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NEURAL MECHANISMS UNDERLYING PROCESSING SPEED IN HEALTHY OLDER ADULTS

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Mecanismos neurais subjacentes à velocidade de processamento em adultos idosos saudáveis

A velocidade de processamento corresponde ao tempo necessário para processar uma certa quantidade de informação. Durante o processo de envelhecimento cognitivo é característico o aparecimento de défices ao nível desta capacidade cognitiva. Por essa razão, um maior entendimento dos mecanismos neurais que estão subjacentes à velocidade de processamento em adultos idosos poderá facilitar a compreensão do processo de envelhecimento e o desenvolvimento de estratégias terapêuticas que visem retardá-lo ou atenuá-lo. Posto isto, o presente estudo propôs-se a compreender alguns destes mecanismos neuronais, focando-se no estudo da conectividade funcional e anatómica. Para tal recorreu-se a imagiologia de tensor de difusão (DTI) para o estudo da conectividade anatómica de 10 estruturas de matéria branca, e a ressonância magnética funcional de repouso (rs-fMRI) de modo a analisar tanto a conectividade funcional existente entre várias regiões de interesse, como de duas redes de repouso muito conhecidas, a Rede de Modo Padrão (DMN) e a rede Frontoparietal (FPN). A amostra consistiu em 57 participantes portugueses destros saudáveis que foram avaliados em relação à velocidade de processamento considerando o índice de Velocidade de Processamento composto por três testes neuropsicológicos. Os resultados apontam que a difusividade radial de várias fibras de matéria branca está negativamente associada à velocidade de processamento, indicando que este é um processo degenerativo com bastante impacto na velocidade de processamento. Para além disso sugerem que a velocidade de processamento pode depender do bom funcionamento da memória, especialmente, memória episódica. Da mesma forma, considerando os nossos resultados, especulamos que o planeamento motor, a atenção e as funções executivas possam ter um papel importante na velocidade de processamento. Assim, considera-se que o presente estudo nos leva um passo mais longe na compreensão dos processos neurais que estão subjacentes às diferenças de velocidade de processamento e a um maior entendimento do processo de envelhecimento.

Palavras-chave: velocidade de processamento, imagiologia de tensor de difusão, ressonância magnética funcional de repouso, conectividade anatómica, conectividade funcional.

Neural mechanisms underlying processing speed in healthy older adults

Processing speed corresponds to the time required to process a certain amount of information. During the cognitive aging process, it is common for the occurrence of processing speed deficits. For this reason, a better comprehension of the neural mechanisms underlying processing speed in older adults may facilitate the understanding of the aging process and the development of therapeutic strategies aiming at retarding or attenuating it. Therefore, this work aimed to understand some of these neural mechanisms, focusing on the study of functional and anatomical connectivity. Therefore, two techniques were used: diffusion tensor imaging (DTI) to study the anatomical connectivity of 10 white matter structures, as well as resting-state functional magnetic resonance imaging (rs-fMRI) to analyze the functional connectivity between several regions of interest, and of two well-known resting networks, the Default Mode Network (DMN) and the Frontoparietal Network (FPN). The sample consisted of 57 healthy, right-handed, Portuguese participants and all were assessed regarding processing speed according to a Processing Speed index composed of three neuropsychological tests. Results point out that the radial diffusivity of several white matter fibers is negatively associated with processing speed, indicating that demyelination is a degeneration process with a strong impact on processing speed performance. Furthermore, our results suggest that processing speed might rely on the optimal functioning of memory systems, with particular emphasis on episodic memory. Likewise, based on our findings we speculate that motor planning, attention, and executive functioning might have an important role in processing speed performance. In sum, we considered the current study brings us a step closer to understanding the neural processes behind differences in processing speed and of having a greater insight into the aging phenomena.

Key Words: processing speed, diffusion tensor imaging, resting-state functional magnetic resonance imaging, anatomical connectivity, functional connectivity.

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Introduction

In developed countries, demographic changes have been arising due to an increase in life expectancy and in the number of elderly individuals in the population (Tumeh et al., 2007). The World Health Organization (WHO) estimates that between the year of 2025 and 2050 the elderly will constitute 30-40% of the world's population (WHO, 1999, 2011, as cited in Lima, 2016). This phenomenon appears to be a consequence of the implementation of successful policies of both public health and social development, such as the rise of living standards and improvements in education and nutrition (Lima, 2016; Cabeza et al., 2018). These changes, according to Paúl and Ribeiro (2012), will have direct repercussions on the socio-political, economic, medical, and financial contexts.

It is expected that this new world's panorama will bring an increase in age-related diseases and cognitive decline (Vidal-Piñeiro et al., 2014; Zettel-Watson et al., 2017). Normal aging is characterized by a set of physical, cognitive, and social alterations (Martins et al., 2017; Simões et al., 2008). Cognitively, certain processes show a more pronounced decline. This is especially true for domains such as memory (and specifically working and episodic memory), attention, executive control, and processing speed (Fjell & Walhovd, 2010; Koen & Rugg, 2019; Vidal-Piñeiro et al., 2014; Wascher et al., 2012).

Furthermore, these cognitive changes have a neurological substrate (Fjell & Walhovd, 2010; Vidal-Piñeiro et al., 2014). At the macroscopic level, aging is related to gray matter (GM) shrinkage, and ventricular expansion (Fjell & Walhovd, 2010). White matter (WM) integrity is also altered, possibly due to damage in the myelin sheath and/or reduction in nerve fibers (Bartzokis et al., 2004; Sala et al., 2012). In addition, aging effects are also visible on functional brain connectivity at rest (Geerligs et al., 2015; Li et al., 2018), which in general is reduced in the elderly (Chapman et al., 2013)

The demographic pressures discussed above, and their associated

costs, reinforce the need for research that focuses on understanding the aging brain and, therefore, help in the identification of risk factors for pathological aging and the development of interventions (Eckert, 2011). In line with this need, this study will uncover functional and structural neural aspects of processing speed in the elderly, measured by functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI), and standard neuropsychological batteries focusing on processing speed such as the Digit Symbol-Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997; port. version, Wechsler, 2008), and the Stroop Colour-Word Test (port. version, Fernandes, 2013).

The dissertation starts with an introductory section to further understand the topic, followed by a description of the main objectives, the methodology adopted, and the results obtained. Then, the results will be discussed, including possible limitations of the study. Finally, a brief conclusion is presented regarding all the addressed aspects of the dissertation, summing up and highlighting the contributions the study may have in the comprehension of the neuronal basis behind processing speed in aging.

1. Background

1.1. Processing Speed

Processing speed is currently defined as the amount of time needed to process a specific set of information, or, alternatively, the amount of information possible to be processed within a certain unit of time (Chiaravalloti et al., 2013). That is, processing speed corresponds to how fast a person executes cognitive tasks, particularly elementary cognitive tasks (Magistro et al., 2015).

Similar to other cognitive abilities, processing speed is not a unitary construct (Eckert et al., 2010). It is widely considered a key cognitive resource that underpins a broad range of cognitive domains (Kail & Salthouse, 1994; Magistro et al., 2015), and a fundamental piece in the efficiency of the whole brain (Kuznetsova et al., 2016).

Thereby, processing speed is normally assessed with timed tasks that require repetitive and speeded behaviors involving multiple perceptual and cognitive functions, including the perception of stimuli, working memory, decision making, motor planning, and motor performance (Eckert, 2011). Generally, these tasks are designed to be easily performed without errors, if given sufficient time (Kuznetsova et al., 2016), and minimally influenced by other processes that might request high cognitive demand (Silva et al., 2018).

A deficit in processing speed, or in other words, a "decrease in the rate at which people perform perceptual, motor, and decision making task" (Eckert et al., 2010, p. 1), may lead to the decline of other age-related higher-order cognitive abilities (Kail & Salthouse, 1994; Waiter et al., 2008), such as attention and memory. For this reason, processing speed stands as a strong predictor of a person's neurocognitive status, especially regarding older adults (Kail & Salthouse, 1994; Gao et al., 2020).

