed to, might be directly linked to a series of detrimental changes in the body that eventually result in cognitive decline. This would imply that despite having the same diagnosis, an individual that has been exposed for a longer period to AF is at a higher risk of showing lower cognitive abilities. Moreover, including to this investigation cardiac markers known to interact with AF could help identify patients that are at higher risk of cognitive decline. However, the available evidence to date is limited.

Within the AF diagnosis there is a wide range in the time during which patients are exposed to arrythmia. As a result, a recent scientific statement has called for the study of the AF burden measured as the time spent in AF or at the very least by using the different subtypes of AF: paroxysmal, persistent, and permanent AF (Chen et al., 2018). Research investigating the AF burden is only recently increasing, and evidence suggests a potentially higher health decline associated with higher AF exposure (Al-Khatib et al., 2013; Ganesan et al., 2016; Piccini et al., 2019; Steinberg et al., 2015), despite that some older studies did not find a difference (Banerjee et al., 2013; Hohnloser et al., 2007). In a retrospective study looking at over 3000 patients who had pacemakers, implantable cardioverter-defibrillators, or cardiac resynchronization therapy devices which continuously monitored the heart rhythm for up to 1 year prior to death, an increase in AF burden has been associated with an increased odds of death (Piccini et al., 2019). Of course, those results need to be interpreted with caution as the researchers could not analyze the heart rhythm (the device interpreted an atrial rhythm >180 bpm as AF), and they did not have access to the patients' comorbidities and treatments prior to death which could

have impacted both AF burden and the risk of death. Similarly, in a meta-analysis including over 100 000 subjects, non-paroxysmal AF (persistent or permanent) was associated with a higher mortality risk and with a multi-variate adjusted hazard ratio of 1.32 compared with individuals with paroxysmal (Ganesan et al., 2016). Clinical trials as well were able to show that individuals with non-paroxysmal AF are at a higher risk of stroke and death regardless of the use of an anticoagulant treatment (Al-Khatib et al., 2013; Steinberg et al., 2015). A retrospective cohort study was able to find a link between AF burden (using ambulatory continuous cardiac monitoring) even within individuals only with paroxysmal AF after controlling for stroke risk factors (Go et al., 2018). This shows that even if the AF episodes are short and self-terminating, a higher exposure to AF can have a detrimental effect. Despite this, a meta-analysis did not find any association between AF burden and stroke risk in asymptomatic AF patients, concluding that there is a need for better markers at identifying asymptomatic individuals that are at risk (Proietti et al., 2016). Those results could also suggest that the effect of AF burden is more evident the more it impacts the body, and the health risks associated with AF might be lower early on before the onset of AF symptoms. This of course, still needs to be investigated in more detail, because AF is hard to detect and study early on in its onset especially if it is asymptomatic.

Although the direct impact that AF burden has on stroke and mortality risks is better established, its relationship with other conditions is more complex. For example, patients with AF are known to be at risk of heart failure (HF), with registries showing that 33% of paroxysmal AF patients, 44% of persistent AF, and 56% of permanent AF patients suffer from HF (Chiang et al., 2012). Although AF more often predates HF, the opposite can also be observed which makes it difficult to conclude that AF has a causal impact on HF, or if it might just be an earlier manifestation of common underlying mechanism (Santhanakrishnan et al., 2016). A similar association exists between AF and markers of cardiac remodeling like the left atrial volume (LAV).

Increased exposure to AF (or arrythmia in general) results in cardiac remodeling (Dzeshka, Lip, Snezhitskiy, & Shantsila, 2015). As such, markers showing the degree of AF cardiac remodeling

could also be, to some extent, considered markers of AF burden. The structural cardiac remodeling characteristic to AF is defined by an increase in the size of the heart muscle, and more specifically the left atrium. The longer the presence of arrythmia, the larger the heart muscle becomes. In fact, the increase in AF-related atrial remodeling (structural as well as electrical) has also been suggested to be one of the primary factors to predict AF progression from paroxysmal to a more sustained type (Heijman, Luermans, Linz, van Gelder, & Crijns, 2021) highlighting the spiral effect between the time spent in AF and cardiac remodeling. The extent of the AF-related structural cardiac remodeling can be captured with the measure of the LAV (Sanfilippo et al., 1990) or the left atrial anterior-posterior diameter (LAAPD) (Dittrich et al., 1999). It has already been showed that having AF is associated with a progressive increase in atrial size and reverting to sinus rhythm results in a decrease of the LAV (Gosselink, Crijns, Hamer, Hillege, & Lie, 1993; Reant et al., 2005; Wozakowska-Kaplon, 2005). Research has shown that those cardiac markers are independent predictors of future clinical cardiovascular events (Kizer et al., 2006; Tsang et al., 2003), and are directly associated with AF burden (Fuchs et al., 2013; Leung et al., 2018; Therkelsen, Groenning, Svendsen, & Jensen, 2005). Moreover, higher AF burden (measured with continuous Holter monitors) was associated with a larger LAV even in patients with nonpermanent AF (Krisai et al., 2020). However, left atrial remodeling can be caused by other medical or non-medical conditions as well (i.e., hypertension, aging, or endurance training), and in fact, it has been shown to be able to also predict, longitudinally, the development of incident AF (Molina et al., 2008; Tsang et al., 2001).

In relation to cognition, the AF burden is not well investigated. However based on the mechanisms proposed to explain the link between AF and cognitive decline (Manolis, Manolis, Apostolopoulos, Melita, & Manolis, 2020; Rivard & Khairy, 2017), it can be argued that an increase in disease burden can result in higher cognitive declines (Chen et al., 2018). In fact, both the Framingham Heart Study and the ARIC neurocognitive study have found AF to be associated with lower global cognitive abilities, and with executive functions and verbal fluency appearing to be particularly affected (Nishtala et al., 2018; Zhang et al., 2019). Among the studies investigating the AF subtypes, it has been found that individuals with persistent AF might have lower executive functions, visuo-spatial abilities, attention, and semantic memory in

addition to lower global cognitive abilities than individuals without AF (Chen et al., 2016; Gaita et al., 2013). Those two studies are also some of the only ones to suggest a potential cognitive difference between paroxysmal and non-paroxysmal AF. Two of the most recent studies looking at AF burden as the relative time spent in AF (from continuous ambulatory monitoring) failed to find an association between AF burden and cognition (Bonnesen et al., 2021; Herm et al., 2020). However, those studies were not designed to test this hypothesis, and their results must be interpreted with caution. One of the studies investigated this association during a 6-month follow-up period post atrial ablation (Herm et al., 2020), while the other study investigated this association over three years while administering anticoagulation medication based on the AF burden score (Bonnesen et al., 2021). Moreover, both of those studies have used cut-offs to split the AF burden into groups, and this approach has been criticized due to a potential lack of validity (Tiver et al., 2021). However, it has been pointed out the AF burden from continuous ambulatory monitors is usually not normally distributed and further research is needed to identify the ideal way to use and analysis this variable. Since the evidence between AF burden and cognition is scarce, authors have already highlighted the crucial need for a more detailed investigation (Chen et al., 2018).

A larger left atrial size has also been independently associated with lower global cognitive abilities as well as lower performances on subscores measuring language and delayed memory (Alosco et al., 2013). To date, only one study has investigated the link between AF, left atrial enlargement (LAE), and cognition (Zhang et al., 2019). The authors found that the presence of both AF and LAE is associated with the lowest cognitive performance on composite scores (global score, executive functions score, and language abilities score), and the presence of AF was associated with the highest decline in cognitive performance even in the absence of LAE. However, the authors did not investigate this relationship within the AF subtypes.

AF has been associated with cognitive impairment and dementia even in the absence of stroke, and independently from shared comorbidities (Diener, Hart, Koudstaal, Lane, & Lip, 2019). Patients with persistent AF seem to have lower global cognitive abilities than individuals with paroxysmal AF, but the evidence is still limited (Chen et al., 2016; Gaita et al., 2013). Whether

this association is explained by AF burden or shared cofactors is uncertain. Overall, those studies suggest that there might be a larger decline in health observed when the disease progresses from paroxysmal to a more sustained form. As a result, studies often pool the persistent and permanent cases in one group and compare them with patients with paroxysmal AF. Therefore, to better understand the full impact AF has on cognition, or on any other health variable, it is important to minimally distinguish paroxysmal from non-paroxysmal AF cases (Chen et al., 2018). Left atrial (LA) enlargement, which is commonly associated with AF, has also been linked with an increased risk of stroke and cognitive impairment in patients with or without AF (Karadag, Ozyigit, Ozben, Kayaoglu, & Altuntas, 2013).

To better isolate the link between AF burden and cognition it is ideal to study a sample without other common factors known to impact cognition, the LAV, or the risk of developing AF. Since all primary variables (cognition, AF and LAV) are known to be associated with advanced age, and cardiovascular comorbidities (e.g., hypertension, diabetes mellitus, congestive heart failure) a relatively healthy young sample diagnosed with AF should be targeted. This would allow to rule out potential confounds, and better isolate the association between AF and cognition.

The present study investigates cross-sectionally the link between AF burden and cognition, in the BRAIN-AF trial. It is expected that individuals with non-paroxysmal AF have lower scores on the Montreal Cognitive Assessment (MoCA) than individuals with paroxysmal AF. Similarly, we expect LAV to be higher in non-paroxysmal individuals. Finally, we expect the AF group difference observed on the MoCA scores to be moderated by the LAV with individuals suffering from non-paroxysmal AF and with high LAV to have the lowest scores. Exploratory analysis will also investigate if there are any group differences (paroxysmal vs. non-paroxysmal AF) on the MoCA subscores.

3.3. Methods

This is a cross-sectional analysis of the baseline data of 195 patients that had complete echocardiographic data from the first 503 patients randomized in the BRAIN-AF trial

(ClinicalTrials.gov #NCT02387229). The current cross-sectional study assessed whether AF burden and LAV were associated with cognition in low-risk AF patients. Exploratory analyses also investigated whether there were any group differences in the Montreal Cognitive Assessment (MoCA) subscores.

3.3.1. Study population

Patients randomized in the internal pilot phase of the BRAIN-AF trial with LA echographic data were included in this study. BRAIN-AF is a prospective, randomized, double blind, controlled trial. This ongoing study is currently assessing whether rivaroxaban 15 mg daily when compared to placebo can reduce the composite outcome of stroke/transient ischemic attack (TIA) or neurocognitive decline (i.e., a decrease in MoCA score > 3 points when compared to baseline) in patients with AF considered to be at a low risk for stroke. The details of this study have been previously described (Rivard et al., 2019). In brief, inclusion criteria include: presence of AF (documented by any electrocardiographic tracing), between 30 to 62 years of age, and a low risk of stroke (e.g., absence of prior stroke or TIA, hypertension, diabetes mellitus, or congestive heart failure). Main exclusion criteria include: indication for oral anticoagulants, known dementia, or a Mini Mental State Examination (MMSE) score lower than 25, valvular AF, severe renal impairment, liver disease, other conditions associated with an increased risk of bleeding, diagnosed depression, and pregnant or breastfeeding women. Five hundred three patients were randomized in the internal pilot phase. Three hundred and eight participants who had missing transthoracic echocardiographic LA values were excluded from the study. The BRAIN-AF trial was approved by institutional review boards at all participating institutions. Participants provided written informed consent before beginning the study.

3.3.2. Neurocognitive assessments

A neuropsychological test battery was administered to participants by trained examiners in a standardized order in one session. Global cognitive functioning was assessed using two cognitive screening tests, first the MMSE (Folstein, Folstein, & McHugh, 1975) and, after a minimal interval of 1 hour, the MoCA (Nasreddine et al., 2005). The MoCA test exhibits

excellent sensitivity in identifying mild cognitive impairment and Alzheimer's disease (90% and 100% respectively) with good specificity (Nasreddine et al., 2005; Zahinoor Ismail, 2010) associated with a cut-off value of 25/30. The MoCA is a paper pencil test that assesses various cognitive domains in approximately 15 minutes. The cognitive outcomes were separated according to the MoCA 7.1 version subscores, which are visuospatial-executive (shortened version of the Trail Making Test part B, copy of the cube and clock drawing), naming (lion, rhinoceros and camel), attention (digit span forward and backward, letter A finger tapping task and serial 7 subtractions), language (sentence repetition and letter F fluency), abstraction (saying what two words have in common), memory (delayed recall; total words spontaneously recalled among 5) and orientation (date, place). Depression status was assessed using the Beck Depression Inventory-II (BDI-II) (Beck AT, 1996). The BDI-II is a commonly used checklist of depressive symptoms. BDI-II scores range from 0 to 63 with higher score indicative of greater symptomatology.

3.3.3. Echocardiographic data

Transthoracic echocardiographic parameters included LAV, LA anterior-posterior diameter, and left ventricular ejection fraction. As recommended by guidelines, LA measurements were performed at the end of systole using biplane disk summation and were indexed to body surface area (Lang et al., 2015). For the current study, LAV was retained as the primary metric of LA size given that the relationship between LAV and LA dimension is non-linear and that LAV is superior to LA diameter in predicting AF (Faustino et al., 2014; Tsang et al., 2001).

3.3.4. Atrial fibrillation diagnosis

Atrial fibrillation was documented by an electrocardiographic tracing and classified as paroxysmal or non-paroxysmal (i.e., persistent or permanent) in accordance with guidelines (Fuster et al., 2011). Paroxysmal AF was defined as a continuous AF episode lasting longer than 30 seconds but terminating within 7 days of onset.

3.3.5. Covariates

The following covariates were collected and included in the adjustment model: age, sex, level of education (years of education), depression score (BDI-II score), and BMI (in units of kg/m^2). Per inclusion/exclusion criteria, no individual in the study suffered from heart failure, diabetes, hypertension, or mitral stenosis

3.3.6. Statistical analysis

Statistical analyses were performed using IBM SPSS version 24.0 for Windows (IBM, Inc., Chicago, IL), with the PROCESS add-on v3.3 for SPSS for the moderation analysis (Hayes, 2013). Normality of data distribution was verified using the kurtosis and skewness of all variables. Although the visual distribution of the cognitive variables appeared negatively skewed, the kurtosis and the skewness scores were between -1 and 1 such that a transformation was not considered necessary (Field, 2013). All reported p-values are two-tailed, and the significance level was set to 0.05.

A hierarchical multiple regression analysis tested whether AF burden (AF subtypes, LAV, LA anterior-posterior diameter, left ventricular ejection fraction) predicted the total MoCA score. Independent variables were included in the model only if they significantly correlated with the dependent variable (only AF subtypes and LAV fulfilled this condition). The MoCA total score was the dependent variable. In the first step of the regression all covariates were included. Sex and BMI were included as covariates because these parameters differed significantly between the two AF groups, while age, education and depressive symptoms were included due to substantive knowledge (i.e., well-established strong associations with cognition and type of AF in the case of age) (Laredo, Waldmann, Khairy, & Nattel, 2018; Larouche et al., 2016). In the second step, we introduced AF subtypes and LAV. A first-order interaction variable (AF group X LAV) was introduced in the third step. If the interaction term accounted for significantly more variance, a moderation analysis was run using the PROCESS SPSS add-on. The moderation analysis model was created with AF subtypes as the independent variable, MoCA total score as the dependent variable, and LAV as the moderator. The same covariates were included.

Exploratory ANOVA analyses were conducted to investigate if there were any group differences (AF subtypes) on the MoCA subscores in this sample. The ANOVA results were reported based on Levene's Test for Equality of Variances.

3.4. Results

3.4.1. Study population

Table 3.1. lists the clinical characteristics of the population. The study population consisted of 195 patients with AF, classified as paroxysmal in 135 (69.2%) and non-paroxysmal in 60 (30.8%). The mean age was 53 years, and 42/195 (21.5%) were women. Compared to non-paroxysmal AF, paroxysmal AF patients had a lower LAV (32.8 mL vs. 45.5 mL, $p<0.001$), were mostly male (91.7% vs. 72.6%, p=0.003), and had a lower BMI (28.6 vs. 30.6 kg/m^2, p= 0.012).

Characteristic	Mean (SD)		
	Paroxysmal AF (n=135)	Non-Paroxysmal AF (n=60)	P-value/ X^2
Age, mean (SD), years	52.7 (7.0)	53.8 (5.9)	.276
Education level, mean (SD), years	11.5 (2.5)	11.5 (2.6)	.881
Men, N (%)	98 (72.6)	55 (91.7)	.003
Race or Ethnicity (N (%) Caucasian)	129 (95.6)	56 (93.3)	.775
Marital Status (N (%) Married/civil union)	101 (74.8)	49 (81.7)	.628

Daily coffee intake, N (%)	103 (76.3)	43 (71.7)	.492
Current Alcohol consumption, N (%)	105 (77.8)	46 (76.7)	.992
≤ 1 drink/week	20 (19.1)	8 (13.33)	
2-3 drinks/week	24 (22.86)	9 (15.0)	
4-9 drinks/week	31 (29.52)	15 (25.0)	
≥ 10 drinks/week	30 (28.57)	14 (23.33)	
Physical activity, N (%)	82 (60.7)	34 (56.7)	.593
Meeting guidelines, N (%)	50 (61)	25(73.5)	.198
BDI-II, mean (SD)	5.8 (6.0)	5.0 (6.6)	.382
BMI, mean (SD), kg/m^2	28.6 (5.2)	30.6 (4.7)	.012
MoCA, mean (SD)	27.9 (1.7)	27.2 (2.3)	.016
ECG QRS, mean (SD), msec*	98 (17)	92 (20)	.030
HR*	65 (16)	79 (22)	<.001
Presence of sinus rhythm, N (%)*	120 (88.9)	9 (15.0)	<.001
SBP mean (SD), mmHg*	123 (12)	121 (12)	.253
DBP mean (SD), mmHg*	77 (9)	78 (10)	.263
LAV mean (SD), mL	32.8 (16.3)	45.5 (23.3)	<.001
LVEF, N (%)	60.9 (4.9)	58.9 (7.5)	.036

LAAPD (mm)	37.4 (6.0)	42.5 (5.8)	<.001
Prior use of VKA, N (%)	20 (14.8)	20 (33.3)	.003
Prior use of NOAC, N (%)	33 (24.4)	23 (38.3)	.048
Current use of NOACs, N (%)	7 (5.2)	8 (13.3)	.069
Past ECV, N (%)	29 (21.5)	20 (33.3)	.078
Previous AF ablation, N (%)	15 (11.1)	4 (6.7)	.334
Pacemaker, N (%)	7 (5.2)	3 (5.0)	.957
ICD N (%)	2 (1.5)	0	.343
Coronary artery disease, N (%)	5 (3.7)	1 (1.7)	.447
Carotid disease, N (%)	1 (0.7)	0	.504
Peripheral artery disease, N (%)	2 (1.5)	0	.343
Dyslipidemia, N (%)	23 (17.0)	14 (23.3)	.301
Sleep apnea, N (%)	26 (19.3)	9 (15.0)	.474

Table 3. 1. – Baseline Descriptive Data

Abbreviations: BDI-II, Beck Depression Inventory-II; DBP, diastolic blood pressure; ECV, electrical cardioversion; HR, resting heart rate; ICD, implantable cardiac defibrillator; LAAPD, left atrial anterior-posterior diameter; LAV, left atrial volume; LVEF, left ventricular ejection fraction; MoCA, Montreal Cognitive Assessment; N, number; NOAC, non vitamin K oral anticoagulants; Physical activity: patients performing regular physical activity at the time of assessment; Physical activity meeting guidelines: number of patients performing more than 150 minutes of physical activity per week among those who are exercising; SBP, systolic blood pressure; SD, standard deviation; VKA, vitamin K anticoagulant.

**At baseline visit*

3.4.2. Association between LAV, AF subtype and cognitive functions

Please see Table 3.2. for details on the regression model. The multivariable regression analysis model 2 including AF subtypes and LAV significantly predicted the variation in the total MoCA score ($F_{(5, 187)} = 4.55$, $p = 0.02$) after accounting for age, sex, education, BMI and depressive symptoms. When introducing the interaction between AF subtypes X LAV, the new model significantly predicted twice as much variation in the total MoCA score ($F_{(8, 186)} = 10.56$, $p < 0.01$, adjusted $R^2 = 0.10$, $R^2_{change} = 0.05$; $\beta_{AF\ type\ X\ LAV} = -0.96$, $p < 0.01$), suggesting that LAV significantly moderates the effects of AF subtypes on the total MoCA score.

Model/Predictor	Adjusted R^2	ΔR^2	ΔF	β	F/t	p	df
Model 1	.02	.04	1.68		1.68	.140	5,189
Age				-.06	-.89	.377	
Sex				.06	.83	.411	
Education				.20	2.70*	.008	
BMI				.02	.33	.740	
BDI-II				.03	.38	.707	
Model 2	.05	.04	4.55*		2.55*	.016	5,187
Age				-.04	-.58	.562	
Sex				.01	.18	.858	

Education				.18	2.51*	.013	
BMI				.07	.93	.354	
BDI-II				.02	.23	.827	
AF type				-.13	-1.75	.082	
LAV				-.14	-1.92	.056	
Model 3	.10	.05	10.56**		3.66**	.001	8,186
Age				-.03	-.43	.670	
Sex				.03	.39	.696	
Education				.20	2.90**	.004	
BMI				.03	.48	.630	
BDI-II				.01	.12	.907	
AF type				.32	2.02*	.045	
LAV				.56	2.46*	.015	
AF type X LAV				-.96	-3.25**	.001	

Table 3. 2. – Summary table - Regression model for AF burden on the general MoCA score

Abbreviations: β = standardized beta; df = degrees of freedom; AF type = atrial fibrillation type (paroxysmal vs. non-paroxysmal); BMI = Body Mass Index; BDI-II = Beck Depression Inventory II; LAV = left atrial volume.

**P < .05; **p < .01*

The moderation analysis (Table 3.3.) was significant ($F_{(8, 186)} = 3.66$, $p < 0.01$, $R^2 = 0.14$), revealing that only the covariate education ($\beta = 0.154$, $p < 0.01$) and interaction between AF subtypes and LAV ($\beta = -0.047$, $p < 0.01$) significantly predicted the total MoCA score. In analyzing the conditional effects of the moderator (LAV) on the association between AF subtypes and cognition, there was significant evidence for a curvilinear relationship only for high LAV values (Figure 3.1.). For example, at a LAV of 56.2 mL (one standard deviation or 19.6 mL higher than average), being classified as having non-paroxysmal AF predicted a lower global MoCA score by 1.29 points ($b = -1.29$, $t(184) = -3.31$, $p < 0.01$). Having a lower LAV did not significantly impact the association between AF subtypes and global MoCA score.

Model	R^2	b	F/t	p	df
Summary	.14		3.66**	<.001	8,186
AF type		-.395	-1.27	.206	
LAV		-.006	-.75	.452	
AF type X LAV		-.047	-3.25**	.001	
Age		-.008	-.43	.670	
Sex		.130	.39	.697	
Education		.154	2.90	.004	
BMI		.013	.48	.630	
BDI-II		.002	.12	.907	

Table 3. 3. – Summary table for the moderation analysis

*Abbreviations: b = standardized slope; df = degrees of freedom; AF type = atrial fibrillation type (paroxysmal vs. non-paroxysmal); BMI = Body Mass Index; BDI-II = Beck Depression Inventory II; LAV = left atrial volume. **p < .01*

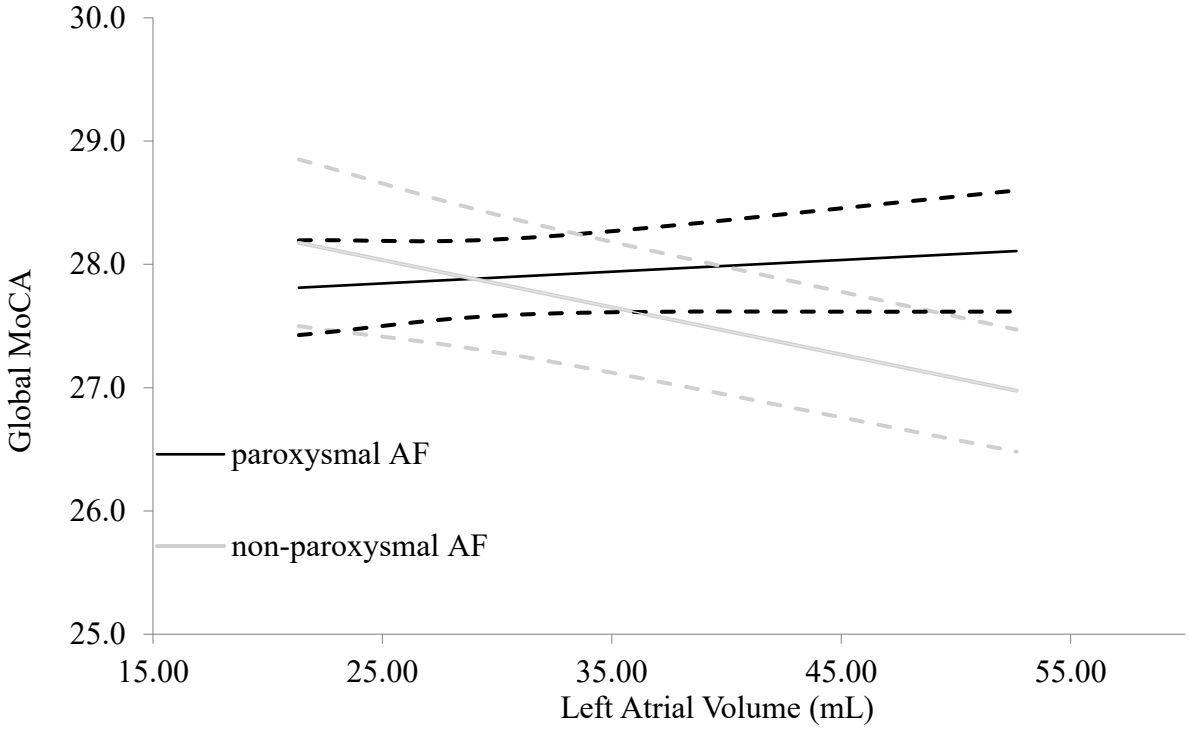

Figure 3. 1. – Conditional effects of left atrial volume on global MoCA scores

Exploratory analyses revealed the paroxysmal group to have higher scores on the global MoCA score (mean difference = 0.717, 95% CI: 0.059 – 1.374, p = 0.03), and on the MoCA visuospatial-executive score (mean difference = 0.319, 95% CI: 0.054 – 0.583, p = 0.02; Figure 3.2.).

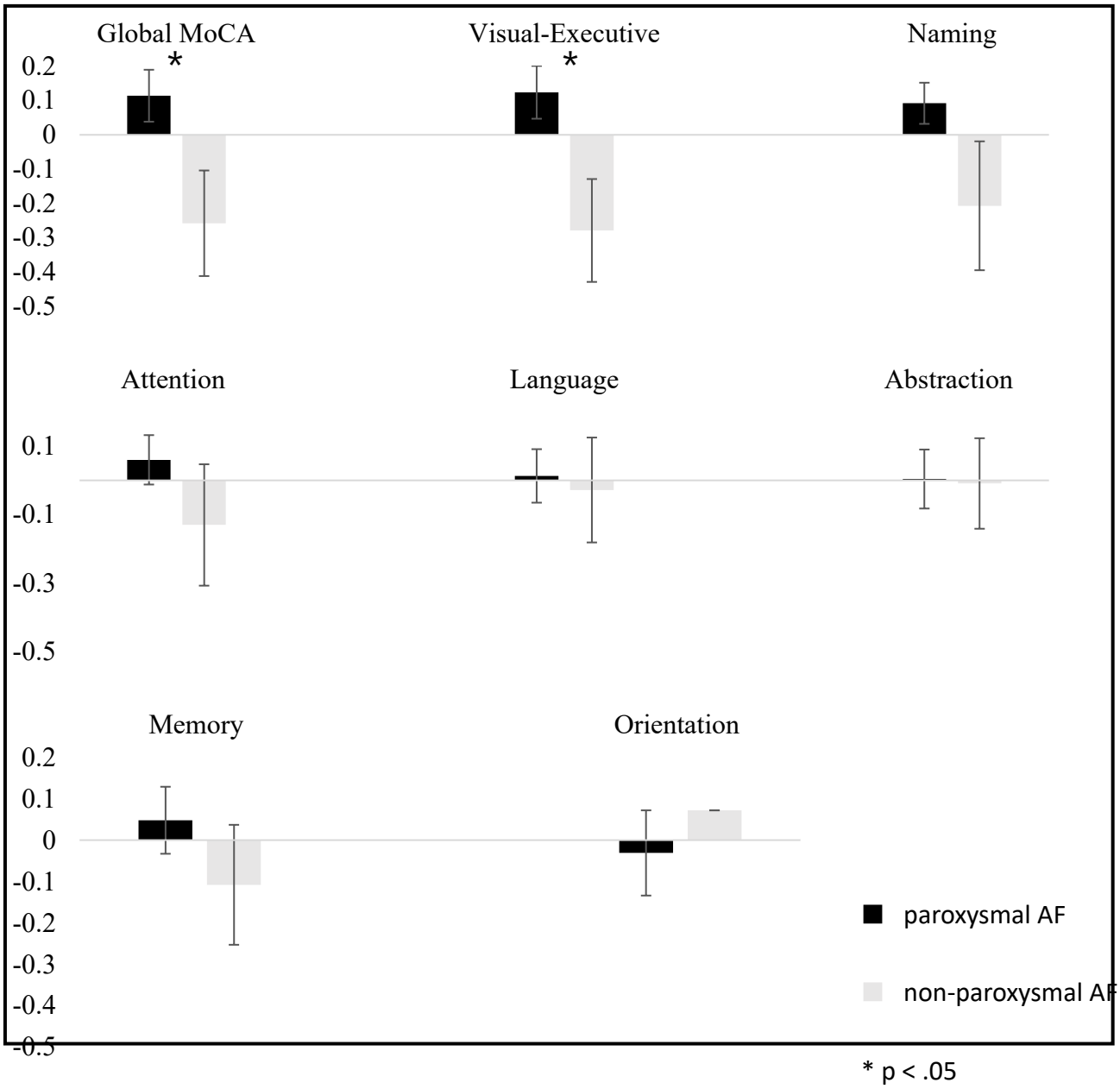

Figure 3. 2. – Group differences on Global MoCA and subscores (Z-score means and SE)

Note: Only for visualization purposes, the MoCA scores have been Z-score transformed. A significant difference was observed only on the global MoCA score and on the visuospatial-executive MoCA sub score (= p < .05).*

3.5. Discussion

The current study investigated the link between AF burden and cognition in an AF population at low risk for stroke. The results show global cognitive abilities to be lower in patients suffering from non-paroxysmal AF than in those with paroxysmal AF. This relationship was moderated by the LAV, meaning the lower cognitive ability of individuals with non-paroxysmal AF was even worse in individuals with large LAV size. Exploratory analysis also found the Visuospatial-Executive subscore to be lower in the non-paroxysmal AF, suggesting a larger decline in higher order cognitive abilities with higher disease burden.