Processing speed deterioration is a robust feature of cognitive aging (Salthouse & Ferrer-Caja, 2003). Thus, determining an individual's processing speed, especially for older adults, may help in establishing clinical diagnosis and prognoses or in the implementation of therapeutic strategies that aim at delaying the age-related decline (Gao et al., 2020). Moreover, as processing speed is of high relevance for human psychometric intelligence, it becomes important to unravel how its plasticity changes across time (Takeuchi et al., 2011). Likewise, understanding the neural substrates behind processing speed can potentially give some insight into cognitive deterioration and how to delay it. Finally, traumatic brain injury, Parkinson's disease, depression, dementia, and multiple sclerosis (Hart et al., 1987; Lezak et al., 2004; Ruet et al., 2014; Sisco et al., 2016) present evident deficits in processing speed. Thereby, the development of rehabilitation programs may benefit from greater knowledge about the brain networks responsible for this essential cognitive function that is processing speed

(Silva et al., 2019).

1.2. Measuring Processing Speed

1.2.1. Neuropsychological Assessment

Neuropsychological assessment corresponds to the process of assessing the cognitive, behavioral, emotional, personalistity, and functional characteristics of an individual by administering standardized tests (Maia et al., 2009; Simões et al., 2016). The administration of these instruments must respect some guidelines that ensure the application occurs systematically according to the same conditions, even when performed by different people. Therefore, the individual's results at the respective tests can be compared with the data collected previously for the correspondent normative sample (optimally by age, gender, and/or years of education). Based on this comparison, it is possible to formulate some qualitative judgments and conclusions regarding the construct under evaluation (Laatsch, 2002).

Neuropsychological assessment is of high relevance for both clinical practice and scientific research (Simões et al., 2016). Several reasons may be underlying its implementation, ranging from helping to establish a diagnosis or monitoring a person's clinical condition throughout time, to identifying strengths, weaknesses, and personal resources in order to delineate the therapeutic or preventive intervention (Simões et al., 2016). For the purpose of scientific research, the neuropsychological assessment allows establishing the link between, for instance, cognitive functions such as memory, attention, language, executive functions, and processing speed and neural concepts like functional and anatomical connectivity.

Regarding the assessment of processing speed, a vast amount of neuropsychological instruments can be used, which are generally time-constrained. Three of the most common and widely used instruments are:

I. **Digit Symbol-Coding Subtest of the Wechsler Adult Intelligence Scale** (WAIS-III; Wechsler, 1997; port. version, Wechsler, 2008): Time-bound (120 secs) and pencil-and-paper task where the subject has to pair numbers (one-to-nine) with abstract symbols, according to a key provided (which establishes that the numbers from 1 to 9 correspond to specific symbols). To do so, the subject has to draw, in randomly numbered blank spaces, the symbols that correspond to the given numbers, as defined by the given key. Performance is based on the number of correct correspondences made within the time constraint, or until the completion of 4 lines of matches (80 matches in total).

This test integrates the Processing Speed index from WAIS-III (Wechsler, 2008) and is consensually used as a processing speed measure (Hirsiger et al., 2016; Joy et al., 2003b). However, it has been shown that other cognitive functions are also recruited during the execution of the Digit Symbol Coding test. These include visual perception and visual discrimination, sustained attention, memory (particularly working memory), motor skill, and incidental learning (Crowe et al., 1999; Davis & Pierson, 2012; Joy et al., 2003a, 2003b; Usui et al., 2009).

II. **Symbol-Search Subtest of the Wechsler Adult Intelligence Scale** (WAIS-III; Wechsler, 1997; port. version, Wechsler, 2008): Time-limited (120 sec) pencil-and-paper test where an individual is asked to determine whether one of the two given target symbols is present in an array of five abstract symbols ("yes" or "no" response). For each set, the target symbols change, and the score is calculated by the subtraction of the number of errors, from the number of correct identifications done within the maximum time provided.

Similarly to the test mentioned above, the Symbol

Search test is part of the Processing Speed Index from WAIS-III (Wechsler, 2008) but other cognitive functions such as short-term visual memory, visual discrimination, attention, as well as psychomotor speed may be at play (Crowe et al., 1999).

III. **Stroop Colour-Word Test** (port. version, Fernandes, 2013): Consists of three timed (45 sec) blocks. The first one - "Word-Reading" (W) - requires reading out-loud color words written in black (e.g., "red", "green", "blue"). The second one - "Color-Naming" - the individual is instructed to name the color in which the strings of "X" is written (e.g., "XXX"). Finally, the third one - "Colour – Word" (CW) or "inference trail" - requires naming the color of the printed words. This is similar to the color-naming task, but instead of strings of Xs, color words are presented and, importantly, the word and the printed color are incongruent (e.g., "brown" requiring the response green).

This test is commonly used as a measure of processing speed and response inhibition (Magistro et al., 2015; Sisco et al., 2016; Takeuchi et al., 2011; Varangis et al., 2019). Nonetheless, this neuropsychological test also requires other cognitive functions such as selective attention, cognitive flexibility, and fluid intelligence (Lezak et al., 2004; Strauss et al., 2006, as cited in Espírito-Santo et al., 2015).

1.3 Neural Substrates of Processing Speed

1.3.1. White Matter Integrity and Processing Speed

The WM's microstructural properties have a crucial role in the speed of the neural signals (Turken et al., 2008), and therefore, in processing speed as a cognitive function, since the efficiency of the neural communication depends on the axon's thickness (once the velocity is proportional to the diameter) and their degree of myelination

(Hou & Pakkenberg, 2012; Tolhurst & Lewis, 1992). Myelin is essential for neural signal transmission because it is the lipidic component present along the axons responsible for insulating them, enabling the conduction of the electric impulses within their structure (Kivipelto et al., 2002).

Nowadays studies make use of magnetic resonance imaging (MRI), particularly diffusion tensor imaging (DTI) to study, *in vivo* and non-invasively, the neural structures and their anatomical connectivity. DTI corresponds to a MRI modeling technique suited to estimate the microstructural properties of white matter tracts derived from the diffusivity of water molecules in the brain (Jacobs et al., 2013; Song et al., 2018). This inference is possible because the diffusion of water behaves differently regarding the characteristics of its environment. Whereas in fluid spaces of the brain (for instance, the ventricles and in gray matter) the diffusion occurs non-directionally (isotropic) due to the absence of boundaries, within the white matter, the diffusion of water is constrained by microstructures like axonal cell membranes, myelin sheaths, and neurofilaments (Bennett & Madden, 2014) and, consequently, the diffusion occurs along a principal direction (anisotropic). Thereby this imaging method, which measures the diffusion coefficients (Tumeh et al., 2007), makes it possible to analyze the integrity of the white matter (WM) structures within interconnected neural networks and determine how its (pathological) changes happen throughout time (Bennett & Madden, 2014). The use of DTI has been exponentially increasing since it provides a more sensitive and refined measure of degenerative changes than volume loss, mostly because the decline of the microstructural properties of the brain tissue, which begins approximately at the age of 23 (Imperati et al., 2011), seems to precede the macrostructural (Hong et al., 2015; Jacobs et al., 2013).

Several metrics can be obtained from DTI. Firstly, the most frequently reported is fractional anisotropy (FA; Yoncheva et al., 2016). This scalar estimation of the WM integrity, which varies between 0 and

1, represents how directionally organized is a determined brain tissue (Tumeh et al., 2007) and may reveal characteristics of the fibers at a voxel level, such as orientation, density, and coherence (Beaulieu, 2002). Higher FA values indicate an increase in the diffusion directionality, meaning diffusion is occurring constrained along WM axons, which can possibly indicate a better transfer of information (Richie et al., 2015). In contrast, lower values (near 0) point out to some loss in the fiber's integrity (Winklewski et al., 2018) as happens in pathologic conditions like Alzheimer's disease (Medina et al., 2006). However, it should be noted that this metric is limited in terms of its interpretation regarding areas with complex WM structures as in crossing fibers (Yoncheva et al., 2016), since the major axis of the respective tensor model may not be parallel to the axon (Madden et al., 2012).

Additionally, an emerging metric, especially among studies focusing on neurodegenerative disorders, is the mode of anisotropy (MA) that corresponds to a tensor shape metric linearly independent of FA. It quantifies second-order geometric properties, defining whether the anisotropy is planar (values similar to -1; for instance, in crossing fibers) or linear (values near 1; areas of one predominating fiber population). Furthermore, studies have reported that MA can detect WM alterations that other diffusion measures cannot (Yoncheva et al., 2016).

Lastly, radial diffusivity (RD) is a measure of the WM integrity that represents the diffusivity perpendicular to the main direction of diffusion within a certain fiber (Burzynska et al., 2017). Literature has been suggesting that this metric is a measure of the axon level of demyelination (Winklewski et al., 2018): higher RD values are indicative of more demyelination (Song et al., 2003).

DTI metrics are fundamental to the understanding of WM degeneration during healthy and pathological aging (Fjell & Walhovd, 2010; Sullivan & Pfefferbaum, 2006). The disruption of the WM's

microstructure caused either by the degeneration or depletion of axons and myelin is the primary genesis of age-related decline in cognitive functions like processing speed and memory (Gunning-Dixon & Raz, 2000). The same deterioration process is subjacent to pathologies such as multiple sclerosis, traumatic brain injury, and depression, which generally present deficits in processing speed (Levine et al., 2006; Madden et al., 2012; Savini et al., 2019). According to several studies, WM degeneration in aging is associated with an overall decrease in the FA values, concomitant with increases in the RD values (e.g., Borghesani et al., 2013; Burzynska et al., 2017; Madden et al., 2012; Sala et al., 2012). These age-related changes are more pronounced in association fibers than in commissural or even projection fiber tracts (Bender et al., 2016) and usually occur as a consequence of neurobiological processes such as the increase of brain water content, the demyelination, the loss of the axons' structure (e.g., decrease of its density and increase of its caliber; Hou & Pakkenberg, 2012), and the diminishing in the number of fibers until they are almost nonexistent (Sala et al., 2012).

The association between the WM's integrity and the cognitive performance on neuropsychological tests assessing processing speed has been consistently reported in the literature (e.g., Bennett & Madden, 2014; Betjemann et al., 2010; Turken et al., 2008). This relationship is not only accounted for the average FA value of the whole brain (Kuznetsova et al., 2016; Magistro et al., 2015; Ritchie et al., 2015; Salami et al., 2012) as would be expected since processing speed is a global function underpinning a broad range of cognitive demands (Penke et al., 2010), but also for specific WM tracts. Namely, higher FA values in frontoparietal WM tracts such as the genu, the body, and the splenium of the corpus callosum, as well as the inferior and the superior longitudinal fasciculi, were correlated with faster processing speed ability (Bennett & Madden, 2014; Kerchner et al., 2012; Salami et al., 2012). Moreover, according to Bennet and Madden (2014) and

Bennett et al. (2012), the genu of the corpus callosum and the superior longitudinal fasciculus, two regions highly susceptible to degenerate with aging (Salami et al., 2012), are strong predictors of processing speed, even after controlling for motor speed. Of note that the corpus callosum is a major commissure WM tract responsible for the interhemispheric communication between homologous cortical regions (Anstey et al., 2007; Delvenne & Castronovo, 2018; Sala et al., 2012). It is subdivided into the anterior region (which includes the rostrum, the genu, and the anterior body), and the posterior region (encompassing the posterior body, the isthmus, and the splenium). The genu connects with the frontal, premotor, and motor cortices, and, on the contrary, the splenium connects with the parietal, the occipital, and the temporal lobes (De Guise et al., 1999; Hou & Pakkenberg, 2012; Mathias et al., 2004). Its degeneration throughout time follows the anterior-posterior gradient commonly observed in aging (Delvenne & Castronovo, 2018; Sullivan & Pfefferbaum, 2006).

In addition to the WM tracts already mentioned, Kuznetsova et al. (2016) also found a relationship between processing speed and the integrity of the bilateral cingulum cingulate gyri, the uncinate, and the arcuate fasciculi as inferred by the FA metric. The study performed by Borghesani et al. (2013), on the other hand, showed an association between processing speed and FA of the ventral areas from the uncinate fasciculus, the inferior frontal fasciculus, and the anterior thalamic radiation.

Another WM tract is emerging as relevant for processing speed is the fornix (Burzynska et al., 2017), a structure that is the main efferent pathway of the hippocampus and generally referred to as essential for the declarative and episodic memory (Syc et al., 2013). Specifically, Burzynska et al. (2017) reported that better integrity of the fornix, assessed by higher FA values, is associated with faster processing speed. Similarly, Alexander et al. (2014) found in a clinical sample composed of non-lesional temporal-lobe epileptic individuals that the

Processing Speed index from Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 2008) was correlated with the FA values of the left fornix.

Moreover, it was also found that WM degeneration in the bilateral parietal, middle frontal, and bilateral temporal lobes positively correlated with processing speed (Schmahmann & Pandya, 2006). This conjunct relation with processing speed, especially in the left hemisphere, might occur due to the long association tracts that are responsible for functionally integrating the three cortices (Schmahmann & Pandya, 2006). The most prominent association tracts are the superior longitudinal fasciculus, the inferior longitudinal fasciculus, the inferior occipito-frontal fasciculus, and the uncinate fasciculus (Turken et al., 2008).

Regarding studies with healthy older age groups, Hong et al. (2015) related a positive correlation between processing speed and the FA values of the frontal WM (viz., anterior and superior corona radiata), the genu, the body, and the splenium of the corpus callosum, the internal capsule, the temporal WM, and lastly, the occipital WM. Finally, it was found that decrements in the WM's integrity, particularly in the external capsule and the body of the corpus callosum, as assessed by the FA metric, mediate the association between age and processing speed. In concrete, it was reported that the deterioration of the WM's microstructure resulting from aging is the leading cause of age-related cognitive slowing (Hong et al., 2015; Kerchner et al., 2012).

Lastly, Jacobs et al. (2013) indicated several WM structures whose RD values were associated with the subject's performance at neuropsychological tests assessing processing speed. These structures corresponded, along with others, to the genu of the corpus callosum and the right fornix stria terminals.

Even though the literature extensively reports this tight relationship between WM degeneration and processing speed, it is undeniable that there is a clear primacy of the FA metric. Nevertheless,

it is worth noting that the referred metric presents limitations and is not sufficient to characterize the fiber bundles since it does not present specific information regarding the diffusion tensor and, hence, how the diffusivity is changing (Alexander et al., 2007). Therefore, in order to overcome these problems, studies should make use of other DTI metrics, such as MA and RD. RD is a particularly interesting metric since it is considered an indicator of demyelination, which, in turn, is one of the earlier expressions of cognitive aging (Bartzokis, 2004).

1.3.2. Functional Connectivity and Processing Speed

It is also possible to study the functional neural mechanisms behind processing speed using functional magnetic resonance imaging (fMRI). fMRI has been considered a prominent tool in the comprehension of the brains' functioning due to its ability to non-invasively measure brain activity from the blood oxygen level-dependent, or simply, the BOLD signal (Allen et al., 2011). The BOLD contrast is a phenomenon that arises from a particular characteristic of the hemoglobin molecule. This is so because the hemoglobin is responsible for the transportation of oxygen through the vessels and, depending on whether it is bonded to oxygen, its magnetic properties change, interfering differently with the scanner's magnetic field: whereas oxygenated hemoglobin is diamagnetic and weakens the magnetic field, deoxygenated hemoglobin is paramagnetic and strengthens it. During neuronal activity occurs an increase in the blood flow, leading to an increment in the supply of oxygen superior to its demand (Huettel et al., 2014). Therefore, this results in an alteration in the BOLD signal that increases with the augment of the oxygenated hemoglobin (Bijsterbosch et al., 2017).

fMRI studies indicate that different brain regions synchronously engage in response to different kinds of stimuli and context, suggesting that these regions are functionally connected and exchanging information. In that sense, functional connectivity refers to a statistical association among two or more anatomically distinct regions whose

activation is temporally correlated (Horwitz, 2003).