Whereas the association between cognition and LA volume was reported in several cross-sectional and longitudinal studies, mostly in elderly patients with comorbidities, this is the first study showing that the association is significant in relation to AF subtypes. Zhang et al. reported a significant association between LA enlargement and lower cognitive functions in a cross-sectional analysis of 3391 elderly AF patients (mean age 74.4 years) included in the ARIC-NCS (Zhang et al., 2019). Most participants suffered from hypertension, and diabetes was present in one third of the population. The authors found that individuals with both AF and LA enlargement had worse global cognitive and language abilities and worse executive functions compared to individuals with LA enlargement without AF, or individuals with AF and without LA enlargement. Type of AF (paroxysmal versus non paroxysmal) was not evaluated, and LA enlargement was not associated with greater cognitive decline after a follow-up of 5 years. Van den Hurk et al found that LA enlargement was associated with lower information-processing speed in 313 individuals but presence of AF was not assessed (van den Hurk et al., 2011). Likewise, Alosco et al. in a cross-sectional study of 50 individuals reported that LA size was independently associated with reduced performance of the repeatable Battery for the Assessment of Neuropsychological Status under the supervision of a neuropsychologist, but AF was not taken into account (Alosco et al., 2013).

The interaction between AF type and LAV on cognition underlines the importance of using multiple markers of AF burden when assessing the health consequences of the disease. In this case, the two markers show a synergetic effect with the individuals showing the highest disease

burden (non-paroxysmal AF and higher LAV) to also exhibit the lowest cognitive abilities. It is possible that this moderation could better reflect the actual amount of time a person spends in arrythmia, and the biological changes associated with the increased exposure. For example, within individuals with non-paroxysmal AF, a small LAV might reflect less cardiac remodeling, and therefore a lower impact of AF on the body. If this is the case, it is also reasonable to expect the cognitive abilities of those individuals to be less impaired. This has been indeed shown in the present results where lower LAV among non-paroxysmal AF patients seems to buffer the decline in cognition associated with the transition from paroxysmal to non-paroxysmal AF. However, it is not clear if a maintained or a lower LAV among this group reflects less exposure to arrythmia, or the body's ability to better tolerate the arrythmia. For a better understanding of this relationship, a more detailed investigation is required.

The present study did not find a significant difference in the cognitive abilities of patients with persistent or permanent AF, suggesting the highest cognitive decline takes place as the disease progresses from paroxysmal to a more sustained type. After this transition, the cognitive decline is less evident. In other words, the biological changes resulting in cognitive decline would have the highest impact as the arrythmia exposure becomes constant. Another possibility is that the differentiation between persistent and permanent AF might not be as sensitive in characterizing the AF burden related to cognition, and other markers like LAV should be used. This finding also highlights paroxysmal AF as a potential window of opportunity when preventive strategies aimed at slowing disease progression could be implemented and hopefully prevent further cognitive decline.

AF is strongly associated with cognitive impairment and dementia in observational studies (Islam et al., 2019; Kalantarian, Stern, Mansour, & Ruskin, 2013; Kwok, Loke, Hale, Potter, & Myint, 2011; Liu, Chen, Jian, Zhang, & Liu, 2019; Saglietto et al., 2019; Santangeli et al., 2012; Udompanich, Lip, Apostolakis, & Lane, 2013). Importantly, this association appears to be independent of stroke and of several risk factors common to both entities (Bunch et al., 2010; Ott et al., 1997). In the present study, the visual-executive cognitive subscore was more sensitive to AF burden. This is consistent with other studies, which found the same cognitive

domain to be impaired in patients with AF (Nishtala et al., 2018). This pattern of cognitive decline associated with non-paroxysmal AF was similar with the neuropsychological profile of vascular cognitive impairment (Garrett et al., 2004). Therefore, this observation provides further support in favor of a vascular mechanism underlying the cognitive decline observed in this population. In addition, the present study highlights the visual-executive MoCA subscale to be particularly sensitive to AF burden. As a result, future studies should investigate if short cognitive scales (potentially including a simplified Trail Making Test and complex drawings) might be sufficient to identify AF patients at higher risk of cognitive decline.

Proposed mechanisms inducing AF-related cognitive dysfunction include silent brain infarcts, cerebral hypoperfusion, inflammation, brain atrophy, microhemorrhage, and genetic factors (Jacobs, Cutler, Day, & Bunch, 2015; Rivard & Khairy, 2017). Supporting evidence for the microembolization hypothesis includes the much higher incidence of silent brain infarcts detected by imaging studies in AF patients, the association between silent brain infarcts and cognitive dysfunction, and a "dose response" relationship between the extent of silent brain infarction and degree of cognitive impairment. Considering that AF is associated with silent brain infarction and transient ischemic attacks (Cullinane, Wainwright, Brown, Monaghan, & Markus, 1998; Ezekowitz et al., 1995; Kempster, Gerraty, & Gates, 1988), the leading mechanistic hypothesis is that small subclinical ischemic events underlie cognitive decline. In the ARIC study, a decline in executive function and verbal fluency was associated with incident AF only in patients with subclinical brain infarcts (Chen et al., 2014). Also consistent with this hypothesis, Gaita et. al found that patients with AF (60.5% of whom had a low risk of stroke) had a higher prevalence of silent brain infarcts detected by MRI and worse cognitive performance when compared to patients in sinus rhythm [OR 11.2, 95% CI (6 to 21); $p<0.01$] (Gaita et al., 2013). Patients with persistent AF had a significantly higher number of silent brain infarcts (41.1±28.0 vs. 33.2±22.8, $p=0.04$) and lower cognitive performance scores when compared with those with paroxysmal AF. In addition, several analyses, including a recent meta-analysis of 99,996 patients, found that patients with permanent AF were at a higher risk of stroke compared to patients with non-permanent AF (Ganesan et al., 2016; Vanassche et al., 2015).

LA enlargement has been associated with higher increased risk of LA spontaneous echo contrast and embolic events (Benjamin, D'Agostino, Belanger, Wolf, & Levy, 1995). In a retrospective registry-based case-control study comparing AF patients at low stroke risk ($CHADS_2$ score of 0 or 1) prior to a cardio embolic event to an AF control group, LA volume predicted cerebrovascular events (Azemi, Rabdiya, Ayirala, McCullough, & Silverman, 2012). In recent years, a newer model suggests that AF is one of the mechanisms implicated in thrombosis and that atrial cardiopathy (defined by LA enlargement) and LA dysfunction are additional causes of thromboembolism (Kamel, Okin, Elkind, & Iadecola, 2016).

Overall, it appears that both AF exposure and LA enlargement are associated with worse cognitive functions. The interaction between AF subtype and LAV on cognition underscores the importance of using multiple markers of AF burden when assessing individuals at higher risk of cognitive decline. In the present study, subtype of AF and LAV show a synergetic effect with individuals having the highest disease burden exhibiting the lowest cognitive abilities.

3.6. Limitations

The cross-sectional design does not allow observing how cognitive scores change over time as a function of the change in AF burden. Secondly, the study had a limited sample size. As such, the conclusions highlighted above should be interpreted in this context, and future confirmatory studies are required. The use of the MoCA as the primary variable also comes with some limitations. Although it is relatively short and easier to implement in the clinical setting resulting in more data collected, this is mainly a screening tool and might not be ideal to look at cognitive variability in individuals without cognitive impairment. However, since we do observe an effect on the MoCA, we expected to observe an even larger effect with other experimental cognitive tests since they are more sensitive in detecting subtle cognitive variations. In addition, small variations on the MoCA score have been shown to be meaningful and to predict further cognitive change over time (Krishnan et al., 2017; Tan et al., 2017). Finally, future studies should consider the potential impact of sex by taking this into account when designing the study and selecting the sample.

3.7. Conclusions

In a young population of participants with lone AF, LA enlargement was associated with cognitive decline in those with non-paroxysmal AF. Furthermore, non-paroxysmal AF patients had lower global cognitive functions and visuospatial-executive scores when compared to paroxysmal AF patients. Future studies should also investigate the potential differential impact of AF treatments on cognition by considering the AF subtypes and markers of cardiac remodeling.

3.8. Funding sources

T.V. was supported by a PhD salary award from the Fonds de recherche du Québec – Santé. P.K. is supported by the endowed André Chagnon research chair in electrophysiology and congenital heart disease. L.R. is supported by research grants from Heart and Stroke Foundation, Canadian Institutes of Health Research and Fonds de recherche du Québec – Santé.

BRAIN-AF is supported by the Canadian Institutes of Health Research (CIHR), the Montreal Heart Institute Foundation, the Canadian Stroke Prevention Network (C-SPIN), and Bayer Inc.

3.9. Conflict of interests

Dr. Rivard received grant money from BAYER Inc., CIHR, Heart and Stroke and salary support from FRQS.

3.10. Author contributions

T. Vrinceanu contributed with the development of the original hypothesis, data analysis, and in writing the article. All other co-authors gave their feedback on the final draft. Co-author L. Rivard created and supervised the study. Co-authors L. Rivard, L. Bherer, P. Khairy contributed to the study design, and supervised the writing of the article. Co-authors M. Payer, C. Gagnon, N. Kaushal, offered significant feedback to the draft, and the data analysis. All other co-authors had medical oversight over the patients and collected the medical data.

N. B.: Research letter

A more concise version of the study and results presented above has been published in Circulation: Arrhythmia and Electrophysiology in the form of a research letter (Appendix 1): Vrinceanu, T., Khairy, P., Roy, D., Payer, M., Gagnon, C., Kaushal, N., Talajic, M., Tardif, J-C., Nattel, S., Black, S., Healey, J., Lanthier, S., Andrade, J., Massoud, F., Nault, I., Guertin, M-C., Dorian, P., Kouz, S., Essebag, V., Ellenborgen, K. A., Racine, N., Nozza, A., Bherer, L.*, & Rivard, L.* (2021). Pattern of Atrial Fibrillation and Cognitive Function in Young Patients with Atrial Fibrillation and Low CHADS2 Score: Insights from the BRAIN-AF Trial. *Circulation: Arrhythmia and Electrophysiology*, accepted: CIRCAE/2021/010462DR2

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Chapter 4 – Article 3

A pilot study investigating the impact of electrical cardioversion for atrial arrhythmia on cerebral oxygenation and cognition

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Note: The present research article draft has not been yet submitted for publication.

4.1. Abstract

Atrial fibrillation (AF) has been associated with cognitive deficits, sharper long-term cognitive decline, and increased risk of dementia even in the absence of stroke. Despite the limited evidence, restoring sinus rhythm has been suggested as a potential avenue for preventing cognitive decline and potentially even reversing some of the AF-induced cerebral physiological changes (i.e., cerebral regional tissue oxygenation saturation or rSO_2). An electrical cardioversion (ECV) is a rhythm control strategy designed to terminate the arrhythmia and return the normal electrical activity of the heart by administering an electric shock to the chest around the heart. Currently there is limited evidence showing the impact of ECV on rSO_2 and there is no consensus on how ECV impacts cognition. The goal of this study is to obtain pilot data for a future multicentric study, which investigates if rSO_2 improves following a successful ECV, and whether this change is associated with improved cognitive abilities in patients with atrial arrhythmia. Among the patients with atrial arrhythmia scheduled for an elective ECV, 22 were eligible and accepted to take part in the short component of the study measuring the rSO_2 during the ECV; among those, 10 accepted to take part in the full study measuring cognitive abilities (global functioning, executive functioning, memory, attention, and processing speed). The sample recruited suffered from multiple cardiovascular comorbidities, suffered from AF for an extended period, and already underwent multiple past ECV. The results show a potentially insignificant decrease in rSO_2 (Hedge's G between -.03 and -.11), a small decrease in the time to solve the trail making test B (Hedge's G = -0.47), a moderate increase in the digit symbol substitution test score (Hedge's G = .58), and a large decrease in AF-related symptoms (Hedge's G = -1.36). Based on the present pilot study the recommendations are to change the sampling method by balancing the number of patients that suffer from recent onset AF to those that suffer from AF for an extended period. The results are further discussed in terms of potential mechanisms through which sinus rhythm restoration might improve cognitive abilities in arhythmic patients.

4.2. Introduction

Atrial fibrillation (AF) has been associated with cognitive deficits (Nishtala et al., 2018), sharper long-term cognitive decline (Chen et al., 2018; Thacker et al., 2013), and increased risk (~40%) of dementia even in the absence of stroke (Chen et al., 2018; Kalantarian, Stern, Mansour, & Ruskin, 2013). Most affected aspects of cognition are attention, executive functions, abstract reasoning, but even global performance (Chen et al., 2018; Nishtala et al., 2018; Vrinceanu et al., 2022). Proposed mechanisms for this association include silent brain infarcts, microhemorrhage, inflammation, cerebral hypoperfusion, brain atrophy, decreased cerebral blood flow, lower cerebral oxygen saturation, and genetic factors (Jacobs, Cutler, Day, & Bunch, 2015; T. A. Manolis, Manolis, Apostolopoulos, Melita, & Manolis, 2020; Rivard & Khairy, 2017). Some brain changes have been proposed to be acutely associated with changes in the heart rhythm. For example, relative to healthy controls, AF patients show lower cerebral perfusion, blood flow, and cerebral oxygen saturation (Gardarsdottir et al., 2018; Lavy et al., 1980; Porebska, Nowacki, Safranow, & Drechsler, 2007). Those results are particularly evident in individuals that are in persistent AF and have been shown to be sensitive to the acute change in heart rhythm in those with paroxysmal AF (Gardarsdottir et al., 2018). Moreover, converting to sinus rhythm has been shown to improve the cerebral perfusion, blood flow, and cerebral oxygen saturation in this population (Gardarsdottir et al., 2020; Petersen, Kastrup, Videbaek, & Boysen, 1989; Wutzler et al., 2014). The ability of the brain to maintain cognitive functioning is closely dependent on the cerebral blood flow and its ability to metabolize oxygen (Girouard & Iadecola, 2006; Goettel et al., 2017; Phillips, Chan, Zheng, Krassioukov, & Ainslie, 2016). So far, only one study showed that cognitive deficits can be linked to the reduced cerebral blood flow in a subsample of AF patients among a heart failure group (Alosco et al., 2015). Therefore, it could be possible that terminating the arrhythmia can result in improvements in brain markers which can translate to improved cognitive abilities. However, some authors doubt that cerebral hypoperfusion is the primary link between AF and cognitive deficits or increased dementia rates, since cerebral autoregulation should prevent major impairments in blood flow (Dietzel, Haeusler, & Endres, 2018; Ding & Qiu, 2018).

The association between AF treatments and cognitive abilities is not fully elucidated (Madhavan, Graff-Radford, Piccini, & Gersh, 2018). Despite the limited evidence, it looks like in addition to an efficient anticoagulating therapy, restoring and maintenance of the sinus rhythm has been suggested as a potential avenue for preventing cognitive decline and potentially even reversing some of the AF-induced physiological changes that underline the cognitive deficit in this population (Gallinoro et al., 2019). Among the rhythm control strategies, pharmacological treatments are known for their side effects and are not often administered long term, but catheter ablation and electrical cardioversion are two promising procedures. Catheter ablation refers to a procedure in which a small portion of the heart tissue known to initiate and maintain the arrhythmia is ablated. Studies using this procedure suggest that reverting sinus rhythm might have a beneficial effect on cognitive function, but results are still mixed due to relatively large number of studies reporting no change or even a decrease in cognitive functions (Efimova, Efimova, Chernov, Popov, & Lishmanov, 2012; Madhavan et al., 2018; Parameswaran, Al-Kaisey, & Kalman, 2021). The decrease in cognitive functions observed following catheter ablation is mostly related to complications that can appear during the procedure, like the formation of new cerebral emboli, or silent cerebral lesions (Madhavan et al., 2018). On the other hand, electrical cardioversion (ECV) has not been associated with a decrease in cognitive performance and, as a procedure, has a smaller chance of complications than catheter ablation, and is associated with few side effects relative to rhythm control drugs (Andrade et al., 2020). ECV is a rhythm control strategy designed to terminate the arrhythmia and return the normal electrical activity of the heart by administering an electric shock to the chest around the heart that is synchronized with the QRS complex on the electrocardiogram (ECG). The procedure has been shown to be relatively successful, safe, with rare adverse events, and with a relative short time of discharge (Andrade et al., 2020). Currently there is no consensus on how ECV impacts cognition.

Studies have shown that a successful ECV is not associated with new cerebral lesions, and on the contrary, it could have a beneficial effect by improving cerebral perfusion (Arvanitis et al., 2020; Gardarsdottir et al., 2020). Similarly, two studies investigated the change in cerebral oxygen saturation following ECV, using near-infrared spectroscopy (NIRS) (Genbrugge et al.,

2021; Wutzler et al., 2014). While Wutzler et al. (2014) showed a significant improvement of about 4% in cerebral tissue oxygen saturation, Genbrugge et al. (2021) found a smaller improvement of about 1% which he suggested is mostly caused by acute changes in blood pressure, which was not maintained after 4-6 weeks. While cerebral perfusion is doubted to be the primary link between the change in heart rhythm and cognitive deficiency (Dietzel et al., 2018) no suggestion has been made in relation to cerebral oxygenation saturation. This is mostly due to the limited literature on this population both in terms of cognition and cerebral oxygenation.

At the point of development of this study, there was no available information on how the ECV might impact cognitive abilities. However, recently two studies investigated this in a similar design, and one study showed that ECV improved Trail Making Test B scores (reflecting executive functions) in patients with new onset AF (< 48h AF duration) (Arvanitis et al., 2020), while the second study did not find any change in cognition (Genbrugge et al., 2021). Due to the limited information, it is not known if other cognitive abilities are sensitive to the return of the sinus rhythm, and if the change in cognitive performance can be linked to the potential change in cerebral oxygenation saturation.

The goal of this study was to obtain pilot data for a future multicentric study, which investigates if cerebral oxygen saturation using NIRS improves following a successful ECV, and whether this change is associated with improved cognitive abilities in patients with atrial arrhythmia. It is hypothesised that both cerebral oxygenation and cognitive performance improves following the ECV, and that those improvements will correlate. As a pilot study, this data will also be used to investigate the feasibility and help future studies determine the ideal sample size for investigating cognitive change following ECV.

4.3. Methods

4.3.1. Study population

All patients with atrial arrhythmia (AF or atrial flutter) scheduled for an elective electrical cardioversion at the Montreal Heart Institute between March 1st, 2021 and April 1st, 2022 were asked to participate in the study if they fulfilled the inclusion criteria. Among all types of clinical arrhythmias (irregular heart rhythm on the ECG, or a deviation from the sinus rhythm), atrial (or supraventricular) arrhythmia refers to any type of arrythmia in which the irregular activity on the ECG is observed on the P-wave of the ECG. The most prevalent type of arrythmia is AF which is a type of atrial arrhythmia in which the electrical activity of the P-wave interval is chaotic and irregular, followed by an irregular ventricular rhythm. The cause for the irregular P-wave activity in AF is in part caused by multiple re-entry circuits. Atrial flutter is a different type of atrial arrythmia often seen in the same situations as AF and considered to sometime bridge the transition of patients from sinus rhythm to AF. Atrial flutter is characterised by multiple regular atrial depolarizations (multiple p-waves on the ECG) followed by regular but very fast ventricular rhythm. The cause for the multiple p-waves in this instance is thought to be caused in part by the formation of one re-entry circuit over the atria. Both AF and atrial flutter are thought to have a similar etiology, are both managed using ECV, and to date there is no reason to believe that they impact brain functioning in the absence of stroke differently (A. S. Manolis, 2017; Tunick, McElhinney, Mitchell, & Kronzon, 1992; Waldo, 2017). As a result, both types of patients were included in the study. All patients that were deemed eligible for an ECV by a cardiologist were anticoagulated for more then 3 weeks prior to the ECV. Patients were contacted if they were anglophone or francophone, had no visual or hearing impairments (or corrected), and were over the age of 50. Exclusion criteria were past diagnosis of dementia, acute cerebrovascular event, or thromboembolism, unstable psychological or psychiatric condition (change in the severity, symptoms or medication in the past 6 months), neurological or cerebral disease, and a minimental state examination (MMSE) score ≤ 24.

4.3.2. Protocol

The patients that had an elective ECV booked were called and asked if they are interested to take part in the full study. If they refused to participate in the full study, they were asked if they are willing to give their consent to record their cerebral oxygenation during the ECV. All patients gave their written informed consent, and the study was approved by the local ethics board.

The Montreal Heart Institute standard ECV procedure was used, which was administered fasting, and involved a QRS-gated biphasic waveform shock performed using a standard defibrillator. If the sinus rhythm was not restored the shock was repeated up to a maximum of three times with incrementally higher energy. An ECV was considered successful if the sinus rhythm was restored and maintained on an ECG recorded within the following hour. For all patients, the anesthesia medication was propofol, and all patients received 5L/min of oxygen during the procedure via a nasal cannula, which was removed after they regained consciousness. The NIRS monitor was installed using two electrodes over the frontal region and started recording the data before the procedure and was left running for 45 minutes after the patient fully regained consciousness.

The patients that accepted to take part in the full study came to the lab for their first session (T0) one or two days prior to their ECV to record a resting ECG, complete a full neuropsychological examination, record their resting cerebral tissue oxygenation saturation levels (rSO_2), and answer questionnaires. The same experimental session was repeated two to three days after their ECV (T1) and thirty days after the ECV (T2).

4.3.3. Outcomes

Demographic data: Data on age, sex, height, weight, medical history as well as a standard resting 12-lead ECG (interpretated by a medical doctor) was collected immediately after signing the consent form.

Regional cerebral tissue oxygen saturation (rSO_2): A NIRS monitor (O3 Regional Oximeter System; Masimo Corporation, Irvine, CA) was used to collect bilateral frontal lobe continuous rSO_2 (%) data using two sensors placed on the forehead. The use of this marker is already validated (Redford, Paidy, & Kashif, 2014) and the monitor is routinely used in the operating room. The data was collected continuously at 5-second intervals. rSO_2 data at rest (seated) was collected right before the cognitive assessment for 5 minutes, and the last two minutes of the recording were averaged and used. rSO_2 during the ECV was also collected. In this instance the monitor was installed and started recording at least 5 minutes before the administration of the anesthesia and was running for 45 minutes after the patient fully regained consciousness. The patient was in supine position the whole time. A two-minute block was averaged before the administration of the anesthesia, forming the ECV rSO_2 baseline. The last two minutes of the recording were also averaged and formed the post ECV rSO_2.

Cognitive assessments: An interview based neuropsychological assessment was performed by a neuropsychologist or a trained student in psychology. The session started by assessing global cognitive functions using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), followed by Hopkins verbal learning test (HVLT; versions 1, 2 and 4 used for each time point) measuring verbal learning and memory (Benedict, Schretlen, Groninger, & Brandt, 1998). The interview session continued with the digit symbol substitution test (DSST) measuring processing speed and complex attention (Jaeger, 2018), the digit span measuring immediate recall, working memory and attention (Schroeder, Twumasi-Ankrah, Baade, & Marshall, 2012), and ended with the Trail Making Test (TMT) A & B measuring processing speed and switching (Tombaugh, 2004). The present cognitive assessments have been selected due to their relative low practice effects, and adequate test-retest reliability (HVLT = .74; MoCA = .92; DSST = .76; digit span > .80; TMT-A = .78; TMT-B = .89) (Nasreddine et al., 2005; Strauss, Sherman, & Spreen, 2006). The cognitive battery was designed to test the most common neurocognitive abilities with a focus on executive functions, which are known to be affected in this population.

Questionnaires: A pack of questionnaires were administered at the end of the session. This included the Geriatric Depression Scale (Yesavage et al., 1982), the Generalized Anxiety

Disorder Scale (Spitzer, Kroenke, Williams, & Lowe, 2006), and the Atrial Fibrillation Severity Scale, measuring symptoms severity for palpitations, shortness of breath at rest, shortness of breath during physical activity, exercise intolerance, fatigue at rest, light-headedness, and chest pain (Dorian et al., 2002; Maglio et al., 1998).

Feasibility: The feasibility of this study was assessed based on the ability to implement the protocol, the acceptance rate to participate in the study, and the reason for declining to take part in the study. The number of individuals that remained in sinus rhythm at the 1-month follow-up was considered to help determine the ideal sample needed to test the hypothesis. The health profile of the recruited patients will be investigated to see if the sample obtained can be considered representative of the AF population.

4.3.4. Statistical analysis

Statistical analyses were performed using IBM SPSS version 24.0 for Windows (IBM, Inc., Chicago, IL). The normality of distribution of all dependent variables has been inspected visually as well as using the kurtosis and skewness scores, and no score was over +/-1.96. The baseline data is presented as mean and standard deviation (SD) for continuous variables and n and percentage (%) for categorical data. A series of repeated measures analyses of variance (ANOVA) were performed on the rSO_2 data and on all cognitive variables, using the Greenhouse-Geisser correction in case the Mauchly's test of sphericity was violated. Only the participants that had a successful ECV were included in the analysis. Due to the pilot nature of this study, no correction for multiple comparisons has been used. All reported p-values are two-tailed, and the significance level was set to 0.05. To better characterize the change in the dependent variables the means, SD, standard errors (SE), and effect size (Hedges' G) has been reported in addition to the F and p-value. The effect size can be interpreted as small ($0.2 \leq ES < 0.5$), moderate ($0.5 \leq ES < 0.8$), or large ($ES \geq 0.8$) (Cohen, 1988). To further characterise the presence of practice effects on the cognitive tests, the Reliable Change Index has been reported for the variables that showed a significant change. The Reliable Change Index takes into account the test-retest reliability of the test in order to evaluate if the change in an individual score is grater than what is expected by random measurement error alone (Guhn, Forer, &

Zumbo, 2014; Jacobson & Truax, 1991). Like a Z-score, values higher than |+/-1.96| reflect a significant change.

4.4. Results

4.4.1. Sample and feasibility

Out of the 47 consecutive referrals, 22 were eligible and accepted to take part in the short component of the study measuring the rSO_2 during the cardioversion. Reasons for non-eligibility included young age (8), past stroke (2), appointment cancelled because of spontaneous conversion to sinus rhythm (5) or did not speak English or French (1). Out of the 22 that accepted to take part in the NIRS recording, 10 accepted to take part in the full study measuring cognitive function. Please see Figure 4.1 for the sample flowchart. Many patients refused to take part in the full study due to lack of time to come to the hospital outside of the ECV appointment because they lived far or due to work; most of the participants that accepted were retired.

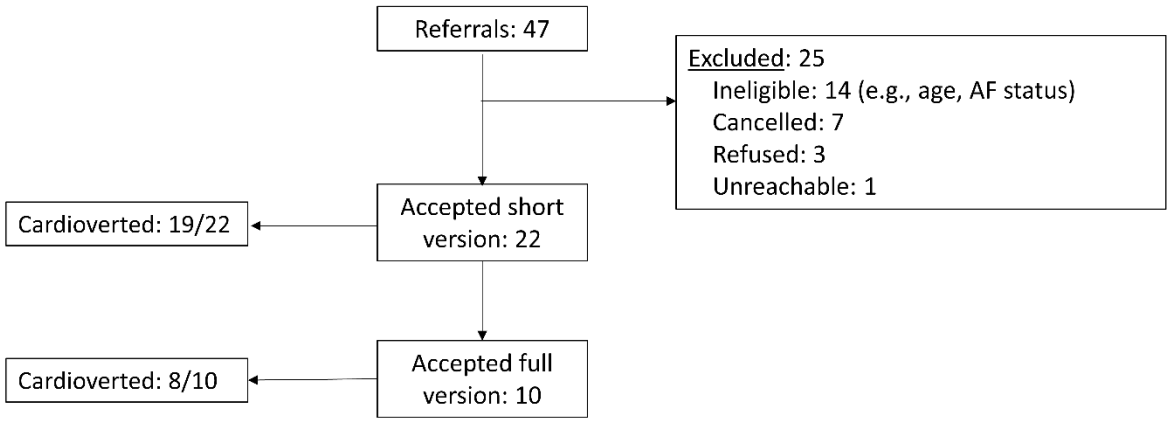

Figure 4. 1. – Participant sample flowchart

All participants referred had persistent atrial fibrillation or flutter. Nineteen of the 22 cardioversions were successful. Among the sub-sample, 8 out of the 10 were successful, and only 4 of them maintained sinus rhythm at the 1-month follow up visit. Table 4.1. shows baseline data on the sample of patients with a successful ECV that took part in the rSO_2 assessment during the ECV, and the sub-sample that accepted to participate in the full study assessing cognitive functions. Overall, the sample of patients is overweight (Body mass index (BMI) = 29.44 kg/m^2), suffers from multiple cardiovascular comorbidities, had suffered from arrhythmia for a very long time (~107 months), and 13/19 patients had undergone past ECV.