Functional brain connectivity can be determined in task-related fMRI designs or in the absence of any external sensory or cognitive stimulus (i.e., in “rest” scans; Smitha et al., 2017; Whitfield-Gabrieli & Nieto-Castanon, 2012). Considering that the human brain is still active during the relaxation state, resting-state fMRI (rs-fMRI) explores the spontaneous low-frequency fluctuations (0.01-0.08 Hz) in the BOLD signal present in rest scans, or in the residuals of task-related fMRI studies (Smitha et al., 2017).

Independent component analysis (ICA) is an analytical method that has been used in rs-fMRI (Whitfield-Gabrieli & Nieto-Castanon, 2012). This technique delimitates networks that are temporally coherent and subserve critical functions (Allen et al., 2011), which is the case of the resting-state networks (RSNs). These networks, although commonly defined as resting-state networks, do not emerge solely during rest. Instead, they are also present during task conditions (Smith et al., 2009). Therefore, it is possible to infer from the level of disruption that a specific network presents under a resting-state condition how its functional integrity will be in task-related designs, and, consequently, how the cognitive function might be affected (Nashiro et al., 2017).

More and more the RSNs are becoming central in cognitive neuroscience, especially after discovering that their disruption has an impact on a large set of neurological and clinical disorders (Sumowski et al., 2010). For instance, alterations in the default mode network (DMN; one of the most important RSNs) are present in Alzheimer’s disease, schizophrenia, depression, attention deficit, and hyperactivity disorder, among others (Reineberg et al., 2015).

rs-fMRI represents a unique approach of exploring functional connectivity (Bonavita et al., 2014). From the large set of RSNs it enables to study, the most reported RSN is the DMN that comprises the medial parietal cortex (including the precuneus and the posterior cingulate), the bilateral inferior-lateral-parietal, and the ventromedial

frontal cortex (Smith et al., 2009).

The DMN distinguishes itself from other RSNs because it presents a specific and distinct pattern of activation while individuals perform cognitive tasks (Rocca et al., 2010). This network has a preferential activation during rest, more precisely, when an individual is not paying attention to the surrounding environment or is in a state of passive thought (Buckner et al., 2008; Damoiseaux et al., 2008). In contrast, in healthy subjects the DMN presents less activation under cognitively demanding situations, such as when executing goal-oriented tasks, or during the activation of the prefrontal cortex (Greicius et al., 2003; Laird et al., 2009; Sumowski et al., 2010).

The DMN's activation at rest is broadly referenced in the literature as being inversely associated with age. On the contrary, its activation at rest was found to be positively associated with the performance of younger healthy adults on neuropsychological measures of memory, as well as with older adult's results on cognitive tests assessing executive attention and processing speed (Damoiseaux et al., 2008).

The proper functioning of the DMN is of high importance for the maintenance of a healthy cognitive state (Rocca et al., 2010). This task-negative RSN is responsible, for instance, for ensuring the shift between the resting-state and the attentional processing (Sala-Llonch et al., 2012). Furthermore, it is considered that the DMN is associated with a multiplicity of cognitive functions (Laird et al., 2009), one of which, according to several studies, corresponds to processing speed (e.g., Bonavita et al., 2014; Savini et al., 2019; Staffaroni et al., 2018; Sumowski et al., 2010). For instance, Staffaroni et al. (2018) indicate that, at rest, decreased DMN's functional connectivity is correlated with slower processing speed. This relation was also present when the decrease in the DMN's functional connectivity was age-related (Andrews-Hanna et al., 2007). Moreover, others corroborated these findings, such as Hirsiger et al. (2016) and Damoiseaux et al. (2008)

who found that the functional connectivity of the anterior regions of the DMN (i.e., superior frontal and bilateral middle temporal gyri, posterior cingulate, and superior parietal) are related with processing speed, alongside with attention, concentration, and executive functioning. According to Damoiseaux et al. (2008), the decrease in the DMN's activation is associated with poorer performance on tasks assessing the cognitive abilities already described, which possibly reflects the reduction of spontaneous thoughts arising from the alterations in the network's activation. The study conducted by Manca et al. (2019) in a clinical sample of multiple sclerosis patients converges in the same direction and, therefore, reinforces the role of DMN on processing speed. However, simultaneously present a novel finding indicating that, besides the DMN, processing speed performance is positively correlated with the frontoparietal network (FPN; with a special predominance of the left hemisphere in the frontal and parieto-limbic areas; Manca et al., 2019). In line with this, Gao et al. (2020) indicate that processing speed can be predicted in older adults based not only on the DMN's functional connectivity, but rather on the functional connectivity across the referred network and the motor, the frontoparietal, the medial frontal, the subcortical and cerebellum, as well as the visual-related networks.

Recent studies have been suggesting that general cognitive performance depends on the interaction of the DMN with the FPN, two networks considered antagonists due to their negative correlation (Silva et al., 2019). These two "anticorrelated networks" subserve numerous functions, and the disruption of their coordinated system (possibly caused by a decrease in the functional connectivity within both networks or by an inability to correctly suppress the DMN during cognitive tasks; Geerligs et al., 2015; Uddin et al., 2009), is associated with some of the most common clinical disorders, as well as with age-related cognitive decline (Marstaller et al., 2015). Moreover, the cognitive decline associated with advancing age might also be an

expression of a decrease in the DMN-FPN negative correlation, which leads to dedifferentiation. Contextualizing, dedifferentiation corresponds to the aging phenomenon of losing the neural networks' specificity that, posteriorly, affects cognitive performance. Normally it occurs by virtue of an increase in the functional connectivity between functionally distinct networks and a concomitant decrease in the intra-network functional connectivity (Geerligs et al., 2015; Nashiro et al., 2017).

The FPN is a task-positive resting-state network related to executive control and the ability to take actions towards predefined goals (Dixon et al., 2017). Generally, this network is active during the performance of spatial-attentional tasks (Naghavi & Nyberg, 2005).

Despite the tight link with DMN, there is also evidence solely correlating FPN with cognitive functioning, and consequently, with processing speed. For instance, several fMRI studies consistently reported that FPN or areas predominantly from the resting-state network were activated during the execution of the Symbol Digit Modalities Test (SDMT; Smith, 1982), a neuropsychological test generically used as a measure of processing speed (e.g., Forn et al., 2011; Forn et al., 2013; Silva et al., 2019; Silva et al., 2018). Likewise, Usui et al. (2019) found a stronger activation of the FPN during the execution of a modified version of the Digit Symbol-Coding Subtest of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 2008), when compared with a control task. In concrete, the bilateral inferior frontal sulci, the middle frontal gyrus, and the left posterior parietal cortex activated preferentially during the processing speed task (Usui et al., 2019). For some authors, the recruitment of FPN's areas during tasks whose performance depends on processing speed reflects a response to the high demand of inherently associated processes of visual search and working memory (Silva et al., 2019; Silva et al., 2018; Usui et al., 2009).

With respect to aging, the integrity and functional connectivity of

the FPN, especially in the right hemisphere, is an essential feature for the maintenance of attentional processes, particularly in what concerns alertness (Robertson, 2013, 2014, as cited in Haupt et al., 2019). Moreover, the same characteristics appear to influence the mechanisms behind active perception and cognitive reserve in the elderly (Haupt et al., 2019). Lastly, Grady et al. (2016) reported that, at rest, the increase in the functional connectivity between FPN and other networks was associated with an enhancement of age differences in memory and, the activation of FPN during the task was correlated with better performance for older adults.

In addition, aging also seems to modulate the way FPN regulates the functional connectivity of other networks. For instance, the between-connectivity of FPN induces a reduction in the functional connectivity within the DMN, solely in older adults. This effect only was observed at rest, possibly due to the absence of external demands that could interfere with cognitive processing (Grady et al., 2016).

Given the high number of aforementioned studies highlighting the strong association between the two well-known RSN and processing speed, it seems interesting to ascertain these findings in a sample with a considerable number of subjects, incrementing this way the statistical power of the analyses performed, and focusing on functional connectivity since it indexes the network's level of disruption. Moreover, a voxelwise approach should be privileged considering it enables one to analyze the RSNs in detail, comprehending which regions within the RSNs are having an impact on processing speed.