Characteristic	Mean (SD) or N (%)	
	ECV NIRS group (n=19)	Cognitive sub-sample (n=8)
Age	64.75 (8.50)	65 (10.01)
Sex, M/F	13/6	8/2
Education, years	15.5 (3.08)	15.5 (3.50)
BMI, kg/m^2	29.44 (4.92)	29.75 (5.27)
HR	76.65 (14.22)	74.75 (8.12)
SBP, mmHg	138.47 (22.45)	145.0 (25.06)
DBP, mmHg	87.35 (13.99)	93.17 (7.88)
Duration since first Dx AF, months	107.28 (38.73)	118.13 (196.25)
Number of past ECV	3.53 (6.83)	5.0 (10.30)

Nb of patients with past ECV	13 (68.42)	5 (62.50)
Cardio disease family history, n (%)	15 (78.95)	8 (100)
Heart failure, n (%)	1 (5.26)	1 (12.50)
Hypertension, n (%)	9 (47.37)	3 (37.50)
Diabetes mellitus, n (%)	4 (21.05)	3 (37.50)
Coronary heart disease, n (%)	0 (0)	0 (0)
Sleep apnea, n (%)	6 (33.33)	4 (50.00)
Thyroid disease, n (%)	2 (10.53)	0 (0)
Past catheter ablation, n (%)	3 (15.79)	1 (12.50)
Current or past smoker, n (%)	11 (57.89)	3 (37.50)
> 10 alcoholic drinks/week, n (%)	4 (21.05)	0 (0)
CHA2DS2-VASc = 0, n (%)	4 (21.05)	1 (12.50)
CHA2DS2-VASc = 1, n (%)	9 (47.37)	4 (50.00)
CHA2DS2-VASc = 2, n (%)	2 (10.53)	1 (12.50)
CHA2DS2-VASc = 3, n (%)	1 (5.26)	0 (0)
CHA2DS2-VASc > 3, n (%)	3 (15.79)	2 (25.00)

Table 4. 1. – Baseline demographic data.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; Dx, Diagnostic; ECV, electrical cardioversion; HR, resting heart rate; n, number; SBP, systolic blood pressure; SD, standard deviation.

4.4.2. NIRS

The rSO_2 has been collected during the ECV as well as at rest before the cognitive assessments for the subsample. No significant change has been found in either of the measures, and the effect sizes showed very small decreases. The mean rSO_2 change recorded during the ECV was from 62.35 % (SD: 5.06) to 62.21% (SD: 5.59) for the left hemisphere, and 63.23% (SD: 3.83) to 62.80 (SD: 5.14) for the right hemisphere. The mean rSO_2 change recorded at rest before the cognitive assessment in the subsample was similar in magnitude and direction. Table 4.2**.** shows the detailed values of the rSO_2 at each timepoint.

	Pre			Post			Pre vs. Post		
	Mean	SD	SE	Mean	SD	SE	Hedge's g	F	P
ECV left rSO_2 (%; N = 19)	62.36	5.06	1.16	62.21	5.59	1.28	-.03	.05	p > .05
ECV right rSO_2 (%; N `= 19)	63.23	3.83	.88	62.79	5.14	1.18	-.08	.56	p > .05
Resting left rSO_2 (%; N=8)	59.93	5.41	1.91	59.42	4.26	1.51	-.09	.10	p > .05
Resting right rSO_2 (%; N=8)	60.01	5.34	1.89	59.38	4.79	1.69	-.11	.26	p > .05

Table 4. 2. – Cerebral tissue oxygen saturation values (rSO_2; %) before and after the ECV procedure, as well as at rest before each cognitive evaluation in the subsample.

Abbreviations: ECV rSO_2, cerebral tissue oxygen saturation during the ECV procedure, measured from immediately before the ECV (pre) to 45 minutes after the ECV (post); Resting left rSO_2, cerebral tissue oxygen saturation measured at rest right before the cognitive assessments in the subsample, at pre (T0), and post (T1).

4.4.3. Cognition

Among all cognitive variables there was a significant improvement from T0 to T1 in the digit symbol substitution test ($F_{(1,7)}$ = 20.90, p = .003, Hedge's G = .578, mean RCI = 4.30), and a reduction in the time to solve the Trail Making Test B ($F_{(1,7)}$ = 6.67, p = .036, Hedge's G = -0.473, mean RCI = -1.1). No other test showed a significant change, and the effect sizes were small. Table 4.3. shows all values for the cognitive variables at each timepoint.

	Pre (T0)			Post (T1)			T0 vs. T1		
	Mean	SD	SE	Mean	SD	SE	Hedge's g	F	P
MoCA, points	25.50	3.81	1.34	26.62	3.24	1.14	0.28	1.06	p > .05
HVLT, points	23.25	7.20	2.54	24.75	6.77	2.39	0.19	.67	p > .05
DSST, points	60.87	17.49	6.18	71.75	18.54	6.55	0.53	20.90	p < .01
Digit Span Total, points	19.62	3.62	1.28	19.87	3.64	1.28	0.06	.26	p > .05
TMT A, sec	34.37	10.95	3.87	34.12	9.86	3.48	-0.02	.01	p > .05
TMT B, sec	96.75	36.42	12.87	78	22.87	8.08	-0.43	6.67	p < .05

Table 4. 3. – Cognitive scores at T0 and T1 in the cognitive subsample that had a successful cardioversion (n = 8).

Abbreviations: DSST, digit symbol substitution test; HVLT, Hopkins verbal learning test-revised, MoCA, Montreal cognitive assessment; SD, standard deviation; SE, standard error; TMT, trail making test.

4.4.4. AF symptoms

The total score of the questionnaire measuring the intensity of all AF related symptoms showed a significant large decrease ($F_{(1,7)}$ = 24.561, p = .002, Hedge's G = -1.36) from T0 to T1 in those with a successful ECV. All participant reported a decrease in AF-related symptoms following the ECV. Among all symptoms, the ones for which patients reported the largest decrease were shortness of breath during physical activity, palpitations, fatigue at rest, exercise intolerance, and shortness of breath at rest (in this order).

When correlating the change in AF symptoms with the change in cognitive performance (DSST and TMT-B) only one significant correlation was noted between the decrease in the total AF symptoms and the improvement in the DSST score (r(8) = -.717, p = .02).

4.4.5. Sample size estimation

The attached cognitive data (means and standard deviation) from table 4.3. can be used to determine the sample size for the future study. For example, targeting a significant change (two-tailed α = .05) in TMT-B at a power of 80%, a minimum sample of 25 patients is recommended by the G*Power v3.1.9.7 software (Faul, Erdfelder, Buchner, & Lang, 2009). Considering that 60% of the individuals reverted to arrhythmia at T2, a sample of at least 63 individuals should be tested. Using the same approach, if a significant change in MoCA is targeted a minimum sample of 205 patients is needed.

4.5. Discussion

The results of the present pilot study show that individuals that have a successful ECV might not show a change in rSO_2. However, they might show a large decrease in AF symptoms, and an improvement in cognitive function (with the largest improvements in the DSST and the TMT-B scores). The effect size for the decrease in rSO_2 is very small, suggestive of almost no meaningful change in the cerebral tissue oxygen saturation value (less than 1%). This is comparable in magnitude with the change in rSO_2 recorded by Genbrugge et al. (2021). While in their case they reported a significant improvement in rSO_2 of about 1%, the authors suggest

that the small rate of change is not meaningful and unlikely to translate in a change in cognitive performance. In the present study, while we do not find a change in rSO_2 we do report an improvement in TMT-B score measuring cognitive switching abilities, and DSST measuring processing speed and complex attention. Those results partially replicate the findings from Arvanitis et al. (2020) who also show an improvement in TMT-B post successful ECV. In their study the patients were suffering from recent-onset AF (<48h), and the present study compliments their results by showing that a similar cognitive improvement can be observed in individuals suffering from AF for a longer duration. This new information suggests that some improvement in executive functions might be affected by other factors beyond AF burden and the AF-induced long term physiological changes.

In the present study, the arrhythmia symptoms show a large significant decrease, and it is possible that part of the cognitive improvement observed following the acute heart rhythm change is related to the symptoms. For example, AF symptoms like palpitations, shortness of breath and fatigue are present at rest and can influence performance on cognitive tests. Fatigue is known to be related to decreased performance in tests assessing attention and processing speed in studies investigating work performance or in studies with patients suffering of chronic fatigue (Fogt, Kalns, & Michael, 2010; Fuentes, Hunter, Strauss, & Hultsch, 2001). In fact, even the simple perception of cardiac symptoms (i.e., elevated heart rate) can impact the performance on cognitive tests under stress (Kindermann & Werner, 2014). This might be particularly evident in tests measuring executive functions, since those are sensitive to attention, require a higher level of concentration, and involve active manipulation of information. Cognitive studies show that executive functions rely on a finite level of cognitive energy, and fatigue or generally depleted cognitive resources can impact the performance on those tests (Persson, Welsh, Jonides, & Reuter-Lorenz, 2007). Moreover, the present results show a significant correlation between the decrease in AF symptoms and the improvement in DSST score, strengthening the link between the two variables. Although impossible to rule out, practice effects can also play a role in studies administering cognitive tests repeatedly. However, the included tests were chosen for their adequate test-retest reliability and the minimal practice effects. The same neurocognitive tests are routinely administered in other

studies investigating cognitive changes in older adults including patients with AF) (Arvanitis et al., 2020; Genbrugge et al., 2021). In addition, the present study showed a cognitive performance change exclusive to those two tests increasing the confidence that the results are not simply related to general cognitive practice effects, but to improvements in certain specific functions.

The very small effect size for the rSO_2 change indicative of no change in the present study could also suggest that the physiological brain changes from sinus rhythm restoration might develop over a long period of time, and therefore cannot be observed acutely. As a result, any improvement might also require the maintenance of sinus rhythm over a longer period before the physiological changes become meaningful enough to translate in cognitive changes. In fact, a meta-analysis of the available research shows that so far it is still unclear if AF treatments can lower the greater risk of dementia in this population (Islam et al., 2019) citing the lack of studies with long-term follow-ups. The authors report that the association between AF and dementia risk is more evident when AF is documented over a longer follow-up period of more than 5 years (Islam et al., 2019). Conversely, it is possible to expect cognitive benefits if the sinus rhythm is restored and maintained for a long period of time, and future ECV studies should try to document this in more detail. Studies that returned and maintained sinus rhythm (through catheter ablation) over a period of 1 to 4.5 years reported cognitive improvements and even a reversal of the AF-related cardiac remodeling (Jin et al., 2019; Saglietto, Ballatore, Xhakupi, De Ferrari, & Anselmino, 2022; Soulat-Dufour et al., 2022). Moreover, we have already shown that higher markers of cardiac remodeling (higher left atrial volume) can better explain the cognitive deficiencies observed between patients with paroxysmal vs permanent AF (Vrinceanu et al., 2022).

Another important mechanism thought to link AF to cognitive disfunction and decline is subclinical cerebral damage (cerebral small vessel diseases including microhemorrhages, subcortical infarcts, silent cerebral infarcts, white matter hyperintensities) (Ding & Qiu, 2018). Those micro-cerebral deteriorations are thought to play a critical role in cognitive aging and are significantly worse in individuals with multiple cardiovascular comorbidities in particular

persistent or permanent AF (Ding & Qiu, 2018; Rivard & Khairy, 2017). Although to date it is still unknown if there is one primary mechanism responsible for the cognitive issues in this population, silent cerebral damage is thought to play a primary role. Research shows that small vessel diseases can even interfere with the cerebral metabolic demands by lowering the cerebral tissue oxygenation and lowering the cerebral blood flow in those areas (Dalby et al., 2019). As such, the silent cerebral damages can impair oxygen saturation and result in cognitive deficiencies. Given that the amount of micro-cerebral damage is increased in individuals with multiple cardiovascular comorbidities and advanced disease severity it is possible that the present sample had increased micro-cerebral damage that interfered with a potential change in rSO_2 following the ECV. Moreover, this micro-cerebral damage accumulates over time, further supporting the importance of early termination of the arrhythmia and maintaining sinus rhythm after restoration.

Although the initial success rate of the ECV procedure is quite high (68% – 98%), the long-term maintenance of sinus rhythm is not reliable (Ecker et al., 2018). In the present study, many of the patients reverted to AF at the 1-month follow-up (4 out of 8). The relapse of arrhythmia following the ECV has been shown to be predicted by higher weight and advanced age, as well as certain comorbidities (hypertension, diabetes mellitus, sleep apnea, chronic obstructive pulmonary disease, renal impairment, hyperthyroidism, and coexisting cardiac diseases) as well as a series of prescription drugs (Ecker et al., 2018). Many of those factors are also known to be associated with impaired cognition (Abete et al., 2014), making hard to identify to what extent the cognition is impacted by mechanism directly linked to arrhythmia vs. the other risk factors. A relapse of AF following ECV has been also linked to higher mortality (Elesber et al., 2006). This could reflect the higher disease severity (advanced cardiac remodeling), or a higher disease complexity (impact of other comorbidities and risk factors) in a subgroup of individuals in which the AF cannot be terminated. As a result, to better understand the population in which this procedure has cognitive benefits, more research is needed while recruiting a sample with a wide range of AF burden. So far, it has been suggested that ECV administered for recent onset AF might be more efficient (Capucci & Compagnucci, 2020), suggesting that there might be a sensitive period potentially before physiological changes caused by AF become significant or

permanent. At the same time, it is also possible that returning and maintaining of sinus rhythm might be easier to achieve in those with fewer risk factors and fewer comorbidities, more often fitting the profile of patients with recent onset AF (as opposed to persistent AF).

One confounding factor related to repeated assessments using cognitive tests is the potential for practice effects. Unfortunately, there is no minimal duration that would prevent practice effects on cognitive tests. The Compendium of neuropsychological tests (Strauss, Sherman, & Spreen, 2006) has highlighted that practice effects can be observed after 1-week or even 12-24 months. This limitation has been addressed in the present study by initially selecting cognitive assessments with high test-retest reliability coefficients (which to some extent implies selection of cognitive assessments with lower practice-effects). Secondly, the use of the reliable change index has been included in the results. This index takes into account each score's test-retest reliability and compares if everyone's score change is greater than what is expected by chance. Finally, the Compendium of neuropsychological tests (Strauss, Sherman, & Spreen, 2006) lists that the expected 1-week practice effects in older adults (aged 55 to 65) for the TMT-B test is in average 9.8s. The results of this pilot study show an average change of 18.25s suggesting a higher change than what can be expected from practice effects. In the case of the Digit Symbol Substitution Test no similar data is available, however, in this case the reliable change index was large and significant.

4.5. Feasibility and protocol recommendations

Two main challenges were identified by conducting this pilot study. Firstly, many patients refused to participate in the full study because they did not have time to come to the hospital outside of the scheduled ECV appointment. Secondly, the sample was suffering from AF for a long time, and it was common to have done multiple previous ECV. This might not be representative of all AF patients and as a result the study might not be able to test if cognitive functions and rSO_2 change in new-onset AF. In order to address this, the study should try to recruit a sample stratified based on the duration of time since the AF diagnostic. Like this, there should be a balanced number of individuals that suffer from new-onset AF to those that suffer from AF for many years. Finally, the future protocol should potentially include the change in

arrhythmia symptoms as a potential mediator for the change in cognition. Other than this, no other protocol-related recommendations were identified.

4.6. Conclusions

The present study is feasible and can proceed by changing the recruitment strategy. A stratified sample should be recruited aiming for a proportional number of patients with new-onset AF and long-term AF. The present results suggest that ECV could result in acute cognitive improvements that could be related to the arrhythmia symptoms. To investigate the long-term impact of sinus rhythm maintenance on cognitive abilities and brain markers long term follow-ups should be prioritized in future protocols.

4.7. Acknowledgments

The present study has been run during the COVID-19 pandemic, and all procedures and patient interactions followed the local public health recommendations.

4.8. Funding

T. Vrinceanu was supported by a PhD salary award from the Fonds de recherche du Québec – Santé. L. Bherer was supported by the Research Chair Mirella et Lino Saputo in cardiovascular health and prevention of cognitive disorders from the University of Montreal at the Montreal Heart Institute.

4.9. Conflict of interests

The Masimo Corporation (Irvine, CA) sponsored this project by providing the NIRS device and consumables free of charge. The Masimo Corporation were not involved in any way in the development of the protocol, data collection or data analysis.

4.10. Author contributions

T. Vrinceanu contributed with the development of the original hypothesis, study design, ethical application, data collection, data entry, data analysis, and writing of the article. Co-authors P. Guerra and L. Bherer supervised the development and running of the study, S. Clavet was involved in data collection, and study development; A. Denault supervised the imaging component, and was involved in study development; and M. Juneau had clinical oversight over the patients at the EPIC Center.

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Chapter 5 – General Discussion

5.1. Discussion

The present thesis brings novel support to the link between cardiovascular health and cognition by focusing on cardiac electrophysiology (please see Figure 5.1 for the proposed model). The first study (Chapter 2) shows for the first time that a cardiac autonomic control marker measuring cardiac ventricular repolarization (QTcD) is associated with global cognitive performance (MoCA score) in healthy older adults (Vrinceanu et al., 2020). This relationship is more evident in individuals with higher QTcD scores suggesting that the marker is more informative in individuals with higher deviations in electrophysiological activity. Although the direction of this association is still unknown, this finding suggests that even subtle changes in heart rhythm could be associated with changes in cognition. Studying individuals with more severe heart rhythm deteriorations (clinical arrythmias) might help better understand how cardiac electrophysiology and cognition are linked. This will also help develop preventive measures to reduce the impact that abnormal cardiac electrophysiology might have on cognition. In the second article (Chapter 3) we show that individuals with atrial fibrillation (AF; the most prevalent type of clinical arrythmia) that have a higher disease severity reflecting higher temporal exposure to clinical arrythmia show worse cognitive performance on the MoCA score (global cognitive abilities) (Vrinceanu, Khairy, et al., 2022). In addition, the study shows that the LAV (left atrial volume), a cardiac marker closely linked to AF exposure might be a better predictor of the degree of cognitive impairment observed in this population. Those results bring extensive evidence supporting a temporal link between AF exposure and cognitive decline. As a result, the termination of AF and maintenance of the sinus rhythm is hypothesized to prevent further cognitive decline in this population. It is also hypothesized that reverting to sinus rhythm could also revert some cognitive decline directly associated with the presence of clinical arrythmia. For example, some mechanisms thought to be responsible for the AF-related cognitive decline like cerebral oxygenation are thought to fluctuate and be dependent on the heart rhythm. That is poorer values are observed when individuals are in AF, and better values are observed when they are in sinus rhythm (Gardarsdottir et al., 2020; Petersen, Kastrup,

Videbaek, & Boysen, 1989; Wutzler et al., 2014). As a result, some cognitive improvements can be expected acutely following the termination of clinical arrythmia because of those improved cerebral markers. The final article (Chapter 4) of this thesis presents the pilot results of a study measuring the cognitive and cerebral oxygenation changes before and after a medical procedure that terminates clinical arrythmia. The results show that such a study is feasible but brings unconclusive evidence in support of the association between cerebral oxygenation and heart rhythm. Despite this, the cognitive performance might show an improvement after sinus rhythm restoration and this improvement could be related to the decrease in AF-related symptoms in addition to any physiological change.

In the absence of clinical arrythmia, the heart rhythm is mostly modulated by autonomic activity. One of the proposed ways in which autonomic activity interacts with cognition is hypothesized by the neurovisceral integration model (Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer & Lane, 2009). This model which can be used to interpret the findings from the first article of this thesis supports a set of neural structures and networks located in the prefrontal cortex which are simultaneously involved in cognition, emotion, and autonomic regulation. Although those three functions involve numerous areas of the central nervous system, neural networks involving the medial pre-frontal cortex and orbitofrontal cortex are identified as a hub integrating all the available information to create a flexible “output” in response to the environmental stimuli (Thayer et al., 2009). In terms of cognition, optimal functioning of those regions is heavily associated with inhibitory functions and are closely linked to executive function performance (Friedman & Robbins, 2022; Miller, 2000). Similarly, inhibitory circuits involved in modulating parasympathetic activity were identified in the same regions (Thayer et al., 2009; Winkelmann et al., 2017). Those associations are supported by evidence from cross sectional studies as well as intervention studies involving pharmacological manipulations and brain stimulation (Schmausser, Hoffmann, Raab, & Laborde, 2022; Thayer et al., 2009). For example, a study which inactivated either the left or the right brain hemisphere using intracarotid sodium amobarbital showed an increase in HR and a decrease in HRV corresponding to a decrease in parasympathetic activity (Ahern et al., 2001). Those results were also corroborated in studies that used noninvasive brain stimulation (transcranial magnetic

stimulation or transcranial direct current stimulation) of the prefrontal cortex to successfully reduce HR and increase HRV (Makovac, Thayer, & Ottaviani, 2017; Schmausser et al., 2022). Similar associations between the change in activity and structure of the frontal and the cingulate cortices and autonomic activity were found in patients suffering from stroke or neurodegenerative disorders (Guo et al., 2016; Naver, Blomstrand, & Wallin, 1996). Those findings support the involvement of the cerebral cortex, in particular the prefrontal, in inhibiting the cardiac sympathetic function controlled primarily by the brainstem and the hypothalamus. This brings strong support for the ability of the brain to modulate heart rhythm. This model could also help better understand how early deterioration in brain heath, notably in the frontal regions, could result in deteriorations in cardiac rhythm.

However, markers of cardiac autonomic control like QTcD could also capture subtle cardiovascular deteriorations that can impact both autonomic regulation and cognitive functioning simultaneously. For example, patients suffering from cardiovascular conditions that can be classified on a continuum from subclinical to clinical (i.e., hypertension, cerebral small vessel disease) are also known to show cognitive deficits and autonomic deteriorations (Malik & Batchvarov, 2000; Zanon Zotin, Sveikata, Viswanathan, & Yilmaz, 2021; Zhang et al., 2021). As such, the association between autonomic cardiac control and cognition could also be explained by a third variable, namely, cardiovascular health. Indeed, the presence of different heart diseases (including arrythmias) has been associated with autonomic and cognitive deficits, as well as long term deteriorations in those variables (Abete et al., 2014; Bigger et al., 1992; Eriksson, Bennet, Gatz, Dickman, & Pedersen, 2010; Shen & Zipes, 2014; Stampfer, 2006; Stefanidis, Askew, Greaves, & Summers, 2018; Verrier & Tan, 2009). Since the available literature supports both the role of the brain in impacting cognitive functioning and cardiac activity, as well as the role of the heart in impacting brain health, cognitive abilities, and autonomic regulation, it is likely that there is, in fact, a continuous bidirectional impact between the heart and the brain health with both organs impacting each other.

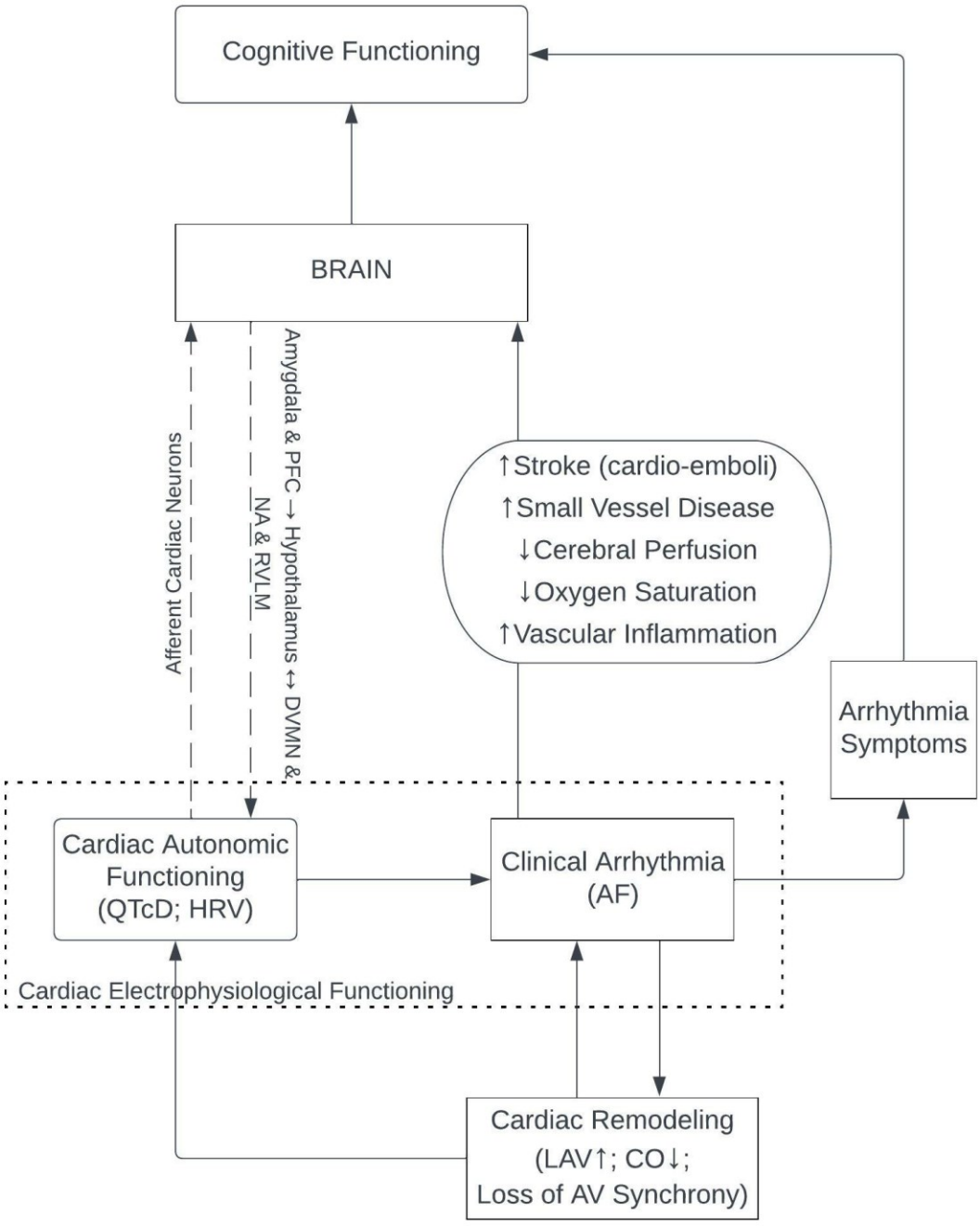

Figure 5. 1. – Theoretical model representing the bidirectional connections between cardiac electrophysiology and cognition

Abbreviations: AF: Atrial fibrillation; CO: Cardiac output; DVMN: Dorsal vagal motor nucleus; HRV: Heart rate variability; LAV: Left atrial volume; NA: Nucleus ambiguous; RVLM: Rostral

ventrolateral medulla; QTcD: QT dispersion; Solid arrows show proposed causal link; Dashed arrows show neurological pathway.

The neurovisceral integration model can also be used in explaining the link between diseases of heart rhythm (like AF) and cognition. For example, autonomic activity is closely linked to AF initiation and maintenance, and therefore the neurovisceral integration model can also be involved in how clinical arrhythmias are linked to cognitive performance. Some of the brain deteriorations associated with AF include the prefrontal cortex in addition to the brainstem (Yuan et al., 2019) and this could partially explain the cognitive deficits profile observed in chapter 3. In addition, this cerebral damage could also play a role in how AF might further cause a deterioration in cardiac rhythm (through autonomic dysregulation) resulting in a progressive deterioration of the arrythmia. This vicious cycle is also supported by the extensive evidence for cardiac remodeling associated with sustained AF exposure, which is known to put people at risk of further AF recurrence and maintenance. In support of this, we have shown that in fact a marker of cardiac remodeling (LAV), was even better at predicting the cognitive deficits observed in an AF population (Vrinceanu, Khairy, et al., 2022). Therefore, the deteriorations in heart rhythm and cognitive functions can be the result of a deteriorated heart-brain axis. This damage can be induced by the heart, by the brain, or by any other factor that impacts the normal functioning and communication of this axis. As such, the invers association between AF exposure and cognitive performance recorded in the second article (Chapter 3) can be the result of a bidirectional impact of the heart-brain axis. Specifically, the cognitive deficit is stronger after a longer exposure to AF, potentially because the AF progressively deteriorates the heart-brain axis. This makes it more likely for the patient to remain in AF (gradually increasing in severity) which can also be associated with a slow long-term decline in cognitive abilities. Therefore, terminating the AF and maintaining sinus rhythm as early as possible could be crucial in preventing the cognitive deficiencies in this population.