Besides the study of RSNs, literature heavily focuses on regions whose activity is demonstrated to be essential for the correct functioning of processing speed. However, there is a lack of studies trying to comprehend which brain areas are working alongside to conjunctly and efficiently respond to the cognitive demands imposed by tasks requiring good processing speed performance. Therefore, to

further comprehend all neural mechanisms behind the processing speed ability, it is imperative to study how the communication between specific regions of interest is affecting it. In order to do so, the first step is to survey areas that are consistently being referred to in the literature as relevant to processing speed.

According to the meta-analysis carried out by Silva et al. (2018), the occipital cortex, the cuneus, the superior parietal lobe, the precentral gyrus, the bilateral middle frontal, the inferior frontal gyrus, the lingual gyrus, and the cerebellum were found to be activated preferentially during the execution of the SDMT. Inversely, the medial frontal gyrus, the anterior and posterior cingulate gyri, and the precuneus stood out for deactivating during a cognitive performance (Silva et al., 2018). Other studies revealed a different set of regions associated with SDMT's performance. For instance, Dobryakova et al. (2016) identified occipital regions, the inferior parietal lobe, the fusiform gyrus, the medial temporal gyrus, the supplementary motor area, and some regions from the prefrontal cortex. Moreover, Genova et al. (2009) corroborated the role of the occipital areas and of the precentral gyrus in tasks particularly challenging in terms of processing speed (like SDMT) and explained these results in light of the visual and motor aspects of those tasks. The authors also identified that in both clinical and control groups, the activation of the anterior cingulate gyrus and of the thalamus was negatively correlated with the task's performance (Genova et al., 2009).

In addition, the literature focusing on other processing speed-related tasks such as the Symbol Digit Coding and the Symbol Search subtests from WAIS-III indicates similar regions to the ones mentioned before. Usui et al. (2009) reported the left superior and inferior parietal lobes, the precentral and postcentral gyri, the precuneus, the cuneus, the lingual gyrus, the cingulate gyri, and the inferior frontal sulcus as regions essential for processing speed performance.

Similarly, Forn et al. (2009) developed an MRI-adapted version

of the SDMT and the study conducted with this modified task revealed that the frontal, parietal and occipital lobes are recruited preferentially during its execution. More concretely the regions corresponding to the cuneus, the inferior parietal lobe, the middle frontal gyrus, the inferior frontal gyrus, the caudate, and the cerebellum.

Lastly, one of the most recent discoveries around processing speed belongs to Tsapanou et al. (2019) that found out that, in older adults, the entorhinal thickness is a predictor of the processing speed ability. This region located in the medial temporal lobe is well-known and widely studied for its essential role in associative and episodic memory (Burggren et al., 2011; Devanand et al., 2007; Rodrigue & Raz, 2004). However, its association with processing speed and with age-related decline is still limited, considering that, as far as we know, besides Tsapanou et al. (2019), no other study addressed this question.

2. Objectives

From a broad perspective, the present study aimed to investigate how the brain's connectivity impacts processing speed in an aging population, relying on two different approaches: studying the brain's structural connectivity (using DTI) and functional connectivity (with fMRI). As such, the following specific objectives were defined:

I. Determine whether the integrity of selected WM structures (i.e., the genu, splenium, and body of corpus callosum; the left and right inferior fronto-occipital; the fornix; the left and right superior longitudinal fasciculus; the left and right uncinate fasciculus), measured by three DTI metrics (FA, MA, and RD) relates to differences in processing speed in elderly individuals.

II. Unraveling how the functional connectivity between different regions of interest (posterior and anterior cingulate; cerebellum; precuneus; left and right entorhinal; left and right superior parietal; left and right inferior parietal; left and right precentral gyrus) relates to differences in processing

speed in elderly individuals.

III. Determine if the functional connectivity within two RSNs - namely the DMN and FPN - is higher in the individuals with faster processing speed.

3. Material and Methods

3.1. Participants

Fifty-seven healthy elderly subjects (23 males and 34 females) ranging from 61 to 79 years old (M=68.61; SD=4.94) participated voluntarily in the study. This study was part of a larger study that seeks to investigate the synergic effects of neuromodulation, specifically, of transcranial Direct-Current Stimulation (tDCS), and cognitive training in episodic memory enhancement of healthy elderly individuals.

All participants were Portuguese native speakers and right-handed as assessed by the *Bateria de Avaliação Neuropsicológica de Coimbra* (Simões, 2008). A large percentage of the sample was composed of highly educated participants (years of education: M=12.28; SD=4.79). None of the subjects had a clinical history of neuropsychiatric disorders (such as dementia, depression, epilepsy, or stroke), head injury, hearing or visual difficulties, or were under medication that could potentially interfere with their performance on the cognitive tests. Moreover, all participants met fMRI criteria.

Participants were recruited through advertisements on flyers, webpages, newspapers, and lectures at senior universities, community health centers, and nursing homes. All subjects received a detailed explanation of the study and signed a written informed consent. The project was approved by the Ethical Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra and respected all the ethical principles regarding research with humans in accordance with the Declaration of Helsinki. At the end of the experiment every participant was compensated with fifty euros on a gift card.

3.2. Screening

Before enrolling in the study, all participants were subjected to a brief screening to ensure they were eligible, which consisted of the administration of the:

a) **Montreal Cognitive Assessment 7.1** (MoCA 7.1; Nasreddine et al., 2005; port. version, Freitas et al., 2013) to assess whether the individuals were cognitively preserved (according to six cognitive domains: i) executive functions, ii) visuospatial abilities, iii) short-term memory, iv) language, v) attention, concentration and working memory, and vi) spatial and temporal orientation.
b) **Geriatric Depression Scale - 30** (GDS-30; Yesavage et al., 1983, port. version, Simões et al., 2015) to briefly identify the presence of depression-related symptoms.
c) ***Inventário de Avaliação Funcional do Adulto Idoso*** (IAFAI; Sousa et al., 2013) to measure the basic and instrumental functional abilities of the individuals.

The aim of this screening consisted of excluding participants that were cognitively and/or functionally impaired and presented depression-related symptoms, once these could represent confounding factors for the results obtained at the neuropsychological tests administered and, also, because the study intended to have a healthy sample. The MoCA's results regarding the subjects included in the study were also used to define the experimental groups, as will be posteriorly explained.

3.4. Processing Speed Assessment

The neuropsychological assessment took place in a room attached to the MRI scanner, where only the participant and the evaluator were present. All the possible distractors were controlled and the assessment occurred in the schedule that best suited the participant. It was told to the participant to interrupt and ask questions whenever necessary and

during the whole evaluation, little breaks were allowed to ensure the participant was not fatigued.

In order to assess processing speed three neuropsychological tests were administered: the Digit Symbol-Coding and the Symbol-Search subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997; port. version, Wechsler, 2008) and the Stroop Colour-Word Test (port. version, Fernandes, 2013). The results obtained at the referred instruments were used to estimate a composite processing speed measure.

3.5. Estimation of a Composite Processing Speed Measure

The scores from the three neuropsychological tests were converted to a normalized metric, ranging from 0 to 1, enabling the creation of a composite index of processing speed. This new composite measure was obtained by averaging the above-described normalized scores (for a similar approach, see Sisco et al., 2016; Varangis et al., 2019). The normalization of the behavioral results consisted of the application of the following linear transformation: SNi = [(Si - Smin)/(Smax-Smin)], in which *SNi* corresponds to the normalized score of the *Si* value (the raw score), and the *Smin* and *Smax* to the minimum and maximum value obtained at the neuropsychological test, respectively.

3.6. Definition of the Experimental Groups

The whole dataset of 57 participants was split into four quartiles according to the individual scores on the composite index of processing speed. Therefore, the first and fourth quartiles were taken into two separate groups - one with the highest composite scores (from now on, high-processing speed group), and the other with the lowest scores (low-processing speed group) -, each constituted of 15 subjects. The two groups were controlled for age ($t(28) = 1.203$; $p = .239$), education ($t(28) = -1.621$; $p = .116$), and performance at the MoCA ($t(28) = -1.554$; $p = .131$), by conducting a two-tailed unpaired two-sample t-

test. In order to achieve these paired groups regarding age, education, and MoCA's performance, some participants had to be shifted with others from the second and third quartile. As expected at the end the groups only differed in what concerns the Processing Speed index ($t(28) = -10.604$; $p < .001$ - Table 1).