Moreover, it is possible that some of the cognitive deficits observed in individuals with clinical conditions might be caused by secondary factors related to their condition. For example,

patients suffering from AF are known to have lower quality of life due to their symptoms (Freeman et al., 2015). As a result, AF related symptoms might also impact cognitive performance acutely when people are in arrythmia. AF symptoms like palpitations, shortness of breath and fatigue are present at rest and can influence performance on cognitive tests. Fatigue is known to be related to decreased performance in tests assessing attention and processing speed in studies investigating work performance or in studies with patients suffering of chronic fatigue (Fogt, Kalns, & Michael, 2010; Fuentes, Hunter, Strauss, & Hultsch, 2001). In fact, even the simple perception of cardiac symptoms (i.e., elevated heart rate) can impact the performance on cognitive tests under stress (Kindermann & Werner, 2014). This might be particularly evident in tests measuring executive functions, since those are sensitive to attention, require a higher level of concentration, and involve active manipulation of information. The decrease in AF-symptoms accompanied by improved cognitive performance observed in the pilot study partially support this possibility. Moreover, this association is strengthened by the significant correlation between the improved digit symbol substitution score and the decrease in AF-related symptoms (Chapter 4).

The present thesis also sought to identify if certain cognitive functions might be more sensitive to variations in heart rhythm. The results suggest that the executive functions might be more likely to be associated with cardiac rhythm both in healthy and in individuals with AF. While all three studies identified executive functions to be sensitive, switching abilities (measured with TMT–B) showed to be particularly associated with changes in heart rhythm as well as disease severity. For example, the second study (Vrinceanu, Khairy, et al., 2022) identified that individuals with higher AF-burden showed lower scores on the MoCA visuo-spatial executive subscore, which is comprised in part by a mini TMT-B. In addition, the pilot study also showed that the individuals that revert to sinus rhythm could also show an improvement in TMT-B. Those results corroborate other studies which identify TMT-B to be a sensitive test in this population. Relative to a control group, individuals with AF have been shown to have lower TMT-B scores cross-sectionally, as well as a higher decrease in this score longitudinally (Nishtala et al., 2018). Moreover, the performance on this score has been shown to improve following

successful rhythm control strategies for AF (Arvanitis et al., 2020; Efimova, Efimova, Chernov, Popov, & Lishmanov, 2012).

The sensitivity of executive functions to variations in heart rhythm could be linked to deteriorations in frontal cerebral areas that are often associated with poorer cardiac activity. Although the well-functioning of all executive functions (i.e., working memory, inhibition, switching) is associated with a different pattern of cerebral activation in areas including the frontal lobe, parietal lobe and motor cortex, all functions seem to significantly rely on a common area which is the pre-frontal cortex (Turner & Spreng, 2012). For example, critical regions involved in inhibition include the ventral prefrontal cortex, presupplementary motor areas, and posterior parietal cortices (Turner & Spreng, 2012). Among the most important areas involved in switching there is the anterior cingulate cortex and dorsolateral prefrontal cortex (Hyafil, Summerfield, & Koechlin, 2009). Finally, working memory is heavily dependent on the lateral prefrontal area (Turner & Spreng, 2012). It is not yet clear why switching was found in this thesis to be more sensitive to deterioration in heart rhythm. However, one possibility is that common cerebral areas involved in both cognitive switching and autonomic control could be affected. This idea is partially supported by Forte, Favieri, and Casagrande (2019) who suggest that different measures reflecting different components of the autonomic system might correlated with different cognitive functions depending on the common cerebral areas involved. This is indeed plausible since the orbitofrontal cortex and the medial prefrontal cortex have been linked to autonomic control (Thayer & Lane, 2009). Although the sub-regions mentioned above do not perfectly overlap, aging is known to be associated with a compensatory change in cerebral activity (Turner & Spreng, 2012) which can play a role in how different cerebral area involved in executive functions and autonomic control might be associated.

More generally, the pattern of cognitive deficits evidenced in this thesis corresponds with frontal cerebral deteriorations that are often observed in conditions that are vascular in origin. Indeed, frontal cerebrovascular damage is often observed in individuals with cardiovascular diseases, like AF. Specifically, small vessel diseases thought to be in part responsible for the

age-related cognitive decline, are significantly more prominent in individuals with arrythmia in particular in the frontal lobe (Ding & Qiu, 2018). This could be one of the main causes for the link between heart rhythm and executive functions deficits, supporting a vascular origin for the cognitive change observed in this population. Small vascular brain deteriorations start much earlier than the first cognitive symptoms and are often too advanced when they are first detected. Therefore, detecting individuals at risk by either using cardiac rhythm markers or promising cognitive tests like the TMT-B could help with the early implementation of prevention strategies for further cognitive decline.

Finally, executive functions are also known to be more complex abilities, relying on many other functions (like attention, reaction time, processing speed, etc.), and any slight deterioration in any of those functions can translate in more obvious deterioration in executive functions. In fact, executive functions decline in aging is known to be able to predict further global cognitive decline and even memory declines (Carlson, Xue, Zhou, & Fried, 2009; Kirova, Bays, & Lagalwar, 2015). As such poorer cognitive switching performance might be the first sign of cognitive change and might predict future cognitive decline in people with heart rhythm deteriorations. Therefore, if future research can confirm the usefulness of TMT-B in individuals with heart rhythm conditions it would help identify people at risk of further cognitive decline. This is particularly important in the context of AF because the condition is not always clinically detected early on due to its episodic nature. Having the ability to identify people at risk of cognitive decline would allow to implement more severe prevention strategies earlier on.

5.2. Cognitive decline prevention

In the context of AF, the cognitive decline has been shown to be limited by administering a proper anticoagulant treatment and potentially by restoring and maintaining sinus rhythm (Diener, Hart, Koudstaal, Lane, & Lip, 2019; Friberg & Rosenqvist, 2018; Rivard et al., 2019). Despite this, normal aging and cardiovascular comorbidities in general are still associated with some degree of cognitive decline (Abete et al., 2014; Livingston et al., 2020). However, research on healthy older adults has shown that some lifestyle preventive strategies are successful in delaying cognitive decline and could even potentially improve cognitive abilities (Bherer &

Pothier, 2021; Livingston et al., 2020; Mowszowski, Batchelor, & Naismith, 2010; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). Similar efforts are currently being made to see if the same effect is observed in individuals with cardiovascular diseases and cardiovascular risk factors. Although still debated, some strategies known to have a beneficial effect on preventing dementia include maintaining a healthy diet, treating hearing loss, limiting pollution exposure, not smoking, avoiding excessive alcohol consumption, regular exercise, social interactions, and cognitive stimulation (Livingston et al., 2020; Plassman et al., 2010). Among all of them physical exercise and cognitive training are of particular interest since they can be implemented at any point in life, they can be individualized in a variety of ways, and have shown promising results even when started later in life (Bherer & Pothier, 2021; Mowszowski et al., 2010). Although not as studies, emerging results have identified only the benefit of exercise in maintaining cognitive abilities in individuals with AF (Lim et al., 2021). In a retroactive cohort study using a Korean national database, individuals that start and maintain a regular exercising routine after their AF diagnosis were less likely to develop dementia during a 6-year period (Lim et al., 2021).

The impact of lifestyle on cognition in older adults and patients suffering from cardiovascular diseases is becoming increasingly popular and supported by recent lifestyle change clinical trials. For instance, additional work done during the PhD (Appendix 2 and Appendix 3) went in more detail and investigated mechanisms through which both exercise and cognitive training can improve both brain markers and cognitive abilities in healthy older adults (Intzandt et al., 2021; Vrinceanu, Blanchette, et al., 2022). For example, a 3-month intervention study administering either cardiovascular training, motor abilities training or cognitive training to healthy inactive older adults was able to show improvements in cognitive dual tasking (Appendix 2) (Vrinceanu, Blanchette, et al., 2022). The cognitive dual task used in the study allowed to look at specific cognitive mechanisms that help improve the performance following the three interventions. The study showed that each group improved the performance on the task by improving specific markers. In fact, this study was the first to show within the same design that different types of physical and cognitive trainings can improve cognitive abilities by improving different aspects of the cognitive task. Specifically, the cognitive training group improved overall the most, with benefits in reaction time and consistency in response times

(intra-individual variability). The motor training group improved the most the ability to perform two simultaneous tasks (dual-task cost). This improvement observed in the motor abilities group is thought to be in part related to the common cognitive demand used both in the dual task and the physical exercises trained. For example, some physical tasks trained in the motor abilities group involved a certain degree of cognitive load, sustained attention, and coordination while doing two exercises simultaneously (e.g., navigate an obstacle course while throwing balls at a target, or maintaining balance on one leg while passing a ball to a partner). On the other hand, cardiovascular training is thought to improve cognitive performance in a more general way by improving global brain markers (Netz, 2019). In line with this hypothesis, a review article investigated if exercise and cognitive training have different beneficial impacts on brain MRI markers in healthy older adults (Appendix 3) (Intzandt et al., 2021). In this systematic review including 38 intervention studies we were able to identify that cognitive training and exercise training might have differential impacts on brain MRI markers (Intzandt et al., 2021). Specifically, it looks like cognitive training might be more likely to improve white matter microstructures thought to reflect functional connectivity, while exercise training was more likely to improve macrostructures likely related to angiogenesis, synaptogenesis, and neurogenesis. Moreover, there seems to be enough evidence supporting that both types of trainings can improve functional changes as measured with the blood-oxygen-level-dependent imaging MRI. Finally, different exercise types might also show different brain changes with aerobic training being more likely to be associated with grey matter volume improvements while resistance training was associated more often with white matter volume improvements. Based on those two publications it appears that a combination with different types of exercise training (involving aerobic, resistance, and motor abilities) as well as cognitive training would be ideal to maximize the cognitive and cerebral benefits. However, it is not yet known if the same mechanism would work in a population with heart rhythm deteriorations. If future research would be able to confirm this, the same type of interventions could be used to prevent further cognitive decline or potentially even improve cognitive performance in this population. The core work included in this thesis also identifies markers (i.e., QTcD, LAV, and AF burden) that are associated with lower cognitive abilities, as well as a cognitive test that could be more

sensitive to heart rhythm deteriorations (TMT-B). Although future work is needed, those markers have the potential of identifying people at risk of future cognitive decline. If this is the case, those people could benefit from a more aggressive administration of preventive strategies (like exercise and cognitive training) to slow down the cognitive decline. However, this would need to be confirmed through rigorous random controlled trials before any recommendation can be made.

5.3. Strengths and limitations of the thesis

The studies included in this thesis present novel evidence supporting the link between cardiac rhythm and cognition. The first article shows for the first time a link between an ECG marker of cardiac ventricular repolarization reflecting cardiac autonomic control (QTcD) and cognition in healthy older adults. The sample used did not have any clinical cardiovascular conditions and was sedentary (was homogenous in terms of physical activity and cardiorespiratory fitness) which helped limit the potential impact of those pertinent covariates on the results. This potentially helped isolate the link between QTcD and cognition and could be part of the reason why other studies did not report a similar association in healthy older adults. The second article brings evidence in support of the link between longer exposure to AF and cognitive deficits (in particular for executive functions). While this result is not the first in the field, it corroborates a novel view on the current understanding on how rhythm diseases might impact cognition. Moreover, the study shows for the first time that the link between AF exposure and cognition might be better explained through the LAV. LAV is known to be impacted by AF and therefore if measured longitudinally in AF patients, it could be used to detect the cumulative effect that AF has on the heart, and potentially identify individuals that are at higher risk of developing cognitive decline as a result of the heart rhythm disease. Finally, the pilot study has great potential because it proposes an investigation of the link between heart rhythm and cognition in the same individuals changing states between arrythmia and sinus rhythm. This allows to partially remove the interaction of other variables (cardiac risk factors, demographic variables), and isolate the heart rhythm change to the potential change in cognitive performance and regional cerebral oxygenation saturation. At the time of development of this pilot study there

was no available data for this type of investigation, and the data collected shows that the study is feasible and led to promising results. Moreover, the inclusion of an extensive neuropsychological battery helps collect and identify changes in specific cognitive functions that might be more sensitive to the change in heart rhythm. Finally, this study is among the few ones to discuss the potential impact that AF related symptoms might have on the acute cognitive performance of those patients.

The studies included in this thesis have of course their limitations as well. Despite the obvious limited sample sizes, the data presented is mostly cross-sectional and is only based on associations. As a result, the interpretation should be cautious because causality cannot be assumed. The first study uses an ECG variable that has been challenged from a clinical point of view. However, it must be noted that unusually high values are still thought to reflect autonomic and cardiac abnormalities (Malik et al., 2000; Malik & Batchvarov, 2000; Rautaharju et al., 2009). The study also used a homogenous healthy sample comprised of older adults, and therefore it is uncertain if the same results can be replicated in other populations. The second article found that high LAV is an important cardiac marker predicting cognitive performance, but it is hard to know what exactly the causes for the increased LAV in this sample are. The LAV can be increased by multiple cardiac conditions including AF, while some individuals might be predisposed to have higher LAV values putting them at risk of developing cardiac issues. The study also shows that individuals that spend more time in AF have lower cognitive performance. However, the time spent in AF is measured using the AF subtype (paroxysmal vs. non-paroxysmal), which is not the most accurate way. While our findings might suggest that the biggest gap in cognitive deficits are better detected when patients move from an early intermittent form to a more sustained form, it would be important to accurately measure this with ambulatory devices. Finally, the pilot study is comprised of a sample which has overall a more severe form of AF (i.e., had multiple past cardioversions, and had the first AF diagnosis, in average, many years prior to the study inclusion). While this data might represent the reality of the clinical population who is assigned to elective cardioversions, a more heterogeneous population should be recruited to better understand how the termination of arrythmia might impact cognitive performance and cerebral regional tissue oxygenation.

5.4. Future recommendations

The present thesis also opens multiple avenues for future research. Firstly, the pilot study results are encouraging and should be carried out as it would help clarify how sinus rhythm restoration can impact cognitive performance in AF patients. Based on those results the treatment and management of AF might be changed. For example, to better clarify this association future studies should better investigate the timing for the termination of AF. It is possible that early termination of AF might be more efficient in long term maintenance of sinus rhythm. To achieve this, a more aggressive detection strategy with ambulatory monitors might be useful. Secondly, different markers and tests stood out as sensitive in the association between heart rhythm and cognition. Specifically, QTcD, LAV, and AF burden were all associated with cognitive performance. Future research should investigate in longitudinal studies how the change on those markers is associated with the change in cognition in relation to cardiac electrophysiology. Moreover, the TMT-B was particularly sensitive to changes in heart rhythm in patients with AF. However, future studies should investigate in more detail if this cognitive test is also able to detect patients that are at higher risk of further cognitive decline in this population. Similarly, it would be important to see if specific values (or a deterioration in values) on any of those cardiac variables are able to identify people at risk of future cognitive decline or future deterioration in disease severity. Experimental designs should also try to replicate those associations to better establish a degree of causality between the variables of interest. Future studies should also investigate if cognitive prevention strategies including exercise and cognitive training are able to slow down or improve cognitive performance in individuals with deteriorated heart rhythm (including healthy and in individuals with clinical arrythmias). While there is evidence for this in healthy individuals, not many studies investigate this in patients with diseases of heart rhythm. Those training programs could also positively interact with current AF management strategies in facilitating the maintenance of the sinus rhythm, but future studies are needed to confirm this.

5.5. Conclusions

The present thesis presented a series of studies that support the link between cardiac rhythm and cognitive performance. In healthy older individuals it has been shown that a marker of cardiac repolarization (QTcD) reflecting cardiac autonomic control was associated with cognitive performance (global and executive functions). The results were more evident in individuals with elevated QTcD values suggesting that higher impairments in cardiac rhythm might have stronger association with cognitive performance. To investigate this further, patients with diseases of heart rhythm (clinical arrythmia) were studied. The second study showed that among patients with AF (the most prevalent type of clinical arrythmia) higher disease burden (as measured by the subtype of AF) was associated with lower cognitive performance (global and executive functions). The study also found that a cardiac health marker (LAV) was able to moderate this association between AF subtype and cognitive performance. This shows that the more severe the condition is the higher the cognitive deficit observed. To test if termination of arrythmia is associated with cognitive improvements and cerebral regional tissue oxygen saturation a pilot study has been conducted. The results show that such a study is feasible by adjusting the recruitment strategy and including a balanced sample of patients that suffer from both new onset AF as well as more severe forms. The results were inconclusive in relation to the cerebral oxygenation, but changes in cognitive performance are expected and could be in part related to the decrease in AF-related symptoms. Overall, the results presented in this thesis are discussed in support of a bidirectional interaction of the heart-brain axis.

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Appendix 1 – Research letter

Pattern of Atrial Fibrillation and Cognitive Function in Young Patients with Atrial Fibrillation and Low $CHADS_2$ Score: Insights from the BRAIN-AF Trial

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Journal: Circulation Arrhythmia and Electrophysiology

Publication date: February 2022

Atrial fibrillation (AF) has been associated with cognitive impairment and dementia even in the absence of stroke, and independently from shared comorbidities.(Diener, Hart, Koudstaal, Lane, & Lip, 2019) Patients with persistent AF seem to have lower global cognitive abilities than individuals with paroxysmal AF.(Chen et al., 2016; Gaita et al., 2013) Whether this association is explained by AF burden or shared cofactors is uncertain. Left atrial (LA) enlargement, which is commonly associated with AF, has also been linked with an increased risk of stroke and cognitive impairment in patients with or without AF.(Karadag, Ozyigit, Ozben, Kayaoglu, & Altuntas, 2013) Here, we sought to investigate the association between AF subtype, i.e. paroxysmal AF vs. non-paroxysmal (persistent or permanent) AF, LA volume (LAV), and cognition in low stroke-risk AF patients.

We conducted this analysis in patients participating in the internal pilot phase of the BRAIN-AF trial (Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation; ClinicalTrials.gov #NCT02387229).(Rivard et al., 2019) In brief, this trial assesses whether rivaroxaban (15 mg daily) reduces the composite outcome of stroke/transient ischemic attack (TIA) or neurocognitive decline in patients with AF at low risk for stroke, when compared to placebo. We used the MoCA score to assess various cognitive domains (visuospatial-executive, naming, attention, language, abstraction, memory and orientation). Depression status was assessed using the Beck Depression Inventory-II (BDI-II). All questionnaires were performed prior to randomization. The study was approved by the local research ethics board and all participants gave their written informed consent.

Of 503 patients enrolled in the internal pilot phase, 195 had complete echocardiographic data. Of these, 135 had paroxysmal AF (69.2%). Mean age was 53 years, 42 (21.5%) were women, 185 (94.9%) Caucasian, 35 (17.9%) suffered from sleep apnea, 9 (4.6%) from vascular disease and 37 (19%) from dyslipidemia. Forty-four (22.6%) consumed ≥10 alcoholic drinks/week and 120 (61.5%) did not meet physical activity recommendations (150 minutes of physical activity/week). Per inclusion/exclusion criteria, no individual suffered from history of stroke/TIA, heart failure, diabetes, hypertension, or valvular AF. The CHA_2DS_2-VASc score was 0 in 148 (75.9%), 1 in 45 (23.1%), and 2 (1.0%) in 2 patients.

A hierarchical multiple regression analysis tested whether AF-related characteristics (AF subtype, LAV, LA anterior-posterior diameter, left ventricular ejection fraction) predicted the MoCA score. Only AF-related characteristics significant in univariable analyses were included in the model (AF subtypes and LAV fulfilled this condition). In the first step of multiple regression all covariates were included. Sex and BMI were included because they differed significantly between AF groups, while age, education and depressive symptoms were included because of substantive knowledge of their association with cognitive decline. In the second step, we introduced AF subtypes and LAV. A first-order interaction variable (AF group*LAV) was introduced in the third step. If the interaction term accounted for significantly more variance, a moderation analysis was run using the PROCESS add-on v3.3 for SPSS.

Compared to non-paroxysmal AF, paroxysmal AF patients had a significantly lower LAV (32.8 vs. 45.5 mL, $p<0.001$), were mostly male (91.7% vs. 72.6%, $p=0.003$), and had a lower BMI (28.6 vs. 30.6 kg/m^2, $p=0.012$). After correction for age, sex, BMI, years of education, and depressive symptoms, non-paroxysmal AF was associated with a lower global MoCA score ($p=0.03$) and visuospatial-executive subscore ($p=0.02$). Figure A1. panel A illustrates group differences in the MoCA score and its subscores. After including LAV as a moderator in the model, AF group was no longer significant, leaving the interaction term (LAV*AF group) as the only significant predictor of MoCA score. A larger LAV significantly moderated the global MoCA difference observed between paroxysmal and non-paroxysmal AF (Figure A1. panel B). Specifically, having LAV one standard deviation higher than average (or 56.2 mL) predicted a lower global MoCA score by 1.29 points, ($p<0.01$) in the non-paroxysmal group than those with paroxysmal AF. In sensitivity analyses that excluded the 15 (7.7%) patients who received oral anticoagulation prior to randomization, results remained unchanged.

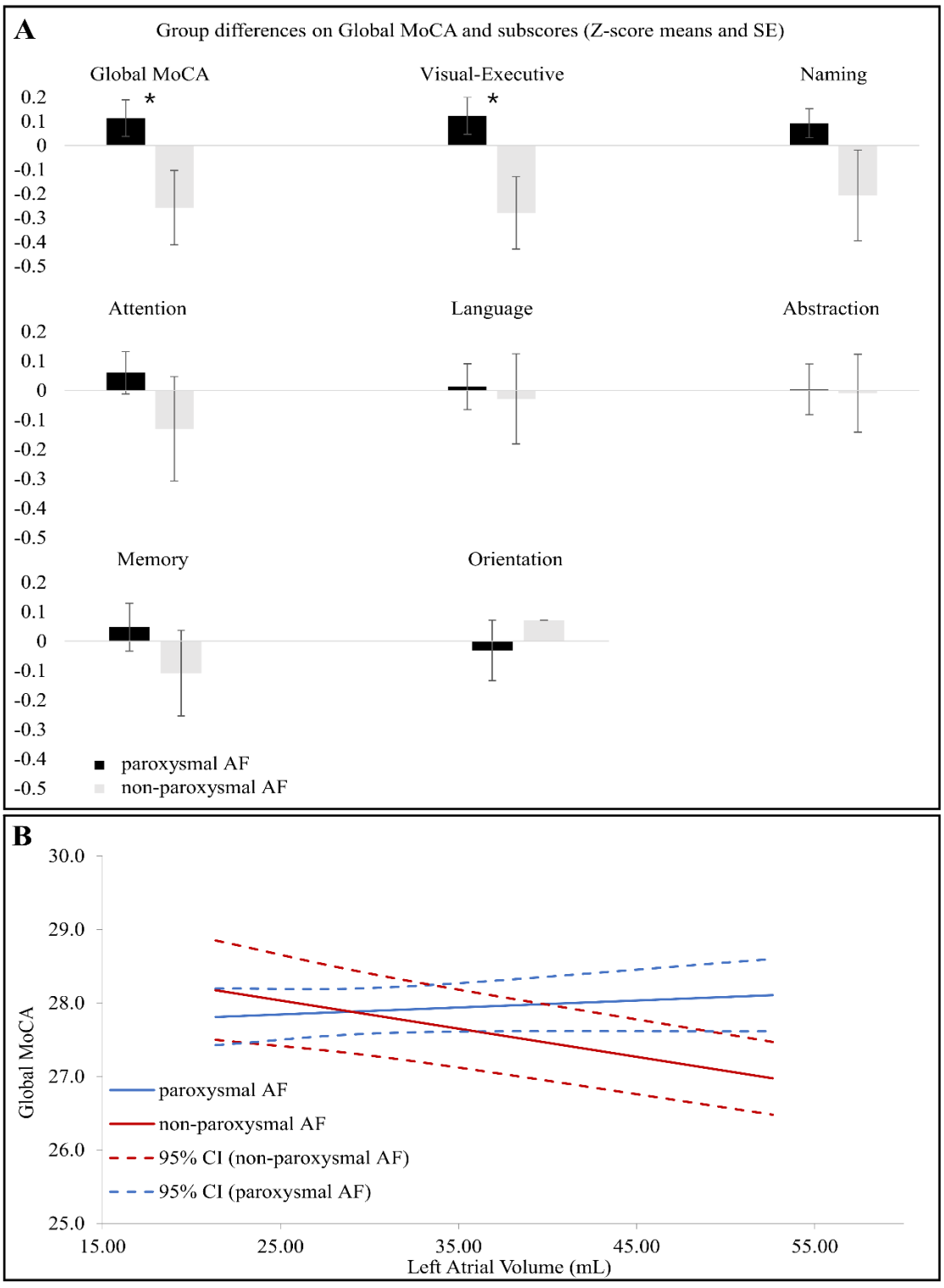

Figure A 1. – Group differences on cognitive performance.

A: *Bar graphs of group differences between paroxysmal vs. non-paroxysmal AF on MoCA scores. Shown are bar graphs for mean Z-score transformed global MoCA scores and subscores in*

*patients with paroxysmal (black) and non-paroxysmal (grey) AF. The error bars indicate standard errors. Significant differences (*p <0.05) between groups were observed for the global MoCA score and visuospatial-executive subscore.* ***B****: Conditional effects of left atrial volume on global MoCA scores. AF, atrial fibrillation.*

Mechanisms proposed to explain AF-related cognitive dysfunction include silent brain infarcts, cerebral hypoperfusion, inflammation, brain atrophy, microhemorrhage, and genetic factors. A much higher incidence of silent brain infarcts has been detected by imaging in AF versus matched non-AF patients; thus, the leading mechanistic hypothesis is that subclinical ischemic events underlie cognitive decline. Furthermore, LA enlargement has been associated with increased risk of spontaneous echo contrast and embolic events. In conjunction with the data here, this finding supports the microembolization/ischemic mechanism. These data are subjected to several limitations. The sample size is relatively small and the cross-sectional design does not allow an analysis of how cognitive scores change over time as a function of AF burden.

Nevertheless, this study reveals that in low-risk AF patients, non-paroxysmal AF is associated with lower cognitive function scores when compared to paroxysmal, and that larger LAV moderates this cognitive deficit observed in non-paroxysmal AF. This association may be explained by a higher risk of thromboembolism and may have clinical implications. Future confirmatory studies are required to better understand the influence of, and interaction between, AF burden and LAV on cognition.

Acknowledgments

The authors thank Antoinette Paolitto and Mary Morello (Montreal Heart Institute) for their help with the manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Sources of Funding

T.V. was supported by a PhD salary award from the Fonds de recherche du Québec – Santé. P.K. is supported by the endowed André Chagnon research chair in electrophysiology and congenital heart disease. L.R. is supported by research grants from Heart and Stroke Foundation, Canadian Institutes of Health Research and Fonds de recherche du Québec – Santé.

BRAIN-AF is supported by the Canadian Institutes of Health Research (CIHR), the Montreal Heart Institute Foundation, the Canadian Stroke Prevention Network (C-SPIN), and Bayer Inc.

Disclosures or Conflict of Interests

Dr. Rivard received grant money from BAYER Inc., CIHR, Heart and Stroke and salary support from FRQS.

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Appendix 2 – Supplementary article 1

A comparison of the effect of physical activity and cognitive training on dual-task performance in older adults

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Journal: Journals of Gerontology Series B: Psychological Sciences

Publication date: December 2021

A2.1. Abstract

Objectives: Studies suggest that cognitive training and physical activity can improve age-related deficits in dual-task performances. However, both of these interventions have never been compared in the same study. This paper investigates the improvement in dual-task performance in two types of exercise training groups and a cognitive training group, and explores if there are specific dual-task components that are more sensitive or more likely to improve following each type of training.

Methods: Seventy-eight healthy inactive participants over the age of 60 (M=69.98, SD=5.56) were randomized to one of three 12-week training programs: Aerobic (AET)=26, Gross Motor Abilities (GMA)=27, Cognition (COG)=25. Before and after the training program, the participants underwent physical fitness tests, and cognitive evaluations involving a computerized cognitive dual-task. The AET consisted of high and low intensity aerobic training, the GMA of full-body exercises focusing on agility, balance, coordination, and stretching, and the COG of tablet-based exercises focusing on executive functions.

Results: Repeated measures ANOVA on reaction time data revealed a group X time interaction ($F_{(2,75)}$ = 11.91, P < .01) with COG having the greatest improvement, followed by a significant improvement in the GMA group. Secondary analysis revealed the COG to also improve the intraindividual variability in reaction time ($F_{(1,24)}$ = 8.62, P < .01), while the GMA improved the dual-task cost ($F_{(1,26)}$ = 12.74, P < .01).

Discussion: The results show that physical and cognitive training can help enhance dual-task performance by improving different aspects of the task, suggesting that different mechanisms are in play.

Keywords: cognitive aging, dual-tasking, physical training, cognitive training

A2.2. Introduction

Worldwide the proportion of seniors is increasing quickly. By 2050 one out of every six individuals will be over 65 years of age, while the proportion of people aged 80 and over is expected to triple (United Nations, 2019). Aging is associated with cognitive changes (Zanto & Gazzaley, 2019), including declines in executive functions, a set of mechanisms which modulate the functioning of a variety of subprocesses and the dynamics of cognition (Miyake et al., 2000; Verhaeghen, 2011). Executive functions are the most sensitive to change throughout the normal aging process, preceding memory declines by up to three years, and functional decline by up to six years (Carlson et al., 2009; Johnson et al., 2007).