Table 1

Means (M), standard deviations (SD), and comparisons regarding age, years of education, MoCA, and Processing Speed index scores between high- and low-processing speed groups

Variables	Low PS		High PS		$t(28)$	p (2-tailed)
	M	*SD*	*M*	*SD*		
Age	69.40	4.641	67.53	3.815	1.203	.239
Education (years)	11.27	4.267	13,53	3.335	-1.621	.116
MoCA	24.00	2.299	25.13	1.642	-1.554	.131
Processing Speed	.3519	.0840	.9741	.0825	-10.604	.000***

Note. ***$p < .001$; Low PS and High PS corresponds to the low- and high-processing speed groups, respectively, regarding the Processing Speed index.

3.7. Imaging Data Acquisition

Whole-brain fMRI data were collected with a 3-Tesla Siemens MAGNETOM trio MRI scanner (Siemens Healthineers, Erlangen, Germany) using a standard 12-channel head coil. High-resolution structural MRI data were acquired using a T1 weighted magnetization prepared rapid gradient echo (MPRAGE) sequence, which entailed the following parameters: a 256 × 256 acquisition matrix, a 256 mm field-of-view (FoV), a voxel size of 1.0 × 1.0 × 1.0 mm^3, a flip angle (α) of 7º, bandwidth (BW) of 200 Hz/px, a repetition time (TR) of 2530 ms and an echo time (TE) of 3.29 ms.

For the resting-state fMRI data acquisition, the participants were

instructed to remain awake, laid supine, and with their eyes open, looking to a fixation cross, for 6 minutes. It was used a T_2^*-weighted gradient echo-planar imaging (EPI) sequence, with the following specifications: a 64 × 64 acquisition matrix, a 256 mmm FoV, a flip angle of 90º, 33 interleaved slices, a voxel size of 4.0 × 4.0 × 4.0 mm^3, BW of 1562 Hz/px, a TR of 2200 ms and a TE of 30 ms.

Diffusion Tensor Imaging (DTI) data were acquired on the same 3T MAGNETOM Trio MRI scanner using an echo-planar sequence with 69 diffusion directions, a TR of 8900 ms, a TE of 86 ms, a b-value 2 of 1000 s/mm^2, 70 slices with a 2.0 × 2.0 × 2.0 mm resolution and 10 non-diffusion weighted (b = 0 s/mm2) volumes, as parameters.

3.8. Image Preprocessing

Both anatomical and functional data were pre-processed using *fMRIPrep* 20.1.1. This pipeline includes standard preprocessing steps, and its implementation aims to respond to the lack of an easy-usage workflow that ensures robustness independently of the data idiosyncrasies and high consistency of the results (Esteban et al., 2019).

All functional data underwent motion correction, realigning all volumes with respect to the first volume from the first functional run. Posteriorly, slice timing correction was conducted, as well as spatiotemporal filtering for frequencies between 0.009 and 9999 Hz. The co-registration occurred by implementing boundary-based registration (Esteban et al., 2019) and, posteriorly the co-registered T1-images were used to spatially normalize functional data into standard stereotactic Montreal Neurological Institute (MNI) space, using the combined volumetric and surface-based (CVS) registration from Freesurfer (version 6.0.0; Zöllei et al., 2010). On the registered functional data was performed an automatic removal of motion artifacts using independent component analysis (ICA-AROMA; Pruim et al., 2015), as well as AROMA remotion of the non-aggressive regressors. Additionally, the “aggressive” noise-regressors were extracted separately from the *fMRIPrep* workflow. The AFNI (Analysis of

Functional NeuroImages; Cox, 1996) was used to extract the components of the cerebrospinal fluid (CSF) and white matter (WM), and perform a second-order polynomial detrending. Lastly, for the ICA analysis the data was smoothed with an isotropic Gaussian kernel of 8 mm3 full-width half maximum (FWHM) to reduce spatial noise.

Concerning diffusion-weighted images (DTI), an image processing pipeline was implemented in MATLAB R2019a, making use of the FDT diffusion module from the FMRIB (Functional Magnetic Resonance Imaging of the Brain's diffusion toolbox) software library (FSL, version 6.0.4; Jenkinson et al., 2012), and incorporating tools from the MRtrix3 software. Firstly, these images were converted from DICOM to NIFTI, and afterward, denoised at the participant level using the MPPCA technique that consists of deriving an objective threshold on the eigenvalues for PCA denoising, from the noise level (Veraart et al., 2016). This denoising method is characterized by preserving local signal fluctuations from any origin other than thermal noise. The non-weighted diffusion images (b0s) were used to generate a whole-brain mask, and motion and eddy current distortions were corrected using the *eddy_openmp* program from the FSL diffusion toolbox referenced above.

Moreover, the computed diffusion tensor maps underwent a nonlinear registration, which consists of aligning each subject and measure map with a standard space (MNI152, $1 \times 1 \times 1$ mm^3).

3.9. Image Processing

3.9.1. Diffusion Tensor Metrics: Defining WM Structures

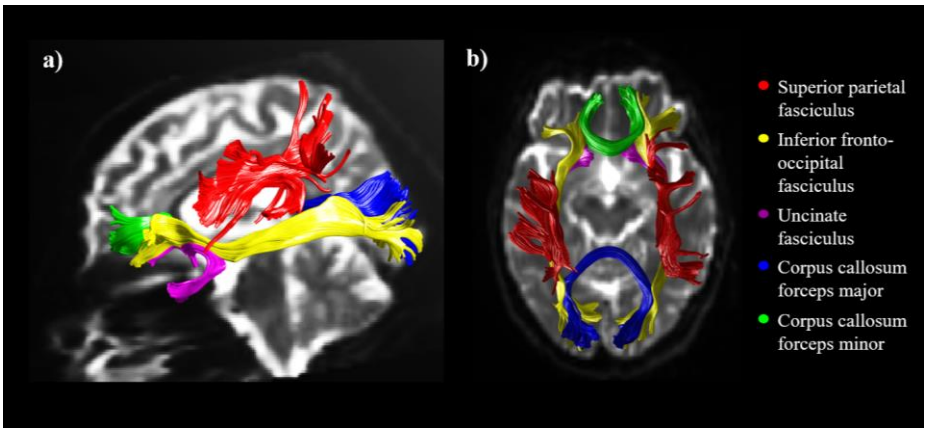
For every subject, the average values of the DTI measures (i.e., FA, MA, and RD) in all WM fiber tracts selected were determined using the JHU-DTI atlas (Wakana et al., 2007) to delimitate the respective regions. The visual representation of the WM structures selected can be consulted in Figure 1.

In order to compute the diffusion tensor derived and eigenvalue-based measures, such as fractional anisotropy (FA),

mode of anisotropy (MA), and radial diffusivity (RD), the diffusion tensor fitting was estimated by the least-square fitting. All the mentioned measures, which are widely used to characterize the diffusion displacement in the microstructures of the white matter, can be obtained by performing the diagonalization of the diffusion tensor estimated for every image's voxel (Almeida et al., 2020). In this case these computations were performed using FSL.

Figure 1

White matter fiber tracts of interest



Note. White matter tracts of interest in a) sagittal and b) axial views. In both images, red corresponds to the superior fasciculus, yellow to the inferior fronto-occipital fasciculus; purple to the uncinate fasciculus, blue to the corpus callosum forceps major, and green to the corpus callosum forceps minor. Forceps major and minor overlap with and contain fibers from the splenium and genu of the corpus callosum.

3.9.2. ROI-to-ROI Connectivity: Defining the Regions of Interest (ROIs)

Twelve regions of interest (ROI) were selected considering their prior reference on literature as being related to processing speed. These regions consisted of the cerebellum, the right and left precentral gyrus, the right and

left entorhinal cortex, the anterior and posterior cingulate cortex, the precuneus, the right and left inferior parietal cortex, and the right and left superior parietal cortex.