A consequence of decline in executive control and speed of processing is a reduced ability to accomplish two tasks simultaneously. Since dual-tasking plays a fundamental role in the independent functioning of older adults (Martyr & Clare, 2012), declines in this domain could have serious impacts. A meta-analysis has found dual-task reaction time (RT) to be consistently slower in older adults, and showed that the RT cost associated with performing two simultaneous tasks cannot be fully accounted for by age-related cognitive slowing, supporting the notion that there is a specific deficit in dual-task ability with aging (Verhaeghen et al., 2003). The present DT involves discriminating between two sets of images by pressing the corresponding button with the correct hand. While there are multiple different paradigms for dual-tasking in the literature, the present study used a simplified one to better isolate, and study specific DT components (RT, DT cost, task-set cost, intraindividual variability; please see section Assessments for a detailed description of all DT components) known to be affected in aging (Fraser & Bherer, 2013). Age-related deficits in dual-task cost can be observed in simple conditions when performing basic discrimination tasks. By comparing the tasks performed in a single condition to a condition in which both tasks have to be performed concurrently, past studies have reported that older adults tend to show larger dual-task effects (Bherer et al., 2005). This has been particularly evident in tasks requiring two motor responses (Hartley & Little, 1999), like in the present study. Studies have also shown an increased intraindividual variability in RT compared with younger adults, suggesting greater response inconsistency

(Bherer et al., 2006; Brydges et al., 2020). This decline of performance in dual-task conditions observed in older adults is most likely multidetermined (Verhaeghen et al., 2003). It can be caused by a potential impairment in the basic cognitive mechanisms involved, a lower ability to dedicate resources to each task, but also a change in the cognitive strategy with which older adults approach dual-task conditions (Bialystok & Craik, 2006; Braver et al., 2008; Fraser & Bherer, 2013). However, studies suggest that dual-task performances can be improved in older adults through cognitive and physical training.

Computerized cognitive training (COG) has shown to improve dual-task ability in older adults (Bherer et al., 2005, 2008; Karbach & Verhaeghen, 2014; Li et al., 2010; Lussier et al., 2012, 2015). Notably, Chiu and colleagues (2018) in a double-blind randomized controlled trial trained 31 older adults three times per week – 30-min per session – for 8 weeks to an executive functions program (focused on switching, working memory and inhibition). Results showed significantly improved task switching and working memory. Other programs of similar length and structure training dual-tasking, either alone or in combination with working memory have also shown a general improvement in dual-task performances on a similar DT to the one used in the present study (Bherer et al., 2005, 2008; Kramer et al., 1995; Lussier et al., 2012, 2015, 2017). In addition to improved processing speed, these studies were able to show improvements in dual-task cost performance, suggesting it impacted the ability to perform two simultaneous tasks. Intraindividual variability has also been shown to improve following COG in different studies training dual-tasking or even general cognitive abilities (Bherer et al., 2006; Brydges et al., 2020; Könen & Karbach, 2015). The cognitive training program used in this study focused on training executive functions based on the Miyake model which identified inhibition, switching, working memory, and dual-tasking as core functions (Miyake et al., 2000). The training included component-specific and variable priority training, designed to maximize learning, and decrease dual-task cost. Adaptive training, where the difficulty and/or stimuli change over time helps counteract the automation of cognitive processes and stimulates plasticity (Düzel et al., 2010; Kim et al., 2017). Feedback, on the other hand, allows participants to adapt their responses based on the demands of the task and ensures progression and understanding (Lussier et al., 2015). When it is continuous and progressive, feedback can also

keep the participant motivated because it allows them to quantify their improvement as training progresses (Strobach & Karbach, 2016). All these aspects, with the changes in demand and the presentation of several stimuli, also contribute to the generalization of learning.

Physical training programs have also demonstrated some benefits on cognitive abilities, including memory, attention, processing speed and executive functions (Bherer et al., 2013; Kramer & Erickson, 2007; Smith et al., 2010), including dual-tasking (Colcombe & Kramer, 2003). Most often those studies used aerobic training (AET), but emerging studies have highlighted the cognitive benefit of other types of exercises like resistance training (Liu-Ambrose et al., 2012) and gross motor abilities training (GMA) (Berryman et al., 2014). More precisely, Berryman et al. (2014) showed that even eight weeks of GMA (including stretching, relaxation, locomotion, coordination, juggling, and balance exercises) was able to improve inhibition scores in a random number generation task. This improvement has been recorded while performing the cognitive task alone as well as during a walking dual-task. The authors argue that the GMA resulted in cognitive benefits as a result of the exercises used, which required the use of coordination and perceptual adaptations. Those results are promising, suggesting that the cognitive benefit of physical training is not limited to aerobic fitness.

Specifically to dual-tasking, the evidence is scarce suggesting only a potential benefit of aerobic training (Bherer et al., 2019, 2020; Hawkins et al., 1992; Madden et al., 1989). Although Madden et al. (1989) did not find an improvement in RT in a dual-task paradigm following AET, Hawkins et al. (1992) showed faster RT while performing a dual-task. Moreover, Bherer et al. (2019) showed that AET can also improve the task-set cost in older adults. Other studies show higher aerobic fitness to be associated with lower intraindividual variability while physical training did not have an impact on this variable (Bielak & Brydges, 2019; Raine et al., 2018). Even though the results in those studies are mixed, they show a potential link between physical training and dual-task performance which might be dependent on the content and the duration of the training program.

Although the evidence suggests that all three training groups have the capacity to improve dual-tasking abilities, it is still unclear how those programs compare against each other. In

addition, it is not clear if the benefits of physical training are comparable between AET or GMA. Thus, this study aims to investigate if the three training groups can improve dual-task performance, and if there are specific dual-task components that are more sensitive or more likely to improve following each type of training. Although all groups are expected to show some form of improvement, it is hypothesized that the COG will show the largest improvement across all parameters, while the GMA group is expected to improve more than the AET in dual-task performances.

A2.3. Methods

A2.3.1. Study population

A total of 133 participants from the community provided their informed consent before starting the study. Table A2.1. documents participants' demographic characteristics. Participants were eligible if: were over the age of 60, were non-smokers and consumed less than 2 standard drinks of alcohol per day. Participants were not eligible if: they had followed a structured exercising program of 150 minutes/week or more in the last year (including home exercising), had contraindications to perform physical activity, had limited mobility, a surgery involving general anesthetic in the previous year, were diagnosed with any orthopedic, neurological, cardiovascular, or respiratory problems within the last six months, were diagnosed or suspected to have dementia (an MMSE score <26; Folstein et al., 1975), had an unstable chronic condition in the past 6 months (new diagnosis or a change in disease presentation or medication) or if they started a hormone therapy program in the past year. Thirty participants were ineligible or dropped out before starting the training program, followed by 17 participants who dropped out during the training period. There was no difference on the demographic parameters between the individuals that dropped out and those that finished the study. Eight participants, who made up the pilot cohort were excluded from the analysis due to changes to the protocol related to the order of the tests administered. The final sample was comprised of 78 participants (AET: 26; COG: 25; GMA: 27). Figure A2.1. shows the sample flowchart.

Characteristic	All sample N=78	AET n=26	GMA n=27	COG n=25	*F* or χ^2	*p*
Age	69.98 (5.56)	69.28 (4.85)	70.21 (5.86)	70.46 (6.07)	F= .32	.73
Education (years)	16.05 (3.62)	16.35 (3.82)	16.26 (3.73)	15.50 (3.37)	F= .41	.66
Attendance (%)	91.99 (5.46)	92.73 (4.79)	90.84 (6.10)	92.44 (5.41)	F= .92	.40
Female (%)	65.4	73.1	74.1	48.0	X^2=4.92	.09
BMI (kg/m^2)	26.10 (4.32)	26.46 (4.60)	25.25 (3.62)	26.63 (4.74)	F= .80	.46
MoCA[a]	26.33 (2.51)	26.88 (2.30)	26.15 (2.46)	25.96 (2.76)	F= 1.08	.34
MMSE[a]	28.49 (1.16)	28.92 (.89)	28.26 (1.29)	28.28 (1.17)	F=2.90	.06
GDS[b]	5.09 (5.66)	3.31 (3.97)	5.74 (5.03)	6.24 (7.33)	F=2.04	.14
Walking Speed 10m ($m.s^{-1}$)	1.38 (.18)	1.43 (.22)	1.34 (.13)	1.37 (.18)	F=1.48	.23
VO_2Peak (mL/kg/min)	20.70 (5.87)	21.58 (6.43)	20.26 (5.32)	20.25 (5.95)	F= .43	.65

Table A2. 1. – Baseline descriptive values (means or percentage, and standard deviations).

Abbreviations: BMI: Body Mass Index; MoCA = Montreal Cognitive Assessment; MMSE = Mini Mental State Examination; GDS = Geriatric Depression Scale; [a]Higher scores indicate better performance, range: 0-30; [b]Higher scores are maladaptive, range: 0-30

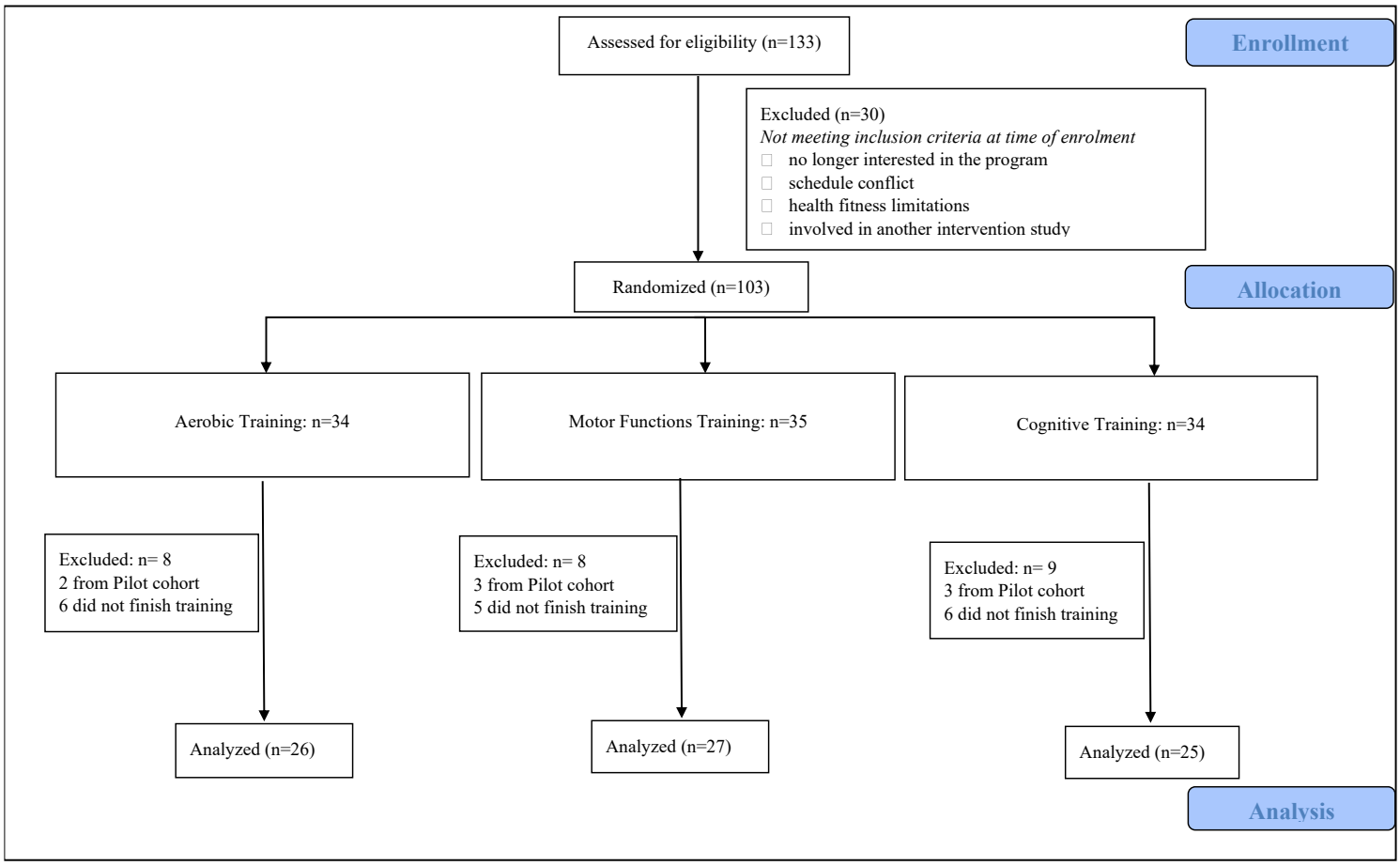

Figure A2. 1. – Participant sample flowchart.

A2.3.2. Procedure

Following a phone interview, participants were invited to four pre-training appointments over two weeks. The eligibility of the participants was evaluated during a medical exam by a geriatrician, and a neuropsychological exam with a neuropsychologist (or a trained and supervised psychology student). An experimental tablet based dual-task was also administered on the last appointment. The mobility of the participants was assessed with a 10-meter walking

test, and their cardiorespiratory fitness measured with a VO_2Peak test completed on a cycle ergometer. The physical tests and trainings were supervised by a kinesiologist. Please see Pothier et al. (2021) for a more detailed overview of the protocol.

A2.3.3. Assessments

VO_2Peak: A maximal graded test was performed on a cycle ergometer (Lode, CORIVAL). Participants were equipped with an electrocardiogram and wore a mask to measure the gas exchange. Participants began at a pre-defined load and were required to maintain a pedaling rate of 60 to 80 revolutions per minute. The test was deemed complete if the kinesiologist observed physiological signs and symptoms reflecting inability to continue. VO_2Peak was defined as the highest relative volume of oxygen consumed over a 30 second interval measured in $ml.kg^{-1}.min^{-1}$. A detailed description of this assessment can be found in Pothier et al. (2021).

10-meter walking test: Usual gait speed was assessed using a 10-m walking test in which participants had to walk in a straight line at their usual pace for ten meters.

Dual-task paradigm: It consisted of performing two visual discrimination tasks either separately or at the same time (Lussier et al., 2020). Participants were instructed to identify stimuli presented on the screen by pressing the corresponding button/s as quickly as possible while making as few errors as possible (RT in ms and percentage of accuracy were recorded). The task was administered on an Apple iPad Air® 2 tablet. Participants performed this task seated at a desk in a quiet room, and the position of the tablet relative to the participant was standardized and remained the same for all. Each task involved 3 different stimuli (drawings of animals or planets) presented for 3 seconds in the center of the screen. The dual-task paradigm involved three different trial types: single-pure (SP), single mixed (SM) and dual mixed (DM) trials. In the SP trials, participants had to answer to one stimulus of a single task set (e.g., participants were presented with one stimulus associated with the left hand alone – animals, followed by a separate block where one stimulus associated with the right hand was presented – planets). In the SM trials, participants were presented and responded to one stimulus of either task set (e.g., one stimulus was presented, each trial at random, sometimes from the set associated

with the left hand, sometimes from the set associated with the right hand). Finally, in the DM trials participants were presented simultaneously with two stimuli, one from each task set (e.g. right and left hand), and they had to answer to both. The participants were asked to respond without prioritizing one hand over the other. Overall, there were 60 SP trials answered (30/each hand), 66 SM trials (33/each hand) and 51 DM trials. The participants started by answering 10 SP trials, followed by SM trials and finally DM trials. After reaching the first DM trials, the task alternated mostly between SM and DM trials with 10 more SP trials halfway and 10 SP trials at the end. Overall, the task lasted roughly 15 minutes. Each trial lasted 3 seconds, whether answered or not. Unanswered trials and wrong responses were labeled as incorrect and were removed from RT means (Table A2.2. details the accuracy data).

In order to better understand the cognitive mechanisms involved in dual-task performance, two costs were calculated from the RT data: task-set cost (SM/SP) and dual-task cost (DM/SM) (Bherer et al., 2019). This approach of calculating the costs is more conservative than a simple subtraction because it takes into account each individual's response time in the previous block, and therefore is less affected by general slowing (similar to a percentage change vs a subtraction change). Therefore, this gives more weight to the findings reported in this study. The *task-set cost* reflects the ability to maintain different response alternatives in working memory and preparing to respond to one stimulus while controlling for the speed of executing one task. Finally, the *dual-task cost* reflects the delay in RT required to perform two tasks simultaneously. *Intraindividual variability* was also extracted, which measures the variability of RT between all trials of the same type for each participant (Bherer et al., 2006). This value was calculated as the standard deviation of RT divided by the mean RT of a given type of trial (SP, SM & DM) and reflects RT response consistency (Bherer et al., 2006).

Psychological constructs known to impact cognitive abilities in aging were also measured in order to rule out their potential impact. Depressive symptoms were assessed using the Geriatric Depression Scale (Yesavage et al., 1982), and anxiety levels were measured using the State/Trait Anxiety Inventory (Julian, 2011).

A2.3.4. Interventions

Following the pre-training assessments all participants were randomly assigned to one of the three training programs: AET, GMA, or COG. The randomization was done using a random generated list created at the beginning of the study by the project manager where groups were matched for age, sex and mobility level. All training programs were held in groups of 3-6 individuals, were supervised by an expert and took place three times a week for approximately 60 minutes each time for 12 weeks. The physical training programs were individually tailored to each participant's abilities, and the trainer offered progress feedback and encouragement throughout the training. Immediately after the end of the training program, the same tests that were used during pre-testing were re-administered in the same order over the course of two weeks. The structure of all three training programs has been determined based on previous studies (Berryman et al., 2014; Lussier et al., 2015, 2017). Although cognitive trainings have been shown to be successful in even shorter programs, a length and structure similar with the two physical training programs has been implemented to have a comparable training exposure across all three groups.

Aerobic training: The AET program was completed on a recumbent bicycle (LifeFitness, Kinequip, St-Hubert, Quebec) and was designed to increase the aerobic fitness. The program consisted of a high intensity interval training (HIIT) component and a continuous component which were done on separate days alternating one at a time. The maximal aerobic power (MAP) was determined during the VO_2Peak at pre-testing. Every training session started and ended with a 10-minute biking session at 50% of the MAP. The target cadence was between 60-80 RPM. The continuous component of aerobic training lasted 20 minutes at 65% of the MAP. The HIIT was comprised of two blocks of 5 minutes each with a two-minute break in between blocks, alternating every 15 seconds between 100% and 60% of the MAP. In order to ensure a progression in training loads, every 4 weeks all power values (during the HIIT and the continuous component) were increased by 5%.

Motor functions training: The GMA was designed to improve walking abilities, based on the program described by Berryman et al. (2014). Each session started and ended with a 10-minute

walking exercise on a treadmill at a slow speed gradually increasing up to 3mph. The remainder of the session was comprised of exercises designed to improve mobility, balance, agility, lower-body coordination, hand-eye coordination. For example: throwing a ball at a target, following an obstacle course, one leg balance, balancing on a stability ball, stationary body weight exercises, walking sideways. In order to increase the difficulty of the GMA, a combination of those exercises was performed at the same time (i.e., one leg balance while throwing a ball at a target). The session concluded with a full body stretching period for the remaining time.

Cognitive training: The COG was designed to improve executive functions with a focus on switching, inhibition, and working memory. Each session was done in groups of 3-6 participants in a room with cubicles. Three tasks were done at each training session - dual-task, modified Stroop, and N-back -, for an approximate duration of 20 minutes each. During all training tasks feedback based on participant's accuracy was provided. A performance bar located at the bottom of the screen displayed comments ranging from "WELL DONE" to "INCREDIBLE!!!!!", and was reset when an incorrect answer was given. The button also flashed green when a correct answer was given or red when it was incorrect. Finally, at the end of each completed session a graph combining errors and reaction time showed the individual progress of the participant.

The dual-task training sessions were similar to the dual-task assessment task. The instructions were the same, however, in order to increase the level of difficulty, participants were instructed to prioritize one hand over the other after two training sessions. An additional feedback on speed was also provided for each hand individually. The stimuli used for training were alternating between fruits and vehicles, and letters and numbers.

For the N-Back task, the participants had to answer if a presented stimulus was the same or different than the one presented one position (1-back), two positions (2-back) or three positions (3-back) before. Stimuli were presented visually and audibly every 3 seconds. During the first month, only 1- and 2- back were presented, from the second month the 3-back was added and the third month consisted of only 2- and 3-back. The stimuli used alternated

between letters and images between training sessions. Participants were instructed to focus on the accuracy of their response rather than the speed at which they answered.

Finally, the modified Stroop task included four conditions: reading, naming, inhibition, and switching. During the reading condition, letters were presented in small groups corresponding to a bigger identically formed letter (e.g. multiple “H” arranged to form a big “H”). The participant had to press the corresponding letter. In the naming condition, asterisks were presented in the same layout found in the reading condition (e.g. asterisks arranged to form the letter “H”). The participants had to report which letter was presented. In the inhibition condition, letters were presented in small groups, but were incompatible with the bigger formed letter (e.g., multiple “H” arranged to form the letter “F”). The participants were asked to identify the bigger formed letter. Finally, during the switching condition a white border surrounded the stimuli meaning the participants had to report the identity of the small letter instead of the bigger formed letter. The stimuli used alternated between letters or symbols (e.g. small bars forming a larger plus sign for the inhibition block) between training sessions.

A2.3.5. Statistical analysis

All analyses were performed using IBM SPSS v.24.0 for Windows (IBM, Inc., Chicago, IL). Normality of data distribution was checked using the kurtosis and skewness of all variables, and outliers were winsorized at 2 SD. All reported p-values are two-tailed. The significance level was set to .05 and a Bonferroni correction was applied for all post-hoc tests. All tablet data (RT, Accuracy, intraindividual variability) were averaged for both hands. The primary analysis consisted of a repeated measures ANOVA with group (AET, GMA, COG) as the between-subjects factor, time (pre vs. post) and trial type (SP, SM, DM) as the within-subject factors on the dependent variables (RT, accuracy, intraindividual variability). Secondary analyses involved repeated measures ANOVAs with group as between-subjects factor, and time as within-subject factor on the two dual-task costs variables (task-set cost and dual-task cost), and on the VO_2Peak data.

A2.4. Results

The baseline characteristics (Table A2.1.) showed no group differences. The sample was relatively fit in terms of mobility (10m walk test usual gait: 1.36 $m.s^{-1}$), and highly educated. Following the training, the VO_2Peak improved only in the AET group (group x time interaction: $F_{(2,75)} = 7.13$, $P < .01$, $\eta^2_p = .16$), with the AET improving from 21.58 (±6.43) to 23.51 (±7.23) $mL.kg^{-1}.min^{-1}$, $F_{(1,25)} = 9.18$, $P < .00$, $\eta^2_p = .27$).

A2.4.1. Dual-task performance

The repeated ANOVA on RT data (Figure A2.2.) revealed a significant improvement through Time, ($F_{(1,75)} = 45.93$, $P < .01$, $\eta^2_p = .38$). However, this effect was characterized by a Time X Group interaction ($F_{(2,75)} = 11.91$, $P < .01$, $\eta^2_p = .24$). Post-hoc tests showed RT to improve only in the COG group (149 ms, $F_{(1,24)} = 44.25$, $P < .01$, $\eta^2_p = .65$) and the GMA group (57 ms, $F_{(1,26)} = 14.24$, $P < .01$, $\eta^2_p = .35$), while the change in the AET group was not significant.

The repeated ANOVA also revealed a Time X Trial Type interaction ($F_{(2,150)} = 21.48$, $P < .01$, $\eta^2_p = .22$). Repeated contrast indicated that reaction time improved significantly in the dual-mixed trials ($F_{(1,75)} = 27.15$, $P < .01$, $\eta^2_p = .26$). Interestingly, this improvement was not characterized by a Time X Trial Type X Group interaction, therefore indicating that the improvement in RT seen in the Dual Mixed trials was present in all groups.

A2.4.2. Dual-task cost

The repeated ANOVA (Figure A2.3.) revealed a significant time improvement ($F_{(1,75)} = 5.19$, $P < .05$, $\eta^2_p = .07$), and a Time X Group interaction ($F_{(2,75)} = 4.39$, $P < .05$, $\eta^2_p = .11$) on the dual-task cost. Post-hocs revealed only the GMA group had a significant decrease in dual-task cost ($F_{(1,26)} = 12.74$, $P < .01$, $\eta^2_p = .33$), while the AET group ($F_{(1,25)} = 3.22$, $P = .09$, $\eta^2_p = .11$), and the COG group ($F_{(1,24)} = 1.21$, $P = .28$, $\eta^2_p = .05$) showed no significant change. No significant differences were observed on the task-set cost.

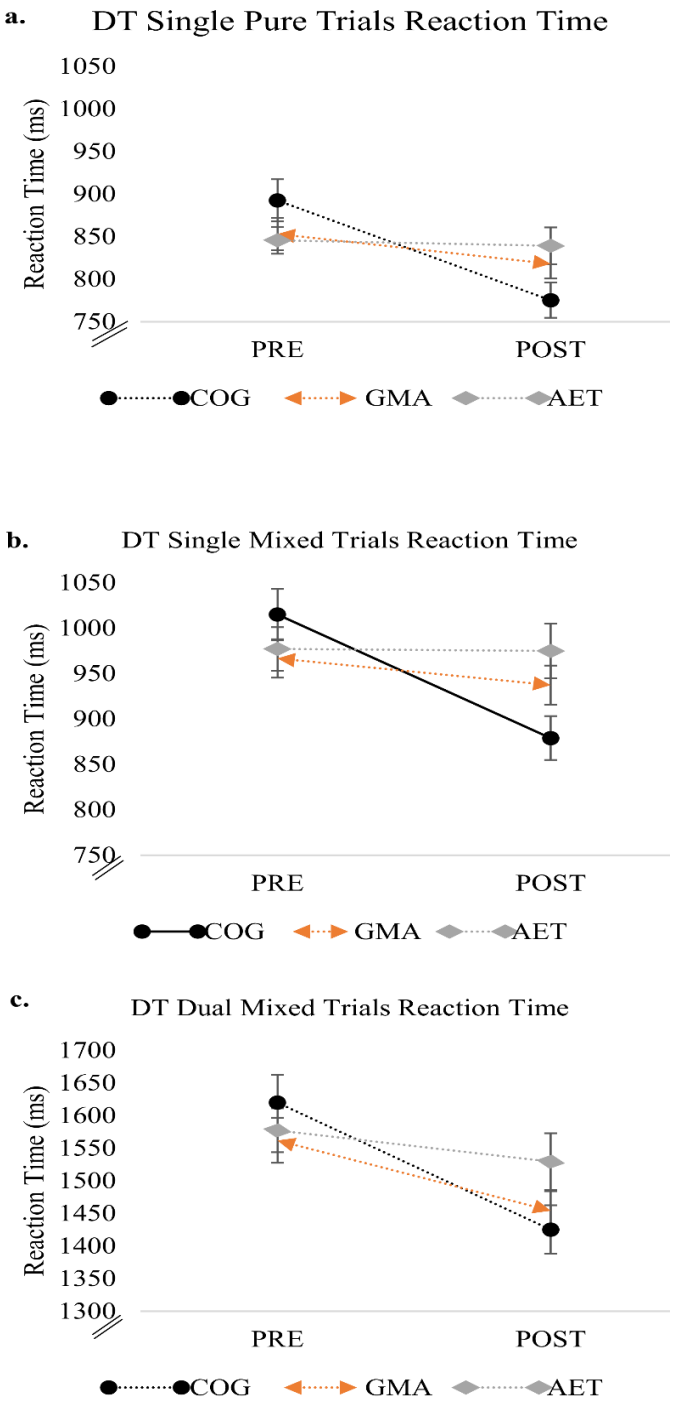

Figure A2. 2. – Change in DT reaction time across all blocks. Graphs showing means and standard error.

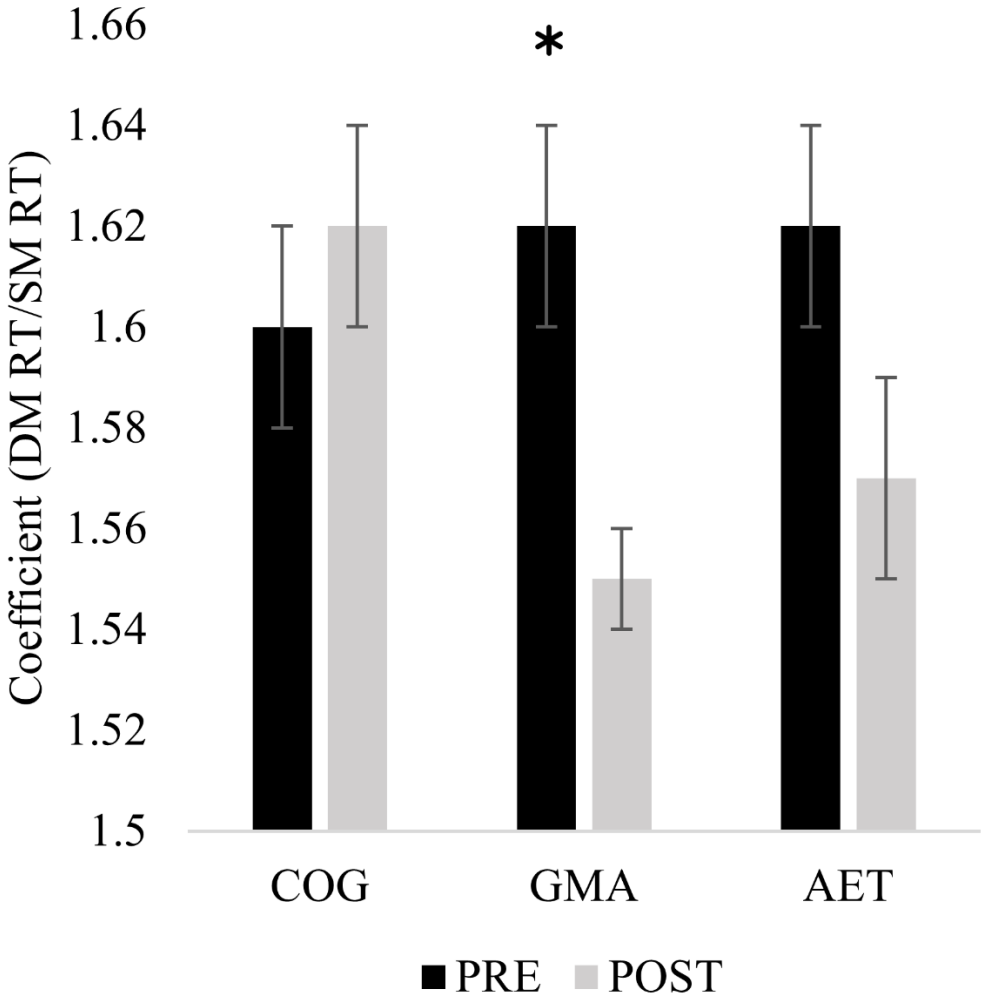

Figure A2. 3. – Bar graph illustrating the post hoc analysis of the change in dual-task cost (means and standard errors).