The ROIs were defined based on the coordinates and cortical parcellation reported in the FreeSurfer atlas (version 6.0.0). Specifically, for every participant and each ROI the functional regions of interest and the correspondent time-series were obtained by masking the preprocessed fMRI data in accordance with the coordinates provided by Freesurfer. In addition, for each ROI the average BOLD time-series was computed taking all voxels within the ROI. This last step was performed with CONN (version 19.c; Whitfield-Gabrieli & Nieto-Castanon, 2012), a MATLAB-based software.

3.9.3. Resting-State Networks: Independent component analysis and dual regression

A group probabilistic independent component analysis (ICA; Beckmann & Smith, 2004) was performed in FSL (version 6.0.3; Jenkinson et al., 2012) MELODIC for 20 components. The selection of a small number of components was used to decompose the data into larger "primary networks", instead of splitting it up into small "sub-networks" (Smith et al., 2009).

The classification of the ICA-derived components as brain networks consisted of cross-correlating the spatial components with the templates of intrinsic brain networks, provided by Smith et al. (2009). The components that correlated the most were selected as the RSNs of interest. Accordingly, components 6 and 10 were identified as the DMN (r = .740) and the FPN (r = .378), respectively, and used as input of the dual regression conducted independently for each network. Employing this last multivariate approach allows to estimate spatial maps and times courses for each

participant, and hence, quantify the functional connectivity between each voxel and each spatial map, while controlling for the remaining spatial maps (Smith et al., 2014). The individual maps that resulted from the dual regressions provide information about the similarity between a particular voxel's time-course and the time-course of the respective component (Haupt et al., 2019).

3.10. Statistical Analyses

3.10.1. Diffusion Tensor Metrics

GraphPad Prism (version 6) was used to conduct an unpaired two-tailed t-test to evaluate differences between groups (low- and high-processing speed on the Processing Speed composite measure) after ensuring that the data were normally distributed with the Kolmogorov-Smirnov test. Likewise, was computed a linear regression for each DTI metric and the Processing Speed index, considering all fifty-seven subjects and a 95% confidence boundary.

The results from both analyses were Bonferroni adjusted for multiple comparisons. Hence, Bonferroni adjusted p values are considered statistically significant at $p < .05$.

3.10.2. ROI-to-ROI Connectivity (RRC)

Firstly, for every participant individual ROI-to-ROI connectivity matrices were computed (size of 12 × 12). These matrices concern the functional connectivity between all possible pairs of ROIS from the twelve selected. Since these matrices are symmetric in relation to their diagonal, only the values above the diagonal were considered in the analysis, which consisted of performing, for each pair of ROIS, an unpaired-samples t-test of the functional connectivity values to determine group differences (between the high- and low-processing speed group). All the results obtained were

corrected for multiple comparisons, ensuring that the FDR rate was at 5% ($p < .05$).

Posteriorly, for each pair, a simple linear regression was performed with the functional connectivity values of all the fifty-seven participants and the scores obtained at the Processing Speed index, considering a 95% confidence boundary.

3.10.3. Functional Connectivity of the Resting-State Networks

To determine group differences regarding each network (both DMN and FPN), voxel-wise unpaired two-sample t-tests (that is, a comparison for each voxel) were performed concerning the individual maps yielded from the dual regression. This step required using the randomise permutation-testing tool (5000 permutations, p = .05) from FSL (Jenkinson et al., 2012), which performs the threshold-free cluster enhancement (TFCE) method and corrects for multiple comparisons with family-wise error (FWE).

4. Results

In order to obtain a more complete understanding of the neural mechanisms underpinning processing speed differences, we focused on three different types of analysis:

I. A two-tailed t-test to ascertain group differences (between high- and low-processing speed) regarding the values of three DTI metrics (FA, MA, and RD) from ten WM fiber tracts; a simple linear regression to comprehend how the anatomical connectivity of those structures is related to processing speed.

II. A two-samples t-test to determine the existence of group differences in terms of the functional connectivity between twelve pre-selected regions of interest; a linear regression to assess how the functional connectivity between those regions

and the scores obtained at the Processing Speed index are related.

III. A voxel-wise two-sample t-test to evaluate if, in the DMN and the FPN, the functional connectivity strength is higher in the high-processing speed group.