A2.4.3. Dual-task intraindividual variability

The repeated ANOVA performed on intraindividual variability (Figure A2.4.) revealed a significant time improvement ($F_{(1,75)} = 5.19$, $P < .05$, $\eta^2_p = .07$), and a Time X Group interaction

($F_{(2,75)}$ = 4.39, P < .05, η^2_p = .11) . Post-hoc analyses showed a significant decrease in intraindividual variability in the COG group only ($F_{(1,24)}$ = 8.62, P < .01, η^2_p = .26), and nonsignificant changes in the GMA group ($F_{(1,26)}$ = 3.05, P = .09, η^2_p = .11), and the AET group (P = .99, η^2_p = .00). As the two exercise groups seem to improve differently, we also checked for any potential group differences post-training. The post-hoc group analysis on the post training data revealed only the COG group to be different than the AET group (p < .01), while the GMA group was not statistically different than either of the other two groups.

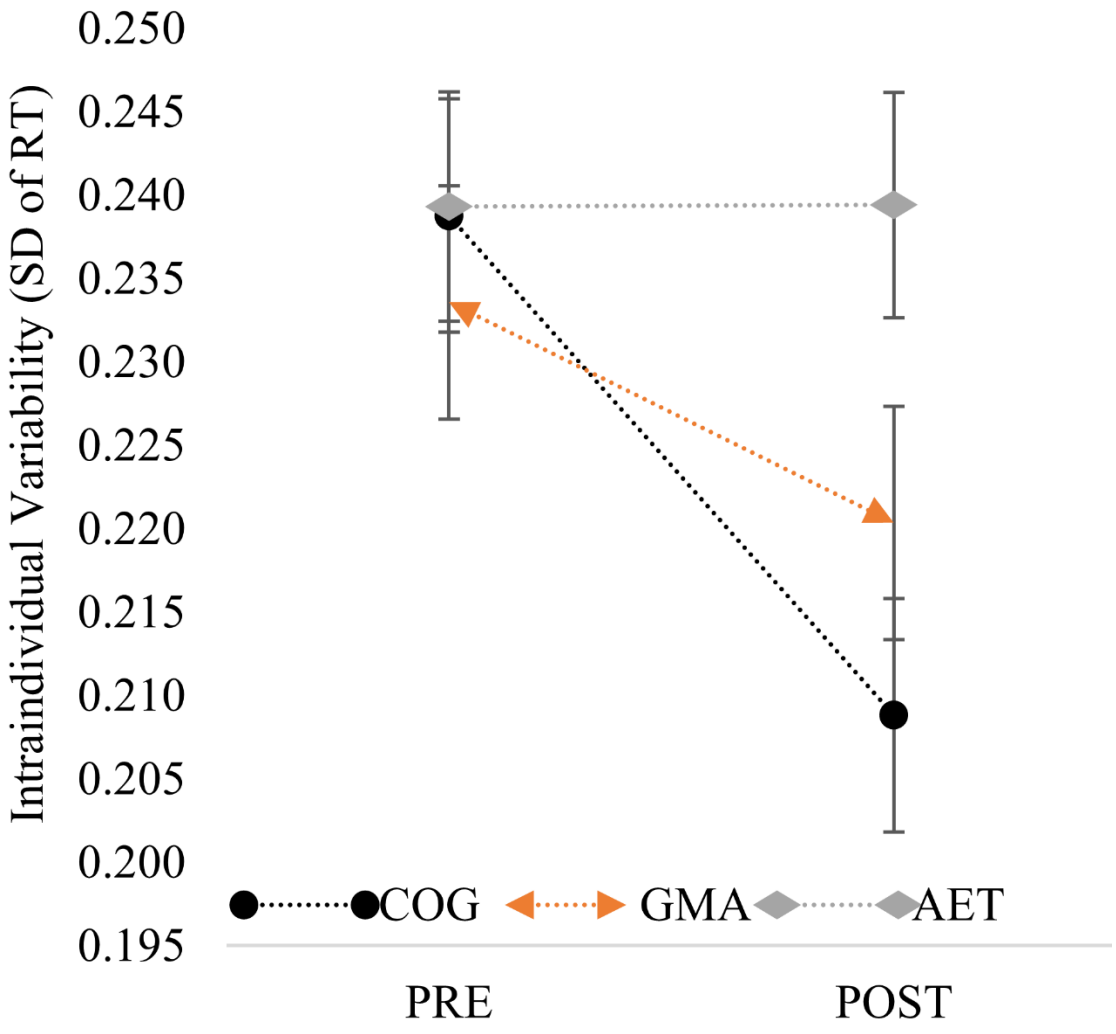

Figure A2. 4. – Change in intraindividual variability

A2.4.4. Dual-task accuracy

There was no significant time effect or Time X Group interaction ($p > .05$) on the accuracy data. This is consistent with previous findings showing high accuracy rates on this tablet task (Lussier et al., 2020). Please see Table A2.2. for all DT data.

	PRE			POST		
Characteristic	AET	GMA	COG	AET	GMA	COG
DT SP RT (SD)	845.69 (81.09)	892.67 (123.61)	852.96 (98.10)	839.17 (109.63)	775.32 (103.74)	818.59 (90.15)
DT SM RT (SD)	977.22 (122.52)	1014.88 (140.98)	966.55 (110.16)	974.86 (153.42)	878.96 (120.53)	937.42 (111.64)
DT DM RT (SD)	1577.24 (171.35)	1619.82 (213.89)	1561.78 (179.60)	1529.17 (222.52)	1425.09 (186.66)	1453.91 (155.98)
DT SP Error % (SD) [range]	2.05 (2.64) [0 – 11]	2.02 (3.16) [0 – 7]	1.38 (1.75) [0 – 13]	2.70 (3.45) [0 -13]	1.20 (1.80) [0 -7]	1.63 (2.09) [0 – 7]
DT SM Error % (SD) [range]	1.71 (1.83) [0-6]	2.44 (2.91) [0 – 8]	1.28 (2.00) [0 – 12]	1.83 (2.91) [0 -13]	1.28 (2.09) [0 – 6]	1.52 (2.05) [0 – 8]
DT DM Error % (SD) [range]	5.83 (7.38) [0 – 31]	4.83 (4.84) [0 – 14]	5.09 (5.22) [0 – 20]	5.30 (7.59) [0 – 37]	3.51 (3.78) [0 – 13]	3.05 (3.94) [0 -13]
DT SP IIV (SD)	0.213 (0.046)	0.209 (0.063)	0.191 (0.046)	0.209 (0.053)	0.178 (0.036)	0.184 (0.035)

DT SM IIV (SD)	0.232 (0.052)	0.228 (0.058)	0.225 (0.061)	0.227 (0.062)	0.191 (0.058)	0.208 (0.055)
DT DM IIV (SD)	0.274 (0.035)	0.279 (0.035)	0.285 (0.034)	0.282 (0.036)	0.257 (0.041)	0.269 (0.030)

Table A2. 2. – Means and standard deviations for all DT variables.

Abbreviations: DT: Dual Task; SP: Single Pure; SM: Single Mixed; DM: Dual Mixed; RT: Reaction Time; SD: standard deviation; IIV: Intra Individual Variability;

A2.5. Discussion

The goal was to compare the effects of two physical training programs relative to a COG program on a cognitive dual-task. The results showed RT to improve only in the COG and GMA groups with the highest improvement in the COG group. The RT improvement was also observed to be the highest in the dual mixed blocks suggesting a potential dual-task cost improvement across all groups. However, further analyses looking at the dual-task cost showed only the GMA group to improve while the AET group was approaching significance. The COG group was the only one to improve the intraindividual variability index. These results suggest that both physical and cognitive training programs can lead to improved performance in dual-task but they impact different aspects of it. In fact, COG led to large improvements in many aspects of the dual-task, including a reduced response variability, while GMA seems to lead to larger benefits in improving task-coordination ability. Although only theoretically hypothesized in the past (Ludyga et al., 2020; Netz, 2019), the present study is the first to bring direct evidence to the separate cognitive mechanisms through which different types of training programs impact dual-tasking abilities.

In accordance with previous research (Forte et al., 2013; Gothe et al., 2019; Rehfeld et al., 2017; Wayne et al., 2014), this study shows that GMA has higher cognitive benefits on the dual-task

than AET. Netz (2019) has suggested that GMA and AET can improve cognition through different mechanisms. The author suggests that physical training programs relying on motor training can improve cognition directly through its cognitive demands and those improvements tend to be task specific. This means that cognitive tasks that rely on similar cognitive abilities to those trained are likely to show higher improvements. On the other hand, AET would improve cognitive abilities through the benefits following improved cardiovascular fitness, and this cognitive improvement tends to be more global. Effectively, this improved cardiovascular capacity helps the efficiency of the transport of oxygen and nutrients to the brain (Ainslie et al., 2008; Vogiatzis et al., 2011). As a result, changes like increased oxygenated blood flow, neurogenesis and angiogenesis improve the brain structure and function which can result in a generalized improvement in cognitive abilities (Brown et al., 2010; Colcombe et al., 2003). In the present study, this differentiation is supported by the specific high dual-task cost improvement observed following the GMA, and the general improvement in RT (although only trending significance) observed in the AET group. The non-significant change in RT cost observed in the AET group here does not mean that aerobic exercise cannot improve dual-tasking, as this has been previously shown using a similar dual-task (Bherer et al., 2019, 2020). This discrepancy might actually suggest that differences in training intensity or volume might play a role in facilitating the cognitive benefit on dual-tasking and should be further investigated. Furthermore, age seems to also play a role in how AET induced cardiorespiratory fitness improvements results in better dual-task performance (Bherer et al., 2019), and should be taken into account in the future.

The improvement on the dual-task seen in the GMA group could be attributed to the higher cognitive load associated with this type of training compared to AET. The GMA program trained coordination skills and sometimes physical dual-tasking and therefore improved those abilities. More specifically, in the present study the GMA group improved dual-task cost, which could be explained by the superior improvement in RT in the dual mixed block rather than the single pure or single mixed blocks. This is as a result of the higher demand during the dual mixed block on switching and coordination skills which were trained as part of the GMA program. The type of dual-task that was performed by those participants involved tasks like keeping their balance

on one leg while throwing a ball at a target, upper body exercises while balancing on a stability ball, or navigating an obstacle course while holding different items. Even though the tablet dual-task is different, the training could have resulted in the generalization of some skills that could have transferred.

Despite the cognitive benefit observed from physical training, COG is the most efficient type of training at improving overall dual-task performance through RT and intraindividual variability. This is expected since the COG used a similar task as part of the training (although with different stimuli, instructions and feedback). Although not extensively investigated, improvements in intraindividual variability have been recorded following only some forms of interventions (Brydges et al., 2020). Consistent with our results, studies have shown intraindividual variability to be less sensitive following general exercise interventions, but showed improvements following interventions that train attention abilities (Bielak & Brydges, 2019; Brydges et al., 2020). The current results also suggest that COG might be superior at improving the general "cognitive processing" that takes place while performing the dual-task, since the improvement in RT is consistent across all trials. The lack of improvement in any of the two costs following the COG in the current study might be due to the way it was calculated. Some studies show cost improvements by subtracting the average RT between the different blocks (Bherer et al., 2005). If the dual-task cost was to be calculated the same way, the current paper would reveal a similar improvement in dual-task cost across all groups. This can be observed through the time effect of the repeated contrasts post-hoc of the primary analysis. However, some studies show improvements in the dual-task cost calculated as a ratio of the RT (DM RT/SM RT) and suggest that this might be more informative as it is taking into account the change in RT relative to the change in the previous block (Bherer et al., 2019). Indeed, the approach in the present study is more conservative and brings further support to these results. In the current study, the RT improvement following COG was large across all three trials (SP, SM & DM; which potentially reflects a "floor" effect), and this resulted in a small dual-task cost.

Although the presence of near vs. far transfer is still debated in the cognitive training literature, the improvements observed in this study can, to some extent, be explained through transfer.

More specifically, the DT improvements observed in the GMA group could reflect far transfer, potentially because this group trained some abilities that are also involved in the DT (i.e., switching, coordination). At the same time, the stimuli used and the task performed were significantly different both perceptually and conceptually (in training vs. testing) which makes this improvement likely to be qualified as far transfer (Barnett & Ceci, 2002). On the other hand, the improvements observed in the COG group could reflect near transfer since the training included a similar task with common specific mechanisms. Although practice effects are also likely to play a role in the cognitive improvements recorded across this study, its impact is considered small because the two physical training groups which had an equal exposure to the DT show a different pattern of improvements.

Moreover, a recent study was able to show that a program using both cognitive and physical training was able to improve the dual-task accuracy task-set cost more than cognitive or physical training alone (Bherer et al., 2020). Similar to the present results, the authors also showed that COG alone was able to improve RT performance while AET did not have a significant impact on the dual-task. This raises questions on other potential mediating variables, or the dose effect of AET.

The present study highlights specific dual-task components that can be improved depending on the training modality, which could be used in the future to better test the efficacy of combined training programs. However, it is unclear how the improvements observed in this study would translate to more complex DT paradigms (i.e., following an obstacle course while performing a cognitive task). The currently used DT requires discriminating between two visual tasks and giving a motor response. Dual-tasks with two motor inputs are more difficult for older adults and more likely to express age-related differences in performance (Hartley & Little, 1999). As a result, it is unclear how the performance observed on the current task might compare to the performance on other DT. In fact, a study suggests that there could be limited cross-modality transfer effects that can be expected following DT training with this task (Lussier et al., 2012). In other words, the improvement in dual-task performance might not generalize as much to a context requiring another response modality or involving other factors that might impact DT

performance. Although the advantage of using this simple DT allows to identify how the three training types impacts specific core components involved in dual-tasking in aging, future studies should try to replicate those results with other more complex DT paradigms.

The results of the present study could be limited by a few factors. First, the relatively small sample size could have impacted the results. Second the simple nature of the DT used in the study helped inform on mechanisms involved in dual-tasking, but this might limit the generalizability of the findings to more complex real-world situations. Future studies could try to replicate the mechanism highlighted above in more ecologically valid paradigms. Finally, the difference in social interactions inherent in each training program is virtually impossible to fully control for when comparing a cognitive training program with a physical training program, and this could have impacted to a certain extent the results.

A2.6. Conclusions

Across all dual-task components, the COG training had the highest improvements, while the GMA training showed superior cognitive benefits than the AET. Specifically, the study shows that COG improves RT the most in a consistent manner, and it might be the best way of improving DT abilities. The results also bring support to the use of lower intensity motor physical training programs as an effective method to boost cognitive abilities in aging. This is relevant because certain older adults might not be able to follow an intense aerobic program, in which case other types of physical activities could be used to boost cognitive abilities in aging. However, since all programs are likely to improve cognitive abilities through specific mechanisms, a combination of different types of physical exercises, as well as supplementing with cognitive training might be ideal. However, evidence for this is still limited and it should be further investigated.

The current results also highlight the importance of using multiple parameters when investigating cognitive performance on computerized tasks. This allows to capture different processes or mechanisms that can be improved through different interventions. Future studies

are encouraged to employ similar approaches especially when investigating the cognitive benefits of different interventions in older adults using other ecologically valid DT paradigms.

A2.7. Funding

This work was supported by a grant from the Canadian Institutes of Health Research (#136859) to LB. TV was supported by a PhD fellowhship from the Fonds de recherche du Québec – Santé. LB was supported by the Canada Research Chair Program. KP was supported by a Postdoctoral research fellowship from The Fonds de Recherche du Québec – Nature et Technologies (#200437).

A2.8. Acknowledgement

This study was not preregistered. Data, analytic methods, and study materials can be made available upon request.

A2.9. Conflict of interests

None.

A2.10. Author contributions

T. Vrinceanu: study conceptualization, data collection, formal analysis, investigation, methodology, validation, writing the original draft, reviewing and editing. C-A. Blanchette: validation, writing –reviewing and editing. B. Intzandt: conceptualization, data collection, methodology, investigation, project administration, validation, writing –reviewing. M. Lussier: conceptualization, data collection, formal analysis, methodology, validation, writing –reviewing and editing. K. Pothier: data collection, investigation, methodology, project administration, validation, writing – reviewing and editing. T.T.M. Vu: conceptualization, data collection, funding acquisition, investigation, validation, writing –reviewing. A. Nigam: conceptualization, data collection, funding acquisition, investigation, validation, writing –reviewing. L. Bosquet: conceptualization, funding acquisition, validation, writing –reviewing. A. D. Karelis:

conceptualization, funding acquisition, validation, writing –reviewing. K. Z. H. Li: conceptualization, data collection, funding acquisition, investigation, methodology, validation, writing –reviewing and editing. N. Berryman: conceptualization, data collection, formal analysis, funding acquisition, methodology, validation, writing reviewing and editing. L. Bherer: conceptualization, data collection, formal analysis, funding acquisition; investigation, methodology, project administration, validation, writing– reviewing and editing.

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Appendix 3 – Supplementary article 2

Comparing the effect of Cognitive vs. Exercise Training on brain MRI outcomes in healthy older adults: A systematic review

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Journal: Neuroscience and Biobehavioral Reviews

Publication date: July 2021

A3.1. Abstract

Aging is associated with cognitive decline. Importantly cognition and cerebral health is enhanced with interventions like cognitive (CT) and exercise training (ET). However, effects of CT and ET interventions on brain magnetic resonance imaging outcomes have never been compared systematically. Here, the primary objective was to critically and systematically compare CT to ET in healthy older adults on brain MRI outcomes. A total of 38 studies were included in the final review. Although results were mixed, patterns were identified: CT showed improvements in white matter microstructure, while ET demonstrated macrostructural enhancements, and both demonstrated changes to task-based BOLD signal changes. Importantly, beneficial effects for cognitive and cerebral outcomes were observed by almost all, regardless of intervention type. Overall, it is suggested that future work include more than one MRI outcome, and report all results including null. To better understand the MRI changes associated with CT or ET, more studies explicitly comparing interventions within the same domain (i.e. resistance vs. aerobic) and between domains (i.e. CT vs. ET) are needed.

Keywords: neuroimaging, magnetic resonance imaging, older adults, cognitive training, exercise training

A3.2. Introduction

The population of older adults is increasing worldwide (Bohnert et al., 2015). According to the United Nations, it is projected that nearly 30% of developed countries' populations will be comprised of older adults by 2030 (United Nations, 2020). This presents health care systems and societies with important challenges due to declines in health that occur during the aging process. For example, the aging vascular system undergoes a cascade of changes that negatively affects the cerebrovascular system, leading to decreases in cerebral perfusion (Asllani et al., 2009; Chen et al., 2011; Parkes et al., 2004; Zhang et al., 2017). Given that continuous blood flow is necessary to maintain structural integrity and neuronal activity (Erecińska and Silver, 1989), decreased perfusion has been related to declines in cognition (De Vis et al., 2018; Staffaroni et al., 2019; Xekardaki et al., 2015). Moreover, aging not only impacts cerebral perfusion, but also causes structural (Aljondi et al., 2019; Lockhart and DeCarli, 2014) and functional changes (Sugiura, 2016), which are also related to cognitive decline (Aljondi et al., 2019; Lockhart and DeCarli, 2014). These declines in cognitive functioning tend to be observed most prominently within executive functions, likely due to the fact that the frontal regions of the brain are very susceptible to low cerebral perfusion and are affected early in the course of aging (Cardenas et al., 2011; Moscovitch and Winocur, 1992; West, 1996). Declines in executive functioning can impact working memory, divided attention, episodic memory and processing speed (Cabeza et al., 2016). The declines in executive functions have also been shown to predict memory decline (Carlson et al., 2009), further global cognitive decline (Clark et al., 2012), future functional decline (Johnson et al., 2007), and even increased mortality (Gross et al., 2016).

It is now established that part of age-related cognitive decline and dementia can be reduced, or delayed, through non-pharmacological lifestyle interventions, such as cognitive stimulation, physical exercise, social networking, and control of vascular risk factors, to name a few (Livingston et al., 2020; Montero-Odasso et al., 2020). However, there is still a relative lack of knowledge on *how* lifestyle factors protect against cognitive decline and impact the underlying cerebral structure and function. Among all lifestyle activities known to protect again cognitive

decline, the strong evidence is in favor of physical exercise, and cognitive stimulation (Daffner, 2010). Those two types of interventions tend to be easier to isolate and study in a randomized controlled trial format. Moreover, the primary mechanism of action for these two types of lifestyle interventions have been suggested to be through the enhancement of neuroplasticity. Neuroplasticity refers to the process by which the brain adapts to the impact of age or aging-related chronic diseases such as dementia, through changes in structure, physiology, connectivity and function (Zilles, 1992). Therefore, comparing side by side their impact on MRI outcomes reflecting neuroplasticity would help clarify if, and potentially what, common mechanisms are at work.

CT has been utilized for the enhancement of cognitive functioning, with a large extant literature investigating this subject in older adults alone. CT involves guided practice and feedback that is cognitively challenging, including increasing the difficulty as the program progresses, for an individual on standardized tasks that involve specific cognitive domains such as executive functions, attention, language or memory (Valenzuela and Sachdev, 2009). While there are currently no standardized principles which guide a CT program, there are numerous aspects that are possible to be manipulated to enhance the learning experience of the participants (Schubert et al., 2014). First, the type of parameters that can be modified in a CT program depend on the cognitive function trained. For example, a specific training program aimed at improving working memory, like the n-back, (i.e., single domain) has fewer parameters that can be altered to personalize the training program rather than a general cognitive training program (i.e., multi domain) which targets multiple cognitive functions in the same program (e.g., memory, processing speed, etc.). Despite this, the difficulty of CT can be increased by augmenting the cognitive load or shortening the practice reaction time window. The trained modality can be manipulated or combined. For example, certain CT programs like dual tasking, are combining multiple modalities (i.e., auditory, visual, motor) as part of the training program. Indeed, the dosage and duration of the CT can also play a role with very short programs not being as efficient and potentially very long ones reaching a plateau. Finally, the efficiency of a CT program can be assessed by observing an improved performance in the trained task, a task

that is slightly different (near-transfer) or significantly different (far-transfer) than the trained task (Noack et al., 2014; Schubert et al., 2014).

To date, inconsistencies in brain outcomes measured using magnetic resonance imaging (MRI) have been reported for structural and functional changes after CT in healthy older adults. Thus far, it seems that there are more changes documented within structural as compared to functional outcomes. However, it is generally assumed that CT is capable of improving both structural and functional outcomes in aging (ten Brinke et al., 2017). Furthermore, positive macrostructural changes reported in the literature following CT involve grey matter volume, cortical thickness, and enhanced white matter integrity (Belleville and Bherer, 2012). CT-related functional changes include a decrease in activation in certain areas, posited to indicate a change in neural efficiency (Belleville and Bherer, 2012). However, these findings are not always reproduced, likely due to the heterogeneous nature of the interventions, (i.e., length of intervention; interventional sessions per week; MRI sequences used), making the interpretation of these findings difficult.

ET has also become widely investigated, with several meta-analyses published in the past few years (Falck et al., 2019; Sansano-Nadal et al., 2019; Sherrington et al., 2019). ET refers to utilizing a group of muscles maintained for a period of time with the intent of improving cardiovascular fitness and/or muscular strength, endurance or power in a planned or structured program (Caspersen et al., 1985). It should be noted that ET programs tend to be guided by the FITT principles (Garber et al., 2011), characterized by their frequency (number of weekly sessions); intensity (i.e., % of maximum heart rate or % of heart rate reserve); time (minutes or hours per session per week) and type of training (i.e., aerobic; resistance or flexibility)**.** Seminal work by Colcombe and colleagues (2004) revealed that ET was capable of enhancing functional brain outcomes (Colcombe et al., 2004). More specifically, participants in the ET group showed a significantly increased BOLD signal during a Flanker task in attentional areas of the brain and decreased activation in the anterior cingulate cortex compared to those in a control group. Importantly, ET has been shown to have beneficial effects on structure as well, where it has been illustrated to prevent decline of, and in some cases increase white matter volume (Best et

al., 2015; Bolandzadeh et al., 2015; Colcombe et al., 2006). Notably, at a time of forced confinement, like during the COVID-19 pandemic, several papers have identified the importance of physical exercise for psychological, cognitive and physical health has resurfaced as paramount from a preventive health perspective (Ammar et al., 2020; Besnier et al., 2020; Letieri and Furtado, 2020). It is important to note however, that much like CT, regardless of MRI outcome, the results of ET studies have shown limited reproducibility, again likely explained by the high heterogeneity of the training protocols and type of outcome used to assess changes.

Magnetic resonance imaging (MRI) is now wildly employed to assess age-related cerebral changes in structure and function. MRI is a versatile imaging technique that is able to measure numerous outcomes that are affected by aging, such as grey and white matter volume, connectivity between structures, indicators of myelin integrity, and cerebral blood flow. As individuals age, overall global cerebral volume is reduced, with the most pronounced reductions taking place in the frontal and temporal lobes (DeCarli et al., 2005). In addition to volume, aging has also been associated with a reduced integrity of the white matter tracts, often observed in frontal areas (Park and Reuter-Lorenz, 2009; Salat, 2011). These tract alterations are caused by microstructural white matter changes, in particular decreases to fractional anisotropy, and increases to mean diffusivity, as well as declines to other measures of diffusivity, also often observed in frontal regions (Abe et al., 2002; Hsu et al., 2010; Ota et al., 2006; Salat et al., 2005). These frontal regions also demonstrate the fastest reductions in cerebral blood flow (Pantano et al., 1984; Zhang et al., 2018), but declines in perfusion have also been consistently identified in the temporal and parietal lobes as well (Chen et al., 2011; Gauthier et al., 2013; Parkes et al., 2004).

Several studies have completed systematic reviews investigating the effects of ET on brain structure and functions in healthy older adults (Halloway et al., 2017; Sexton et al., 2016) and one has been published for CT in healthy older adults (ten Brinke et al., 2017). It is evident that CT and ET are capable of enhancing brain structure and function in healthy older adults, yet it is currently not well studied if either modality of lifestyle intervention is superior to the other for improving these outcomes, as only one study to date has compared the effects of ET to a CT

intervention with MRI as the primary outcome (Chapman et al., 2016). More specifically, they found a significant increase in CBF after the CT intervention, whereas the ET group did not demonstrate a statistically significant change. Therefore, more studies directly comparing these lifestyle interventions would allow for further understanding of the relative impact of each training modality on brain health and provide more information about what future training programs should focus on to maximize their cerebral benefits in aging. By further studying CT and ET interventions in isolation, with the use of advanced MRI techniques (Tardif et al., 2016), we can gain a better understanding of their underlying mechanisms of action in isolation. Moreover, although the investigation of other lifestyle interventions that are relevant to cognitive health in aging are warranted, CT and ET have been the most extensively studied in the aging literature, providing a more robust body of literature. Other preventive lifestyle factors known to have a protective effect for cerebral health, such as diet or social networking, tend to often be conducted alongside CT or ET, and are less often isolated and studied in relation to MRI outcomes. Thus, the present review also focused on ET and CT because they can be similar in terms of theoretical framework and experimental approach, meaning that they can be administered in the form of a training program. Moreover, the present review hopes to identify specific training components that might be more successful at predicting MRI enhancements. Thus, allowing us to detect specific training components that might be more effective at improving cognition and perhaps reducing the risk of developing age-related cognitive decline.

Therefore, the purpose of this systematic review is to compare the effects reported in intervention studies involving CT or ET on brain health measured with MRI. Here, we aim to describe the literature encompassing CT *or* ET studies from different aspects of MRI including macrostructural, such as volumetric outcomes of grey and white matter, as well as microstructural, such as diffusion weighted imaging, and functional outcomes, as in task-related BOLD changes, resting state functional connectivity or perfusion differences. That being said, although interventions including a combination of both CT *and* ET do have their merit, it is important to first understand how each intervention, in isolation, is potentially improving cerebrovascular health and cognition in older adults.

A3.3. Methods

A3.3.1. Search strategy

A systematic computer-based search of PubMed-Medline, PsycINFO and EMBASE databases was conducted from June 7th, 2017 until June 12th, 2020. The search included articles that were written in English and included either a CT intervention or ET intervention. CT interventions were included if they involved any of the following (including a combination thereof): executive function, attention, working memory or set shifting. The ET intervention could be any type of intervention that included any form of physical activity such as aerobic, resistance training, dance, yoga and could also be a combination of these types of physical activity.

Search terms included “older adults”, “elderly”, “aging”, “exercise”, “aerobic training”, “resistance training”, “strength training”, “executive function training”. The full search strategy, including MESH terms, used can be found in supplementary material Figure A3.1. Unique search terms were used for each database with the consultation of an academic librarian. We also supplemented database searches with reference lists found in other reviews and of those papers that were included in the review. Dates of inclusion of papers were limited to those published on or before June 12th, 2020. Data was then extracted into covidence.org, a systematic review software for screening, as well as to complete the Cochrane bias component.

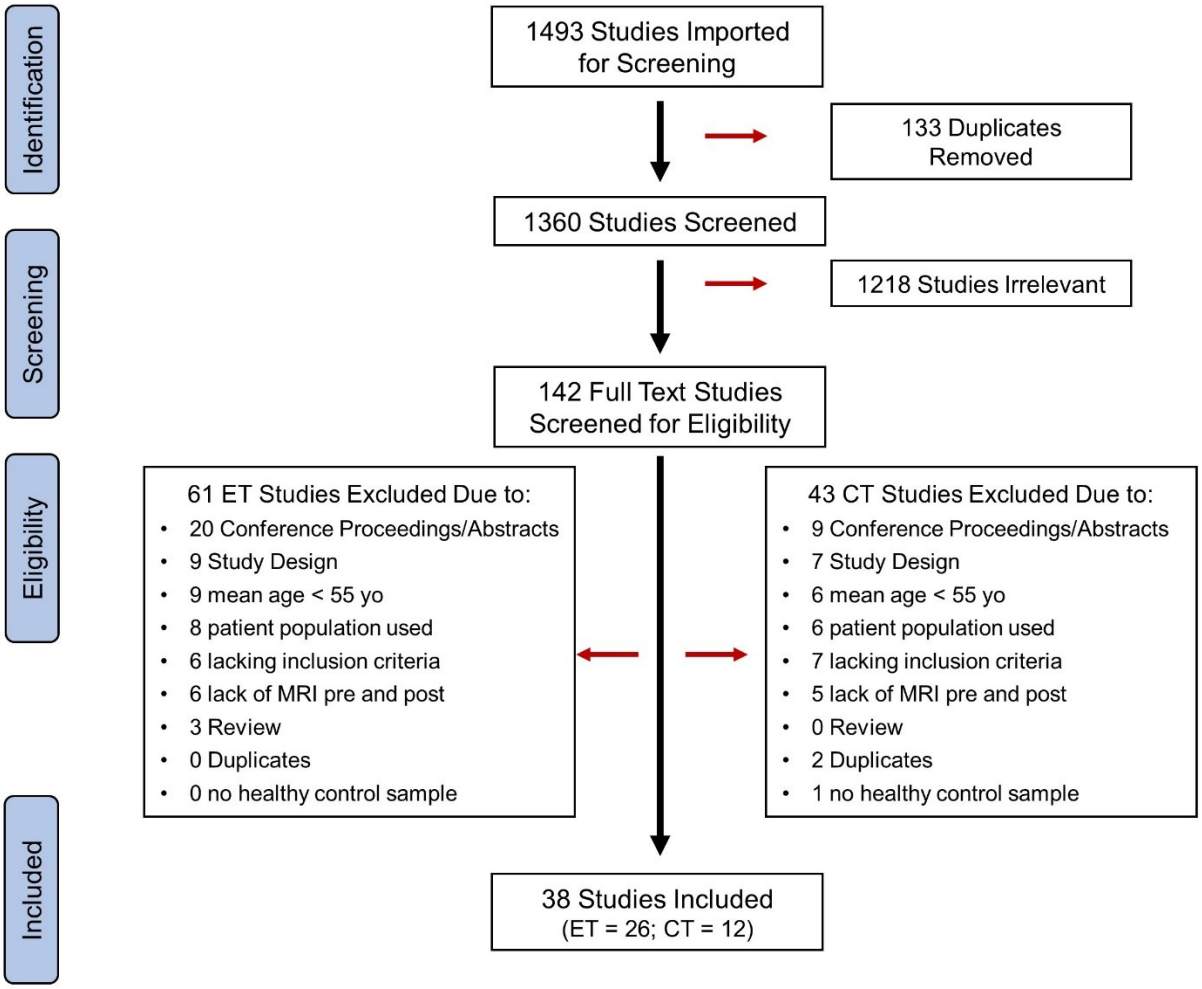

Figure A3. 1. – PRISMA Chart demonstrating the literature search and inclusion/exclusion for the systematic review

A3.3.2. Inclusion and exclusion criteria

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (Shamseer et al., 2015). Articles were included if they investigated the effects of cognitive training, aerobic training, resistance training, or other exercise interventions on the cognitive function of healthy older adults (≥ 55 years of age) with no known cognitive impairment. As many studies included participants 55 years old and over, we set this age criteria to be more inclusive. All studies were also required to include MRI acquisitions before

and after the intervention. Study designs included were randomized controlled trials (RCT's) and quasi-experimental studies.

We excluded studies with participants who had known neurological or motor disorders, such as Alzheimer's disease, Mild Cognitive Impairment, Parkinson's disease, dementia, and multiple sclerosis. Those with cardiovascular risk factors were included (e.g., diabetes, hypertension), but studies with patients suffering from coronary artery disease and heart failure were excluded (excluded studies are listed in figure A3.1.). Other studies excluded were if: the mean age of participants was below 55; it was another review; meta-analyses; abstract for conferences (i.e. conference proceeding); dissertations; or there was no healthy control group that participated in some form of non-intervention, whether that be a passive or active control group.

Finally, it was determined that an intervention could not include a combination of exercise and cognitive interventions in one intervention group. The rationale for this was that the investigation of ET interventions and CT interventions in isolation of each other would provide a more accurate inference for understanding the underlying mechanisms leading to brain enhancements in each intervention. For example, in situations where the ET intervention stated explicitly that they manipulated a cognitive load associated with the ET (e.g. dance movement interventions) then they were excluded as this training would be considered a combination of ET and CT. However, if a study compared the two interventions to each other, without combining them, then they were included. This had an exception in terms of ET, where those studies that included a combination of ET (e.g., aerobic plus resistance training, or resistance training plus balance and flexibility) were still included.

A3.3.3. Selection criteria

Two authors (BI and TV) independently screened articles initially by title and abstract for articles that did not meet the inclusion criteria. The full texts of the remaining studies were then also screened for eligibility. Disagreements were resolved through discussion, and if necessary, included one of our expert authors (see Figure A3.1.). Risk of bias in individual

studies was also assessed independently by the two reviewers using the guidelines outlined in the Cochrane Handbook (Higgins and Green, 2008) which is reported in Table A3.1.

Study	**Random Sequence Generation**	**Allocation Concealment**	**Blinding Participant**	**Blinding trainers**	**Blinding assessors**	**Incomplete Outcome data**	**Selective Reporting**
Best et al., 2015	?	?	?	?	?	-	-
Bolandzadeh et al., 2015	-	-	?	?	-	+	-
Brehmer et al., 2011	-	-	?	?	?	?	-
Chao et al., 2020	+	+	+	?	?	?	-
Chapman et al., 2016	-	?	-	-	?	-	-
Chapman et al., 2015	?	?	?	?	?	-	-
Colcombe et al., 2006	-	+	?	?	?	?	-
de Lange et al., 2016	+	?	?	?	?	+	+
Hampstead et al., 2012	-	-	-	-	-	-	-
Hampstead et al., 2020	-	-	-	-	-	+	+
Heinzel et al., 2017	+	+	+	+	+	?	-

Heinzel et al., 2014	+	+	?	?	?	+	-
Ji et al., 2017	+	?	?	?	?	-	-
Kleemeyer et al., 2016	?	?	?	?	?	-	-
Lovden et al., 2010	+	+	?	?	?	-	-
Maass et al., 2016	-	-	?	?	?	-	+
Maass et al., 2015	-	-	?	?	?	-	+
Muller et al., 2017	-	?	?	?	?	+	+
Niemann et al., 2014	+	?	?	?	?	+	-
Flodin et al., 2017	?	?	?	?	?	-	-
Norcera et al., 2017	?	?	?	?	?	-	-
Motes et al., 2018	?	?	?	?	?	-	-
de Lange et al., 2017	+	?	?	?	?	+	+
Adnan et al., 2017	?	?	-	-	-	-	-
Kim et al., 2017	?	?	?	?	?	-	-

de Lange et al., 2018	+	?	?	?	?	+	-
McGregor et al., 2018	?	?	?	?	?	-	-
Rosano et al., 2017	?	?	+	+	-	+	+
Sexton et al., 2020	-	-	-	-	-	-	-
Shaaban et al., 2019	-	-	-	-	-	+	+
ten Brinke et al., 2015	-	-	+	?	-	-	-
Voelcker Rehage et al., 2011	+	?	?	?	?	+	+
Voss et al., 2013	?	?	?	?	?	?	-
Voss et al., 2010	?	?	?	?	?	?	-
Voss et al., 2019	?	?	?	?	-	+	-
Rehfeld et al., 2017	+	?	?	?	?	?	-
Wu et al., 2018	?	?	?	?	-	-	-

Table A3. 1. – Cochrane Risk of Bias Assessment

Abbreviations: + = high risk of bias was present; - = low risk of bias; ? = risk of bias could not be assessed due to lack of information.

The two authors independently extracted the following information from all included full text journal articles; participant demographics (sample size; mean age, % female, type of population, education, MoCA, MMSE), intervention (length, type, frequency, duration, intensity, adherence rate, dropouts), control (type, adherence rate), physical function outcome measure (reported change), cognitive function measures (reported change), structural outcomes (sequence used, echo time [TE], repetition time [TR], slice thickness, resolution if available otherwise field of view [FOV] and matrix to calculate resolution, volume of slices, flip angle, software use to preprocess and processing of data), structural changes (if present, location, type of change), functional outcomes (sequence used, TE, TR, Slice thickness, resolution or FOV and matrix, volume of slices, flip angle, software to preprocess and processing of data), functional changes (if present, location and type of change), physical function outcome related to imaging measure, and cognitive function outcome related to imaging measure. Any discrepancies in the data extraction (e.g., number of participants for a particular study or type of MRI scanner) were discussed and solved amongst the authors. The primary outcome of interest were the results from MRI, including structural and functional changes. Secondary outcomes included behavioural results of cognitive outcomes within the domains of executive function and attention. Other secondary outcomes included results of exercise training improvement (i.e., VO_2peak, muscle strength, etc.).

A3.3.4. Visualizing of results

MRI regions of interest that were reported to be investigated by each study were individually recorded. The multi-level bootstrap analysis of stable clusters (BASC) atlas (Bellec et al., 2010) was chosen as the standardized brain image to graph results on. Macrostructural and functional data were plotted on different images, as were all the regions for ET and CT studies. Regions for each study were then coded as 1 for increases displayed in red; 2 for decreases which are in blue; and 3 for no change to regions, as shown in yellow. For regions that had disagreements among studies, for example one study observed an increase in hippocampal volume, but another demonstrated no change, these were then coded as a combination of the colors for

increase and no change, with the appropriate weighting (i.e. if 2 found increases and 1 no change, it would be weighted heavier towards the increase [red] color hue). Only those regions that were reported to have one of the three conditions (e.g. increase, decrease, no change) were parcellated and color-coded systematically for both types of interventions in macrostructural and functional outcomes. The reported changes, or lack thereof, were recorded as the within group change from baseline to follow up in the intervention groups. This was completed because only a minority of studies statistically compared the intervention-related MRI change relative to the control group. In-house scripts were created to plot on a standardized brain using Nilearn in Python 3 (Pedregosa et al., 2011).

A3.4. Results

A total of 1493 studies were imported for screening, with 133 being duplicates. Thus, 1360 studies were screened, with 142 of these considered for full-text screening. The final number of papers included in this review is 38 studies. Figure A3.1. shows a flowchart of the studies excluded and rationale for exclusion, as well as those included. A simplified version of all results is presented in Table A3.2. A Cochrane Risk Assessment was completed for all studies included (See Table A3.1.), however due to lack of information for many components of this, we were unable to assess whether studies had high or low risk of specific biases. Figure A3.2. and A3.3. show macrostructural (a) and functional (b) changes in the intervention groups, respectively for CT (Figure A3.2.) and ET (Figure A3.3.), on a standardized brain using the BASC atlas (Bellec et al., 2010)**.**

A3.4.1. Cognitive training

Of the 38 studies included in this paper, a total of 12 were CT interventions. The results are categorized into the following sections: 1) structural outcomes; 2) functional outcomes; 3) correlation between imaging and secondary outcomes. These studies ranged in length of intervention from 2 to 24 weeks, with a range of frequencies (1 to 5 times per week) and time per session (45 to 120 minutes) in those that reported these values (8 studies). Figure A3.2. provides visualization of the changes reported in the intervention group**,** where studies

reported increases, decreases or no change after each intervention in the specific regions of interest, particularly within frontal, parietal and hippocampal regions.

Structural outcomes: A total of eight of the twelve cognitive training studies included structural outcomes, where five reported significant changes and two did not report correlational analyses between the cognitive outcomes and imaging (Hampstead et al., 2012; Lövdén et al., 2010). Overall, the majority of the CT studies found that their control, (i.e., *non*-intervention groups) demonstrated a change, in particular, an increase in mean diffusivity (MD) over time, within the frontal-occipital fasciculus, inferior and superior longitudinal fasciculus and uncinate fasciculus (de Lange et al., 2018, 2017), as well as the genu of the corpus collosum (Lövdén et al., 2010). Furthermore, these studies demonstrated a relative decrease to MD which was related to the CT interventions (de Lange et al., 2018, 2017; Lövdén et al., 2010), although these changes were reported in different areas of the brain for each study, suggesting widespread decreases to MD. Others saw decreases of fractional anisotropy (FA) (Chapman et al., 2015; de Lange et al., 2018, 2017; Lövdén et al., 2010) which was explained as an age-related decline in white matter microstructure. Three of the studies demonstrated an increase in FA due to the intervention (Chapman et al., 2015; de Lange et al., 2018; Lövdén et al., 2010), specifically in the white matter tracts adjacent to the default mode and central executive network (Chapman et al., 2015) and in the areas where a change in MD was identified in the control group (de Lange et al., 2018, 2017; Lövdén et al., 2010). It should be noted, that de Lange and colleagues (2017) found that only the controls (compared to the memory training group), had significant decreases in FA, and increases in MD, and radial diffusivity (RD) throughout the brain including the corticospinal tract, corpus callosum, superior longitudinal fasciculus and the anterior thalamic radiation, following a 10-week intervention (de Lange et al., 2017) .

Functional outcomes: Eight of the studies measured functional MRI outcomes before and after the interventions. Specifically, five studies investigated task-related BOLD changes, one study investigated cerebral blood flow (CBF) (Chapman et al., 2017) and another functional connectivity (Chapman et al., 2015). The in-scanner tasks that were completed included a 3-back task (Heinzel et al., 2017, 2014), a visuospatial working memory task that had two load

conditions (Brehmer et al., 2011), and an object location association memory test (Hampstead et al., 2020). Of those investigating task-related BOLD changes (Table A3.2.; Figure A3.2.b), four demonstrated *decreased* BOLD signal after the interventional period, ranging from two (Hampstead et al., 2020) to four weeks (Heinzel et al., 2017, 2014) and up to five weeks (Brehmer et al., 2011), within the frontal and parietal regions (Brehmer et al., 2011; Heinzel et al., 2017, 2014), as well as decreases within hippocampal regions (Brehmer et al., 2011) and the occipital lobe (Hampstead et al., 2020). In contrast, the other two studies and that by Hampstead et al. (2020) demonstrated increased BOLD signal during a face/scene delayed matching task (Adnan et al., 2017) a multi-source interference task (with two conditions (Kim et al., 2017), and the object location association memory task (Hampstead et al., 2020) in some of the same areas (frontal, parietal and hippocampal) as well as temporal (Hampstead et al., 2020 only) after their two (Hampstead et al., 2020), five (Adnan et al., 2017) and eight-week (Kim et al., 2017) interventions. Chapman and colleagues also found after a 12-week intervention, that there was overall improved connectivity within the default mode network and the central executive network (Chapman et al., 2015). Moreover, Chapman and colleagues found that the CBF in their cognitive group increased 7.9% from pre-testing to the halfway point (6-weeks) and remained at this level until post-testing. They also completed a voxel-wise analysis and found that there was a significant increase in the cognitive group compared to the control group in the left middle temporal, superior medial and inferior frontal gyrus.

Relationship between imaging and cognitive performances: Nine of the twelve studies included statistical analyses to investigate the potential relationship between imaging outcomes and cognitive measures. Microstructural improvements were related to the cognitive outcomes for de Lange and colleagues in multiple articles, (de Lange et al., 2018, 2017, 2016) where negative relationships existed between MD and memory improvements (de Lange et al., 2017, 2016) within the corpus callosum, inferior fronto-occipital fasciculus and anterior thalamic radiation (de Lange et al., 2017). Conversely, those older adults with a frontal FA above the mean FA for young adults were found to have the largest increase in memory performance compared to those older adults with FA below this level (de Lange et al., 2016). In their 2018 paper they found MD at pre-test had a positive relationship with memory, whereas at every time point

onwards, they shared an inverse relationship, indicating a change in microstructure or behavior (de Lange et al., 2018). Yet, others who attempted to relate their cerebral and cognitive outcomes did not find any relationships. For example, Lövdén and colleagues found no correlations between changes in FA or MD with changes in working memory, episodic memory or perceptual speed (Lövdén et al., 2010). This lack of relationship between microstructural and cognitive outcomes was also reported by another group**,** where after a 2-week training intervention, healthy older adults demonstrated no relationship between MRI outcome and cognitive outcomes (Hampstead et al., 2012).

The few groups who reported functional changes with cognitive improvements did have positive findings. In particular, Chapman and colleagues demonstrated that the mean changes in their test of strategic learning and similarities outcomes were correlated with mean changes between groups for CBF in the temporal lobe, anterior and posterior cingulate as well as the superior medial frontal gyrus (Chapman et al., 2015). Finally, performance was related to widespread activity decreases throughout the frontal, parietal, temporal, subcortical and occipital lobes during the working memory condition, where those who had the largest BOLD signal decreases in memory and attention related areas, tended to be those who gained the most from training.

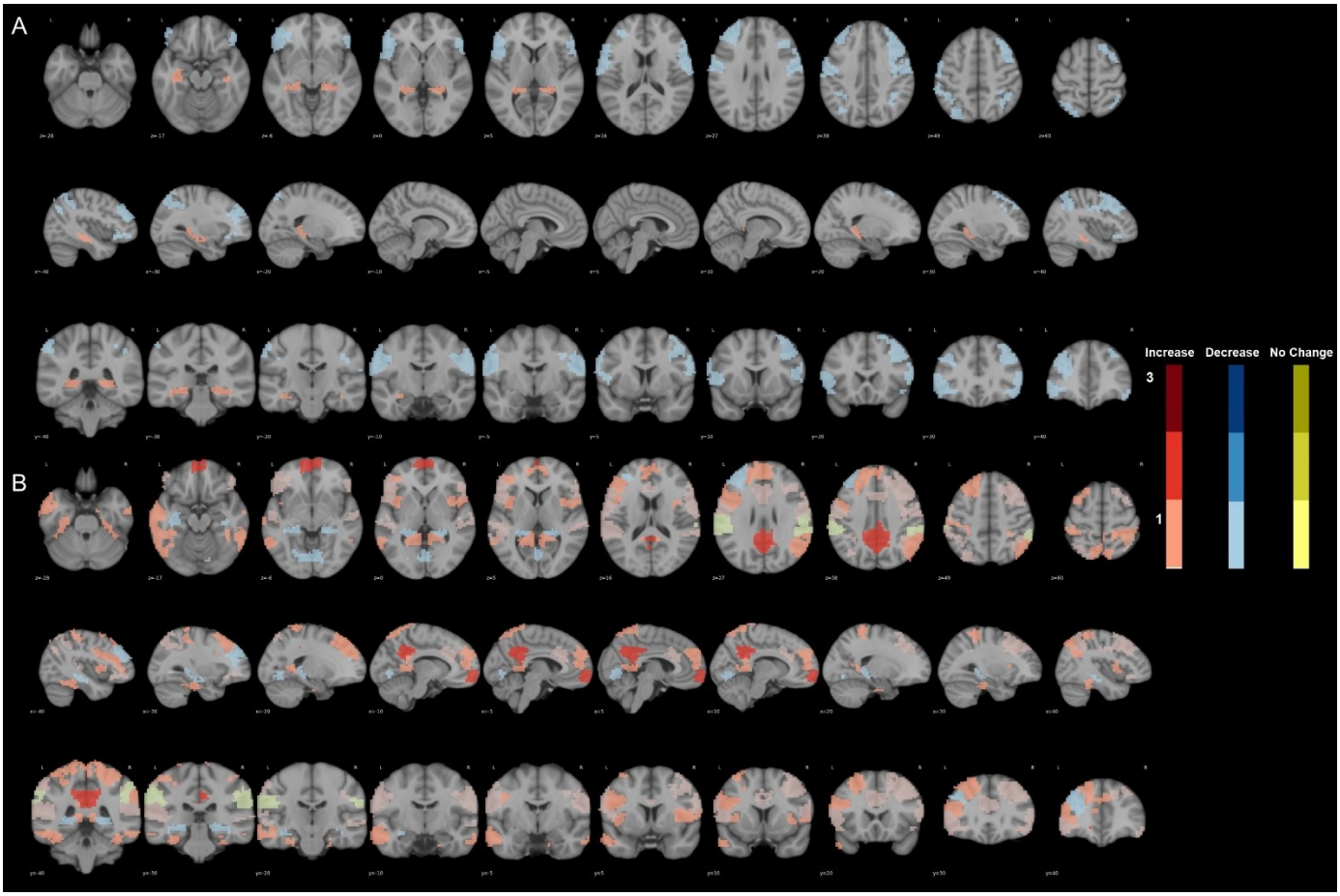

Figure A3. 2. – Standardized brain demonstrating regions where CT studies reported macrostructural and functional changes within the CT groups after the intervention.
Increases in regions within the intervention group are identified in red, where the lightest color represents that one study investigated this region out of all 12 CT studies and found a significant increase. The color's increasing intensity represents a greater number of the 12 studies observing an increase in this region, up to 3 studies which is the most intense, or darkest of all the colors. This same pattern occurred for studies demonstrating decreases, as represented in blue and studies observing no changes as indicated in yellow. For studies that demonstrated differential findings, for example 1 study found an increase and another 1 decrease, the colors for these two intensities were overlaid to provide a combination of those colors. The maximum number of studies reporting the same direction of changes per region was 3, thus, this was set as our threshold. a) Macrostructural regions. b) Functional regions.

A3.4.2. Exercise training

Of the 38 studies included in this review, 26 employed a form of exercise training. In general, these studies varied in length (from six to 135 weeks), range of frequencies (1 time per week to daily) and length per session (10 to 90 minutes) in those that reported these values. See Figure A3.3. for a visualization of the imaging results in the interventional groups of increases (red), decreases (blue), no change (green) or a combination of such, after ET in macrostructural and functional outcomes, which appeared to be spread quite globally throughout the brain.

Structural outcomes: Seminal work by Colcombe and colleagues (2006) reported increased grey matter volume in some frontal and temporal regions as well as the anterior cingulate cortex following an aerobic intervention as can be visualized in Figure A3.3.a (Colcombe et al., 2006). Two other studies observed significant increases to grey matter volume within some of these same regions, particularly the frontal (Ji et al., 2017; Müller et al., 2017), parietal and cerebellar regions (Ji et al., 2017) as well as parahippocampal regions (Müller et al., 2017). As seen in Figure A3.3.a, the increased hippocampal volume was confirmed by numerous studies (Kleemeyer et al., 2016; Müller et al., 2017; Niemann et al., 2014; Rehfeld et al., 2017; Rosano et al., 2010), yet others observed no change to the hippocampus (Maass et al., 2015; Sexton et al., 2020). Moreover, when comparing their resistance training group to control group, Müller's study found no difference (in contrast to their aerobic group) (Müller et al., 2017).

Several groups also investigated changes in white matter volume, lesion load and microstructure. White matter lesion volume was significantly less compared to a control group after a 12 month intervention, but only in those who trained two times per week, not the group who trained once weekly (Bolandzadeh et al., 2015). This same study found that the twice-weekly resistance training group showed a significant decrease in white matter cortical atrophy (the white matter immediately below the cortical grey matter area) at the 2-year follow-up compared to those in the control group, with no differences again between the once weekly and control (Best et al., 2015). Colcombe and colleagues also found a significant increase in

overall white matter volume in their exercise group compared to controls (Colcombe et al., 2006). A recent study, found that their aerobic group did not have worsening white matter hyperintensity grade after the intervention, but that their health education group had an 18.8% worsening of white matter hyperintensities grades (Shaaban et al., 2019). In terms of changes in microstructure, one group found that when there was a significant increase in fitness after the intervention, MD within the hippocampus was decreased (Kleemeyer et al., 2017). Moreover, two groups found no change after their ET intervention for any of the diffusion outcomes (Sexton et al., 2020; Voss et al., 2013).

Finally, one group used more complex MRI outcomes to investigate changes after their 24-month intervention (Shaaban et al., 2019), in particular the identification of cerebral blood vessel tortuosity, length of venules and microbleeds identified by susceptibility-weighted images. They observed that those in the aerobic intervention had a significant increase in the percentage of straight venous length from baseline to 24 months, and the tortuosity ratio declined from baseline to follow-up by 33.2% compared to the control group. However, this was not statistically different. It was also found that both the aerobic group and the control group over the two-year intervention had a significant increase in microbleed count, but it was not statistically different between the two groups.

Functional outcomes: Five groups investigated functional connectivity, four of which found increased connectivity within the default mode and central executive networks (Chao et al., 2020; McGregor et al., 2018; Voss, 2010; Voss et al., 2013). In another study by Voss and colleagues, they did not find a significant change within the default mode network, or any of the other three networks investigated (Voss et al., 2019b). The four studies that investigated task-related BOLD signal changes all used varying in-scanner tasks: a number Stroop hybrid task (Wu et al., 2018), a Flanker task (Voelcker-Rehage et al., 2011), Digit-Symbol Verification task (Motes et al., 2018) and a semantic verbal fluency task (Nocera et al., 2017). Of these four, two found increased BOLD signal activation within frontal (Voelcker-Rehage et al., 2011; Wu et al., 2018), and one in parietal and thalamic areas after coordination training (Voelcker-Rehage et al., 2011). On the other hand, Voelcker-Rehage and colleagues found that their aerobic training

group demonstrated decreased BOLD signal change within frontal and temporal regions, a finding that was also observed by Nocera et al. (2017) using a different task (semantic verbal fluency)(Nocera et al., 2017). These discrepancies, as well as lack of BOLD-task related change (Motes et al., 2018) can be visualized in Figure A3.3.b.

Some studies investigated changes in more fundamental physiological and signal properties. A 6-week daily Wii exercise program demonstrated a decrease in amplitude low frequency fluctuations (ALFF) and regional homogeneity within the precuneus cortex, whereas increases were found in subcortical structures(Ji et al., 2017). Finally, after a 12-week aerobic intervention Maass and colleagues found that there was a significant increase in cerebral blood flow and volume within the hippocampus compared to the control group (Maass et al., 2016, 2015). Of the four studies that investigated perfusion changes (Chapman et al., 2015; Flodin et al., 2017; Maass et al., 2015; Motes et al., 2018), only one group reported changes to perfusion, specifically a within group analysis found increases in resting cerebral blood flow and cerebral blood volume within the hippocampus after ET as indicated in red in Figure A3.3.b (Maass et al., 2016, 2015).

Relationship between imaging and secondary outcomes: Out of the 26 studies on ET, 13 reported the relationship between the imaging outcome and changes to fitness or a physical activity improvement. Specifically, groups found that greater fitness after the intervention was associated with increased prefrontal and temporal FA (Voss et al., 2013), lower MD (Kleemeyer et al., 2017), and increased connectivity between the default mode network and the frontal pole (Flodin et al., 2017). Yet, another group found that the changes in connectivity were not related to changes in fitness (i.e. VO_2max) but were associated with percentage of time spent in higher heart rate zones. Rosano and colleagues found that those who attended a greater number of sessions over two years had a significantly increased hippocampal volume (Rosano et al., 2017). Whereas, another study discovered that a maintenance in gait speed was associated with decreased white matter lesions (Bolandzadeh et al., 2015). In terms of functional outcomes and fitness, higher VO_2max was found to be related to decreased BOLD activation throughout frontal and temporal lobes, during a Flanker task, in the aerobic group,

whereas in the control group there was increased activation related to decreased VO_2max (Niemann et al., 2014). Conversely, others found that increased VO_2max was related to greater BOLD activity during a semantic verbal memory task, within frontal regions (Nocera et al., 2017). Flodin and colleagues (2017) found that BOLD signal variability was negatively correlated with VO_2max, as was the ALFF (Flodin et al., 2017). Finally, another group, reporting in two articles, found no significant relationships between hippocampal subfields and balance (Müller et al., 2017; Rehfeld et al., 2017), whereas Sexton and colleagues found that the change in fitness was not associated with hippocampal volumes, global FA, AD or RD (Sexton et al., 2020).

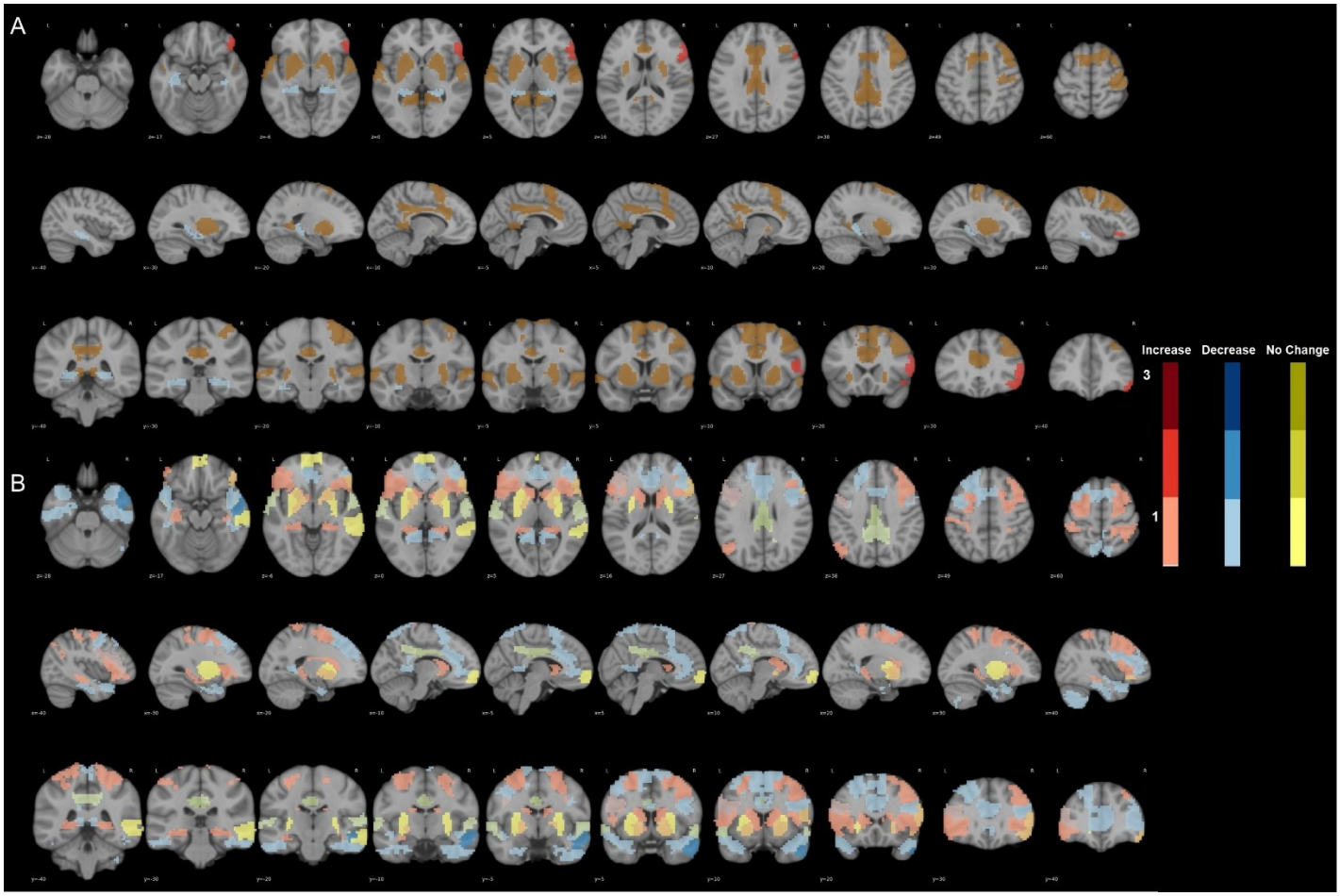

Figure A3. 3. – Standardized brain demonstrating regions where ET studies reported macrostructural and functional changes after the ET group intervention.

Increases within regions within the intervention group are identified in red, where the lightest color represents that one study investigated this region out of all 26 ET studies and found a

significant increase. The color's increasing intensity represents a greater number of the 26 studies observing an increase in this region, up to 3 studies which is the most intense, or darkest of all the colors. This same pattern occurred for studies demonstrating decreases, as represented in blue and studies observing no changes as indicated in yellow. If studies that demonstrated differential findings, for example 1 study found an increase and another 1 decrease, the colors for these two intensities were overlaid to provide a combination of those colors. The maximum number of studies reporting the same direction of changes per region was 3, thus, this was set as our threshold. a) Macrostructural regions. b) Functional regions.

A3.4.3. Comparison of cognitive and exercise interventions

One study, reported in two articles (Chapman et al., 2016; Motes et al., 2018) compared a cognitive to an aerobic intervention and a wait-listed group (Motes et al., 2018). Specifically, in their 2016 article, Chapman and colleagues reported that the cognitive training group increased global cerebral blood flow by 7.9% at the halfway mark of the intervention (6-weeks) and maintained this CBF increase at the end of the intervention within frontal areas, whereas those in the aerobic group did not significantly increase their CBF, although the percent change was not reported (Chapman et al., 2016). Neither group demonstrated significant changes to cerebrovascular reactivity after the interventions. In their follow-up study, they found no significant task-related BOLD signal change after either intervention, however when investigating the reaction-time related coefficients during the task, they found those in the cognitive training had faster reaction times that were associated with less BOLD signal change, whereas the aerobic and waiting-list group demonstrated a decrease in the association between the reaction time and BOLD signal change.

Study	GMV	WM	DWI	BOLD	CBF	Connectivity
COGNITIVE TRAINING						

Chapman et al., 2015			↑		↑	↑
de Lange et al., 2017			↔			
de Lange et al., 2018			↓ MD, RD, AD ↑ FA			
Lovden et al., 2010			↓MD ↑FA			
Heinzel et al., 2014	↔			↓		↔
Heinzel et al., 2017				↓		
de Lange et al., 2016						
Adnan et al., 2017				↑		
Brehmer et al., 2011				↓		
Hampstead et al., 2012	↔	↔				
Chapman et al., 2016					↑	
Kim et al., 2017				↑		
Hampstead et al., 2020				↑ and ↓		
EXERCISE TRAINING						

Motes et al., 2018				↑	↔	
Chapman et al., 2016					↔	
Voss et al., 2013						↑
Voss et al., 2010						↑
Rehfeld et al., 2017	↑	↑				
McGregor et al., 2018						↑
Wu et al., 2018				↑		
Kleemeyer et al., 2016	↑		↑ MD			
Voelcker-Rehage et al., 2011				↓aerobic ↑coordination		
Rosano et al., 2017	↑					
Norcera et al., 2017				↓		
Muller et al., 2017	↑					
ten Brinke et al., 2015	↑aerobic ↔ resistance					
Bolanzadeh et al., 2015		↓WML				
Best et al., 2015		↓WM atrophy				

Colcombe et al., 2006	↑					
Flodin et al., 2017				↔	↔	
Ji et al., 2017	↑					
Maass et al., 2015	↔				↑	
Maass et al., 2016						
Niemann et al., 2014	↑					
Chao et al., 2020						↑
Sexton et al., 2020	↔	↔	↔			
Shaaban et al., 2019		↓ WMH grade				
Voss et al., 2019			↔			

Table A3. 2. – Simple MRI Results

Simple table demonstrating if studies (separated into CT and ET) observed changes to magnetic resonance imaging outcomes after each intervention. A blank cell represents that this outcome was not measured in this study; "↑" demonstrated an increase to said outcome; "↓" decrease to that outcome after the intervention; "↔" dictates no change observed after the intervention. GMV= grey matter volume; WM= white matter: DWI= diffusion-weighted imaging; BOLD = blood oxygenated level dependent signal; CBF=cerebral blood flow; MD= mean diffusivity; RD = radial diffusivity; AD: axial diffusivity; FA = fractional anisotropy; WML= white matter lesions.

A3.5. Discussion

A3.5.1. Summary

We aimed to investigate the effect that two different lifestyle interventions, CT and ET, have on the cerebral structure and function of healthy older adults. In general, the literature thus far can be viewed with cautious optimism. The results of this review demonstrate a mixed picture of *how* and, in some cases, *if* some forms of lifestyle interventions influence brain structure and function, as can be seen in Figures A3.2. and A3.3. It's important to note however that there was significant heterogeneity in the findings among studies, which could partially reflect the variability in outcomes utilized (e.g., resting state fMRI versus perfusion versus voxel-based morphometry), with little overlap between studies for imaging technique employed, especially for CT versus ET. Nevertheless, it was possible to identify some patterns across studies, such as improvements to white matter microstructure after CT interventions, macrostructural enhancements post ET studies and both forms of interventions associated with changes in the BOLD signal. Generally, although the studies reported in this review differed greatly on several parameters, CT studies tended to be shorter in length than ET, ranging from 2 to 24 weeks with 5 to 36 sessions which were 25 to 60 minutes in length each session. Conversely, ET studies were conducted over a 6 to 72-week intervention period, ranging from once a week to weekly sessions that were from 10 minutes to 90 minutes in length per session.

A3.5.2. Effects of CT on structural outcomes

Notably, only two CT studies investigated the effects on structural outcomes where neither found a significant change to grey matter volume, or white matter volume (Hampstead et al., 2012; Heinzel et al., 2014). Interestingly, of the twelve CT studies included in this review, the majority reported that T1 sequences were acquired for registration purposes only (Adnan et al., 2017; Brehmer et al., 2011; Chapman et al., 2015, 2016; Hampstead et al., 2020; Heinzel et al., 2017; Kim et al., 2017; Lövdén et al., 2010). Therefore, the images necessary to investigate volumetric outcomes are being collected but volumetric results are not being reported. This could potentially be due to null findings, or to the data not being analyzed. More studies

reporting volumetric findings, null or otherwise, are needed to conclude whether CT has the potential to change tissue macrostructure.

Four diffusion-weighted imaging (DWI) studies reported positive outcomes in the interventional groups compared to individuals in control groups. More specifically, increased fractional anisotropy (FA) for the interventional group was reported (Chapman et al., 2015; Lövdén et al., 2010), with decreased FA in the control group (de Lange et al., 2018, 2017, 2016). These studies demonstrate the normal trends of aging over interventional periods within the controls and that during this time, CT interventions likely maintain or improve DWI outcomes. In other words, the CT intervention is seemingly able to ward off age-related brain decline in white matter tracts or at least maintain their integrity, which was perhaps most eloquently revealed by de Lange and colleagues (de Lange et al., 2018). In this study, periods of rest were interspersed in between interventional periods, where FA and MD were observed to be improved in the intervention group as compared to the control group (which showed a time-dependent decrease in FA and increase in MD) during the interventional periods and the opposite during rest periods**.** Thus, exhibiting the potential specificity of CT on white matter microstructural integrity.

A3.5.3. Effects of CT on functional outcomes

The functional outcomes for CT are seemingly more promising in terms of beneficial changes. These enhancements were seen as changes in the BOLD signal, although the directionality of change was inconsistent across studies. For example, Hampstead et al., 2020 demonstrated an *increase* to BOLD signal activation during an episodic memory task within the prefrontal areas. Whereas, during working memory tasks BOLD signal activation was reported to *decrease* in the dorsolateral prefrontal cortex, (Brehmer et al., 2011; Heinzel et al., 2017, 2014). Some groups observed *increased* BOLD signal during attentional tasks, within frontal and parietal areas (Adnan et al., 2017; Kim et al., 2017). The differences in directionality of the signal changes could be due to the type cognitive task (i.e., working memory versus episodic memory versus attentional) or the varying number of intervention sessions completed for each study; leading to the debate of increased resources (potentially associated with increased BOLD signal) or

increased efficiency (potentially associated with decreased BOLD signal). Conversely, the answer could lie within the nature of the BOLD signal, which is known to be physiologically ambiguous, and represents a change from an unknown baseline (Gauthier and Fan, 2018). Thus, it is not possible to interpret these changes in terms of underlying neural resources directly. For this to be a possibility, studies need to include other vascular or metabolic outcomes that are known to determine subcomponents of the BOLD signal, such as CBF or the cerebral metabolic rate of oxygen consumption (Gauthier and Fan, 2018; Tardif et al., 2016).

Importantly, one group (disseminated in two studies) investigated resting CBF and found that perfusion was increased after CT within the frontal lobe and cingulate cortex (Chapman et al., 2015, 2016). They also demonstrated increased functional connectivity within the default mode and central executive network (Chapman et al., 2015). An extension of this study (Motes et al., 2018), reported BOLD signal increases after a digit span verification test in the CT group within the prefrontal cortex, a region demonstrating increased resting CBF in their earlier study (Chapman et al., 2016). Therefore, one could postulate that increases in resting CBF and BOLD signal in the same region indicates that these changes could be due to a combination of vascular or metabolic properties (potentially including, but not limited to neuronal resources). Interestingly, resting CBF was increased but not CVR, consistent with the recruitment of more resources (i.e., BOLD signal is increased, but not vasodilatory potential per se). Thus, it is possible to conclude in this case, that there are likely more resources (versus increased efficiency) recruited after this form of CT, indicating the utility of groups using *multiple* functional sequences in one study (i.e., BOLD, CBF and CVR).

Although half of the CT studies did find functional changes, five did not report changes However, the studies not reporting changes tended to have a shorter length of intervention and the number of total sessions, with the exception of Lövdén and colleagues, yet it is not clear how many weeks the 101 sessions were completed in (Lövdén et al., 2010). A potential explanation for lack of functional BOLD signal changes is that there were no transfer effects following CT, only improvements on the trained task, indicating a learning effect only.

A3.5.4. Effects of ET on structural outcomes

Notably, ET studies reported a greater number of changes to structural outcomes than CT. All the studies that reported structural improvements were at least 16 weeks in length, except for Ji et al., 2017 whose intervention length was only 6 weeks, but was *daily*, potentially demonstrating that for structural changes to occur, a specific volume of ET is required (Chao et al., 2020; Ji et al., 2017; Kleemeyer et al., 2017; Müller et al., 2017; Niemann et al., 2014; Rehfeld et al., 2017, 2017; ten Brinke et al., 2015). This is further confirmed by studies observing no changes to hippocampal volume (Maass et al., 2015; Sexton et al., 2020), grey or white matter volume as well as DWI outcomes (Sexton et al., 2020) after 12-week, three times weekly, interventions. This could be extended to the lack of volumetric changes reported in CT studies, as CT interventions tended to be shorter in length and overall volume of intervention. (volume = length of intervention [total number of weeks] x frequency of sessions [times / week] x length of each session [minutes / session]). This remains to be demonstrated conclusively however since not all studies reported the necessary outcomes for dosage to be calculated and accounted for**.** It is also possible that studies that did not report changes (including CT) are, in part, due to the standard MRI techniques employed with 3T MRI, which may not have been sensitive enough to detect small changes (microlevel) that are occurring during shorter time periods. Thus, it is possible that larger changes to structure need to occur before it can be detected using MRI volumetry at the voxel size typically used. Finally, changes to grey matter volume, or lack thereof, should be interpreted with caution as it is not physiologically specific and can represent an array of changes at this level (i.e., angiogenesis, gliogenesis, neurogenesis).(Tardif et al., 2017, 2016)

Importantly, a decreased presence of white matter lesions and atrophy, compared to a control group over a two-year time period was also observed (Bolandzadeh et al., 2015). Others employing ET for two years found that the aerobic group maintained their white matter hyperintensity gradings, but those in the control group demonstrated a 20% grading deterioration (Shaaban et al., 2019). Those investigating changes to DWI outcomes after a 26 week ET intervention, found MD was significantly decreased in the hippocampus (grey matter

structure) after the intervention (Kleemeyer et al., 2016), which might be driven by different physiological processes than the decreases to MD found in white matter after CT. Yet others, found no changes to DWI outcomes after their 12-week intervention, again possibly indicating that there is a minimal volume of ET necessary to induce changes (Sexton et al., 2020). Taken together, results from the above studies demonstrate that ET can maintain cerebral white matter structure, potentially through the prevention of age-related vascular decline in the white matter.

Surprisingly, most ET studies did not report measuring white matter microstructural outcomes. It is well documented that cerebral white matter is vulnerable to vascular changes, such as changing cerebral blood flow (Bahrani et al., 2017; Giezendanner et al., 2016; Pantoni Leonardo et al., 1996). Furthermore, a recent review (Badji et al., 2019), identified that white matter changes were consistently associated with arterial stiffness. Thus, presenting a unique opportunity to those investigating ET to target plasticity within white matter microstructure in response to the vascular changes (i.e., decreased arterial stiffness) that tend to occur after exercise (Seals et al., 2019). It is likely that if studies investigated white matter, improvements after ET would be found alongside CBF increases. This is further highlighted by novel work demonstrating ET promoted cerebral small vein integrity (Shaaban et al., 2019), which, the authors speculate may suggest that ET promote endothelial functioning and an increase of nitric oxide through the maintenance of shear stress and CBF, thereby contributing to maintain the health of vessels. Thus, it would be valuable for future studies to assess white matter outcomes, including DWI, to clarify if ET can enhance white matter micro and macrostructure given that ET interventions seem to enhance vasculature at the micro and macro levels.

A3.5.5. Effects of ET on functional outcomes

Four of the exercise studies investigated task-related BOLD signal changes. Much like the task-related BOLD changes after CT training, the results were heterogeneous, likely due to the differing in-scanner task (i.e., response inhibition; processing speed; verbal ability and/or executive control). However, one group found intriguing results demonstrating that the change to the BOLD signal and the corresponding brain location could be dependent on the mode of ET

(i.e., aerobic versus coordinative training) (Voelcker-Rehage et al., 2011). Specifically, the aerobic group showed *decreased* BOLD activation compared to the controls, within frontal (superior and middle) and temporal regions, whereas those in coordination training demonstrated *increased* activation within frontal (inferior) and parietal regions. These directions of BOLD signal findings in specific regions was replicated by later work, that found decreased BOLD signal in the temporal regions after aerobic training, and increased BOLD signal in the frontal (inferior) regions after coordinative exercising (Nocera et al., 2017). Though not compared in the same study, the middle frontal gyrus demonstrated these same trends, with decreased BOLD signal activity after aerobic training in one group, (Voelcker-Rehage et al., 2011) but increased BOLD signal activity following a Tai Chi intervention, which is a form of coordinative exercise (Wu et al., 2018). Therefore, it would be useful for future work to not only compare to a control group, but among exercise training modalities to identify how each type of exercise can influence the brain and if this is region-specific.

Of the four studies that included perfusion, only one found significant changes after the intervention (Maass et al., 2016, 2015). Aerobic ET (the intervention used in all four of these studies), is employed to, primarily, improve the cardiovascular system and is thought to have generally beneficial vascular effects. Given this known enhancement to the peripheral vasculature, it has been hypothesized that these benefits should also extend to the cerebral vasculature (Barnes and Corkery, 2018). Thus, the lack of results in changes to perfusion is quite surprising yet, can be explained by a few rationales. Firstly, perfusion changes could be taking place earlier on in the course of the interventions. However, Chapman and colleagues (2016) acquired an MRI halfway through their intervention and did not find a statistically different change in perfusion for the ET compared to the CT, although if there was any change *within* the ET group, this was not indicated (Chapman et al., 2016). These results reveal that ET might not induce enhancements to perfusion but could still be associated with a maintenance effect, preventing decline to CBF. However, no study to date has measured perfusion changes after ET that has been longer than 12 weeks, making it difficult to conclude if only maintenance occurs, or if changes to the cerebrovascular system require more time to transpire. Conversely, previous work has indicated that macrostructural changes can occur without alterations to

functional outcomes (Chen et al., 2011), introducing the possibility that ET is perhaps capable of causing structural changes more so than perfusion changes. Finally, it could be that given the low SNR of ASL and its' generally low spatial resolution, it is not able to appropriately capture subtle changes that occur within 12 weeks of an ET intervention.

This low SNR of ASL can be overcome with the use of contrast agents such as gadolinium. Maass and colleagues used this approach to investigate cerebral blood flow and cerebral blood volume in the hippocampi (Maass et al., 2015). They sub-divided their sample into old and younger older adults and found that those who were considered younger had increased hippocampal perfusion after the intervention, whereas those who were older had a decrease in perfusion compared to baseline. Thus, this final study might indicate that the effect of ET on the vasculature may be dependent on age. It is possible that from a biological standpoint, older adults have decreased ability to initiate the plasticity response, such as angiogenesis for example, initiated by exercise.

A3.5.6. The relationship between behavioural and MRI outcomes

Roughly half of the CT studies demonstrated associations between cognitive improvement and changes to imaging outcomes. This suggests that the changes between the two are not linearly linked due to one outcome potentially having a plateau at some point, and the other outcome continuing to change. On the other hand, it is possible that perhaps training protocols need to be longer in order to detect a direct association between the two. It could also be the case, as it was with ET for structural enhancements, that the relationship between cognitive and MRI outcomes is modality dependent. Importantly Chapman et al. (2016) found that increased CBF was related to increased cognition after their CT intervention, thus providing a window into an underlying physiological mechanism of *how* CT improves cognition in healthy aging. Moreover, one group found that individuals with higher FA prior to the CT intervention were those who had greater improvements in memory at the end of the intervention, indicating that more resources to begin with might allow for greater improvements to cognition (de Lange et al., 2016). Contrary to this, 10 of the 12 ET studies that reported relationships between the fitness outcome and MRI, indicated a change in fitness was related to a change in an imaging outcome.

Suggesting that if an intervention has a sufficient dose to change fitness, it could be that the dose of the intervention is then also enough to cause these cerebral enhancements.

A3.5.7. Comparison of CT and ET studies

Given the heterogeneity of the length and design of the CT and ET studies, as well as the varying MRI outcomes that were measured before and after the interventions, it is difficult to make any solid conclusions when comparing the two. In particular, there were few overlapping MRI outcomes reported for the two forms of interventions. Yet, of those that were, it seems that both CT and ET interventions can influence the BOLD signal during a task-related outcome, specifically within the frontal, parietal and temporal lobes, with both demonstrating increases and decreases to the signal, respectively. Perfusion changes and enhancements to the white matter microstructure were observed predominantly in CT interventions, with only one study reporting these types of outcomes for the ET interventions. Conversely, ET studies tended to report more enhancements to connectivity and macrostructural outcomes (e.g., grey and white matter integrity), although it is unclear if this is due to lack of investigation from the CT studies or reporting bias. Future studies should aim to explicitly compare ET to CT in the same study with MRI at pre and post intervention to identify if there are potential synergistic effects on cerebral health in older adults.

A3.6. Limitations

The studies included in this systematic review were highly heterogenous, in many aspects previously discussed but also in the moderators that were included as covariates. A limitation to this review is that moderators could not be formally evaluated. It should be noted that in many instances, moderators such as sex, age, and cognitive status, were included as covariates in statistical models. In order to further disentangle these relationships between lifestyle interventions and brain outcomes, it is imperative that future work attempt to disaggregate this data a priori (i.e., males versus females; younger versus old older adults) to identify what other factors could be influencing the effects that ET or CT has on cerebral health.

Furthermore, while we included studies that had a control group present, whether they were active or passive, the nature of the control group could influence results. The use of active only control groups is superior to passive only, as it allows to control for all interventional confounding factors (e.g., social interaction, time exposure, etc.) and better isolates the effect of the intervention itself. Seven of the CT studies had active controls (with three of them being from the same study), whereas all but three of the ET studies *had* an active control, making it unclear for the CT studies if the improvements were due to the intervention itself, or due to social interaction. However, some of the CT studies in this review were better able to capture the natural decline associated with aging through the use of passive control groups. In turn, this allowed for a more nuanced examination of maintenance versus increased resources due to the intervention. Studies including only an active control group were maybe less able to capture this difference. Thus, ET studies should also include a passive group, or even within the active groups, to plot what the actual decline is when they are not in a true intervention. This is particularly relevant for variables such as CBF which is known to decline by 0.35% per year over the lifespan, whereas GMV declines approximately 0.85% annually (Chen et al., 2011).

Of note, only one study (Chapman et al., 2016; Motes et al., 2018), directly compared a CT intervention to an ET intervention, both of the same length, time per session, and number of sessions. Future work should aim to replicate this form of study design to attempt to disentangle specifically the underlying mechanisms for improving cerebral health of each type of intervention.

A3.7. Conclusion: future directions and recommendations

In conclusion, our systematic review provides evidence to support that participation in CT or ET intervention provides benefits to cerebral health in aging, which tend to extend to behavioural cognitive outcomes. These observations suggest that CT and ET interventions are promising means to enhance and maintain cognition, and to prevent cognitive decline associated with aging. Yet, there are potential approaches that would advance this area of study much more effectively by probing the mechanisms behind the improvement of cerebral health after either a CT or ET intervention.

From a structural standpoint this review shows that: i) CT interventions either do not see changes to structure unless they are at least 10 weeks in length; ii) they are not reporting volumetric changes as they are either not being measured or not being reported due to null results. If the latter is the case, it is suggested that these results are reported despite being null, to enable a better understanding of the impact of CT on brain health. For example, if it is true that CT does not find volumetric changes but does find changes to FA and MD, based on their mechanisms of change, it would be indicative that either neuronal process remodeling or myelination were occurring, rather than neurogenesis for example. Furthermore, it is suggested that studies begin to use measures that are more sensitive to microstructural changes, such as myelination. Thus, sequences such as quantitative T1 outcomes, fractional anisotropy and magnetization transfer should be employed to further investigate the microstructure of white matter, where more subtle changes might be occurring over shorter periods of time. On the other hand, volumetric changes occurred in many of the ET studies. The underlying mechanisms of plasticity that are associated with volumetric changes (Tardif et al., 2016) such as angiogenesis, synaptogenesis, and neurogenesis, have all unsurprisingly been associated with ET interventions in animals**.** Although insufficient evidence exists at this point, this review would suggest, that based on the studies presented here in older adults, aerobic training might be more capable of enhancing grey matter volume, whereas resistance training seems to have a greater effect on white matter volume. Others have also suggested that there are modality unique alterations to cerebral outcomes (Montero-Odasso et al., 2018; Stillman et al., 2020) due to the potentially different underlying physiological mechanisms induced by each ET type (see (see Herold et al., 2019; Voss et al., 2011 for in-depth reviews). However, there is currently insufficient evidence to assess these effects. Future work should compare unique ET modalities with multi-modal imaging across the lifespan to investigate if this is the case.

In terms of functional changes, it seems as though BOLD changes can occur within as little as four weeks, though the underlying meaning of these changes are ambiguous unless studies measure other vascular outcomes as well, such as CBF (Gauthier and Fan, 2018). In fact, it is suggested that calibrated fMRI be employed, as it presents a unique opportunity to disentangle if changes that are occurring are more metabolic or vascular in nature. Calibrated fMRI is a

technique able to separate the BOLD signal into its vascular and metabolic sub-components, allowing a better appreciation of whether the changes observed after an intervention are more linked to changes in the vasculature, or neuronal resources and metabolic efficiency.

Moreover, as many of the changes observed following ET seem to be localized in the hippocampi, future studies should pay particular attention to the structure of the hippocampus, as well as its vascular measures to identify which component is changing, (i.e. is it more cerebral blood volume, or cerebral blood flow, etc.) (Erickson et al., 2009; Maass et al., 2015; Voss et al., 2019a). By furthering this understanding, we will be able to uncover the underlying mechanism and better understand *why* the hippocampus and memory improve after ET interventions. Furthermore, this could extend to the Alzheimer Disease and Dementia literature to give us an indication as to why ET seems to be able to slow the disease-related cognitive decline once it is already present (Bherer et al., 2013). In the same token, it is also suggested that future work attempt not only region of interest analyses (as is the case with the hippocampus) but should also employ voxel-wise/whole brain approaches, to investigate the effects of ET on the whole brain.

Furthermore, work by Chen et al. (2011) indicates the importance of studies collecting and *reporting* on more than one form of MRI outcome, including non-significant outcomes. This would provide the literature with a more robust body of data (i.e., GMV, connectivity, and perfusion). Moreover, to better assess reliability of findings, future studies should aim at better reporting design, outcomes, interventions, and statistical analyses, according to the Cochrane Collaboration's tool for assessing risk of biases.

Overall, the heterogeneity in the implementation of the interventions and outcome measures renders interpretation of the results somewhat tentative. However, given the positive outcomes that generally were identified by each form of intervention, a combination of both CT and ET would likely be ideal to target specific pathways that are impacted in aging, but also to enhance global brain health. It is imperative to first better understand how CT and ET, in isolation, are potentially improving cerebrovascular health and cognition in older adults to be able to efficiently couple the magnitude of their enhancements.

A3.8. Funding

This work was supported by: Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal student scholarship (BI); Fonds Nature et Technologies (JH); Henry J.M. Barnett Heart and Stroke Foundation New Investigator Award (CJG); Michal and Renata Hornstein Chair in Cardiovascular Imaging (CJG); Mirella and Lino Saputo Research Chair in Cardiovascular Health and the Prevention of Cognitive Decline from the Universite de Montreal at the Montreal Heart Institute (LB).

A3.9. Author contributions

Brittany Intzandt contributed to conceptualization; methodology; validation; formal analysis; investigation; data curation; writing of the original draft as well as reviewing and editing; project administration.

Tudor Vrinceanu contributed to methodology; validation; data curation; formal analysis; investigation; writing of original draft and reviewing and editing.

Julia Huck contributed to methodology; validation; formal analysis; writing – review and editing.

Thomas Vincent contributed to methodology; data curation; writing – reviewing and editing.

Dr Manuel Montero-Odasso contributed to validation; writing - review and editing; supervision.

Claudine J Gauthier contributed to conceptualization; methodology; formal analysis; writing – original draft and reviewing and editing; supervision.

Louis Bherer contributed to conceptualization; methodology; formal analysis; investigation writing – original draft and reviewing and editing; supervision.

A3.10. References

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Appendix 4 – List of publications

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