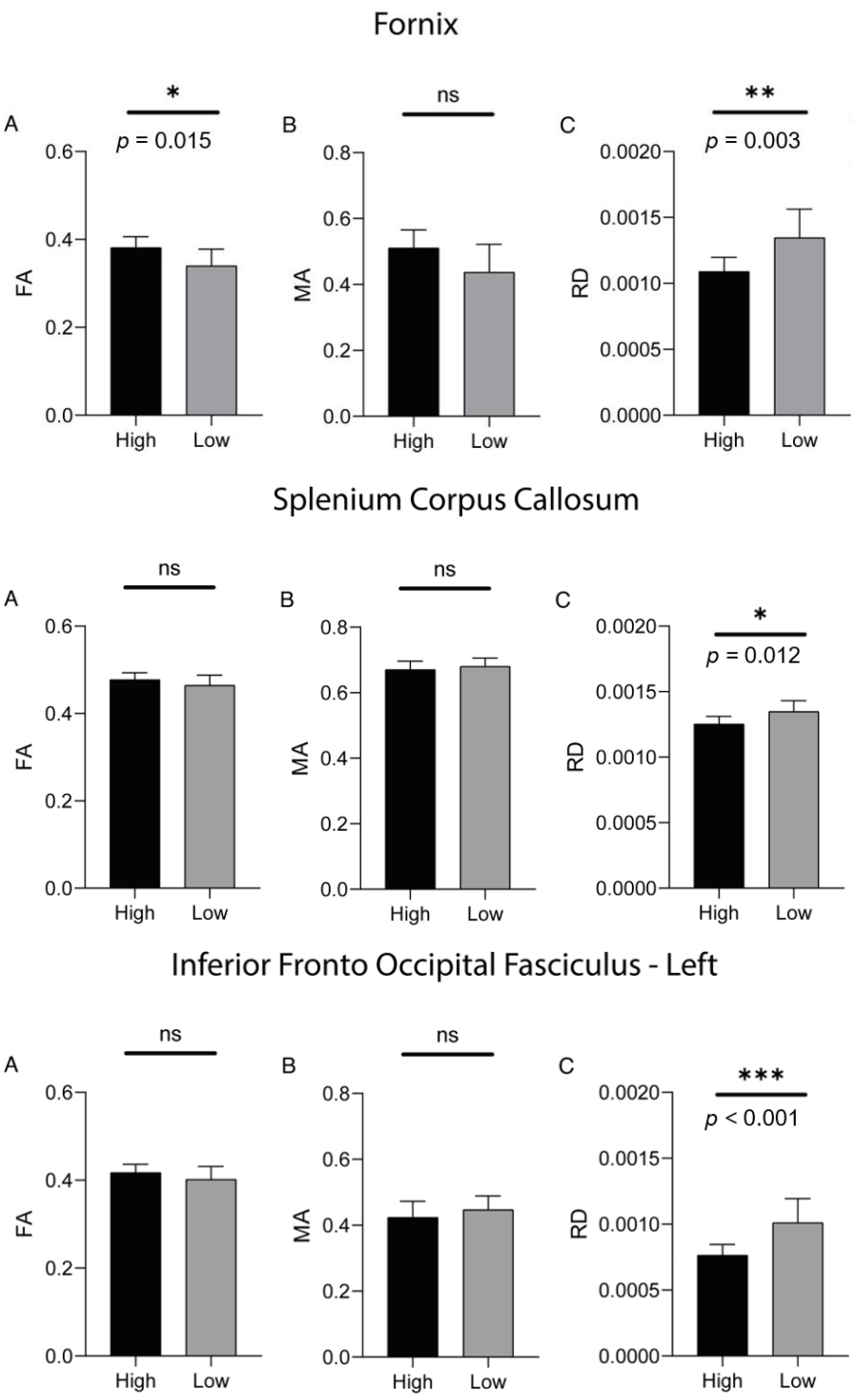
4.1. Diffusion Tensor Metrics

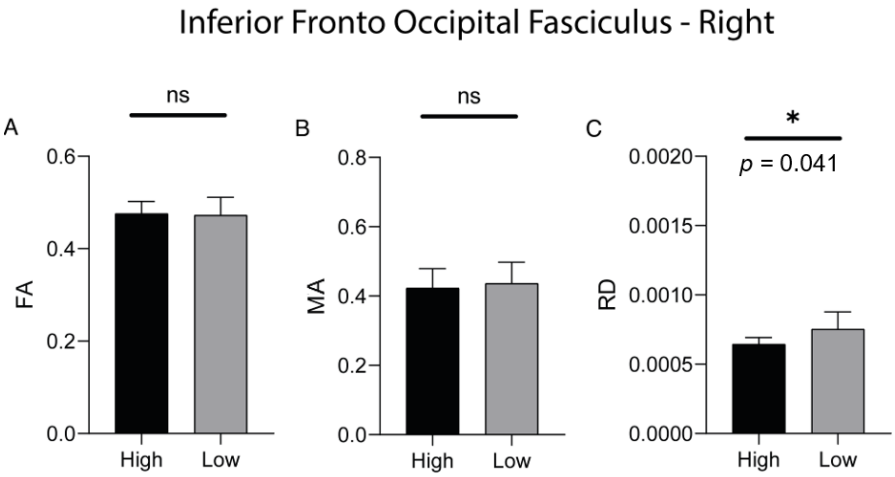
The fornix was the only fiber presenting two metrics that significantly differed between the two experimental groups: FA ($t(28) = 3.513$; $p = 0.01$) and RD ($t(28) = 4.117$; $p = 0.003$; both p values were Bonferroni-adjusted), in which the high-processing speed group revealed greater values than the low-processing speed group at the FA metric, and inversely, lower RD's values.

Regarding other fiber tracts, only the RD metric presented significant results. Concretely, group-differences in relation to this metric were found for the splenium ($t(28) = 3.616$; $p = 0.012$) of the corpus callosum, as well as the left and right inferior fronto-occipital fasciculus ($t(28) = 4.780$; $p < 0.001$; and $t(28) = 3.127$; $p = 0.041$, respectively). In those tracts the mean RD value was lower for the high-processing speed group when compared with the low-processing speed group. No other metric achieved statistical significance in any WM tract. All the above-described results are represented in Figure 2.

Figure 2

Comparisons between the high- and low-processing speed groups regarding the DTI's metrics (FA, MA, and RD) of the selected WM tracts



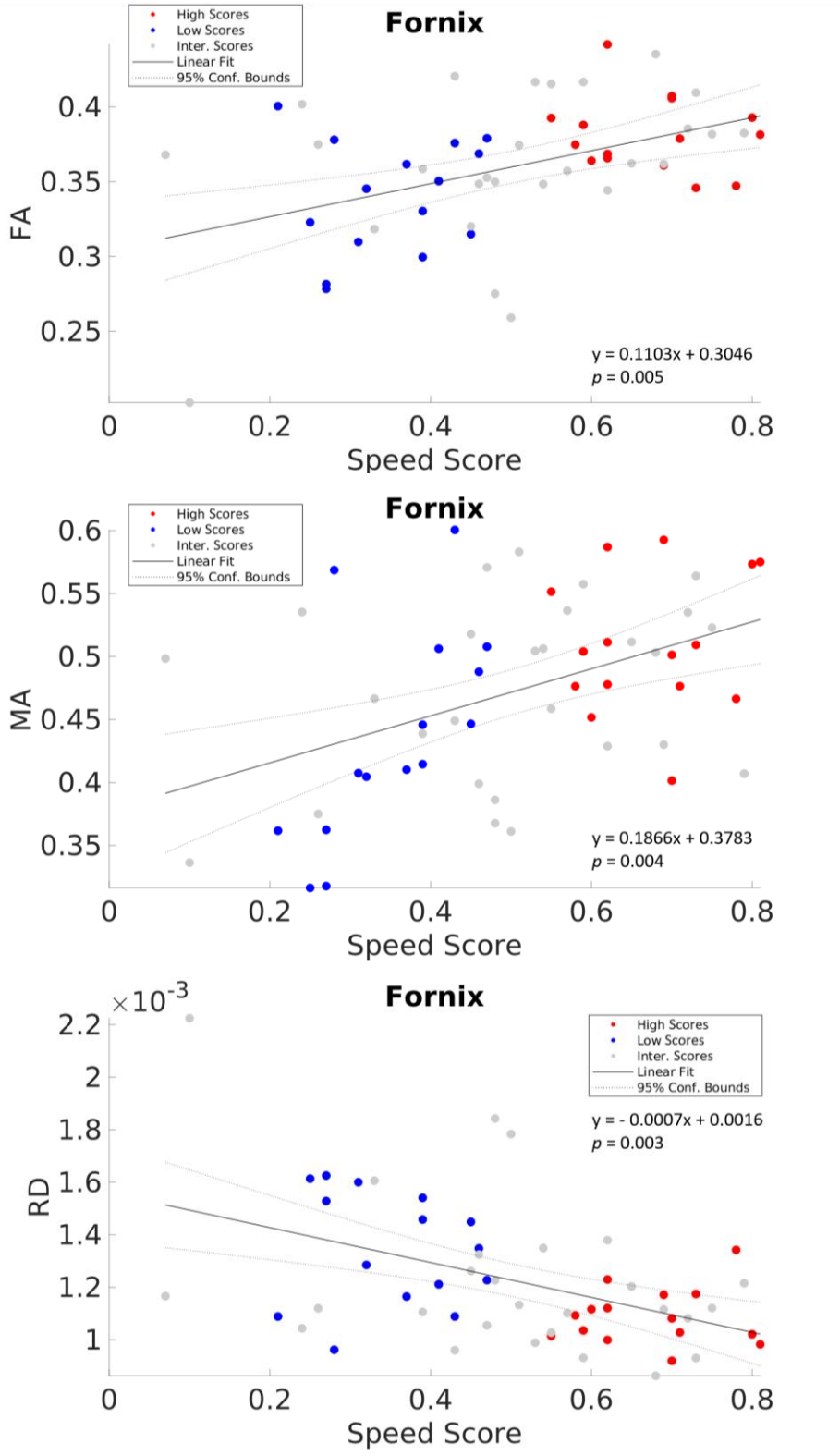


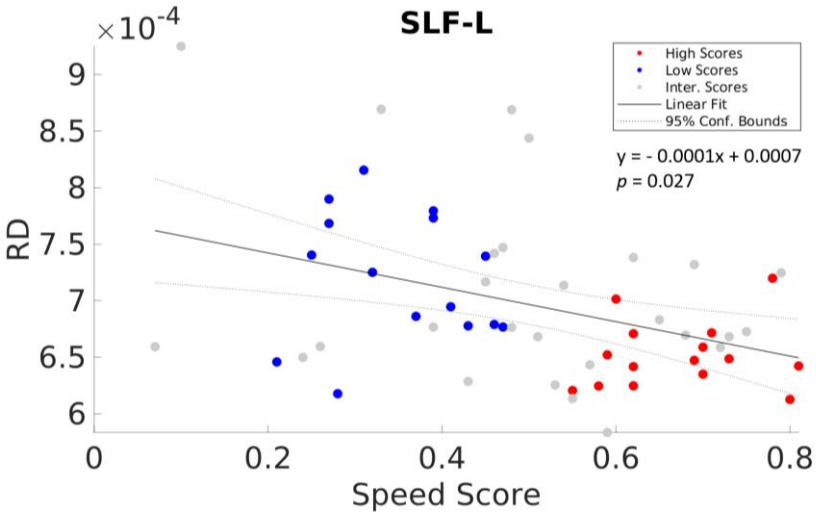
Note. *p < .05; **p < .01; ***p < .001; ns = non-significant, all *p* values were Bonferroni adjusted; FA = fractional anisotropy; MA = mode of anisotropy; RD = radial diffusivity. From A) to C) are presented the group-differences regarding the mean values of each DTI metrics (FA, MA, and RD) in different WM tracts. The black bars correspond to the high-processing speed group and the grey to the low-processing speed group.

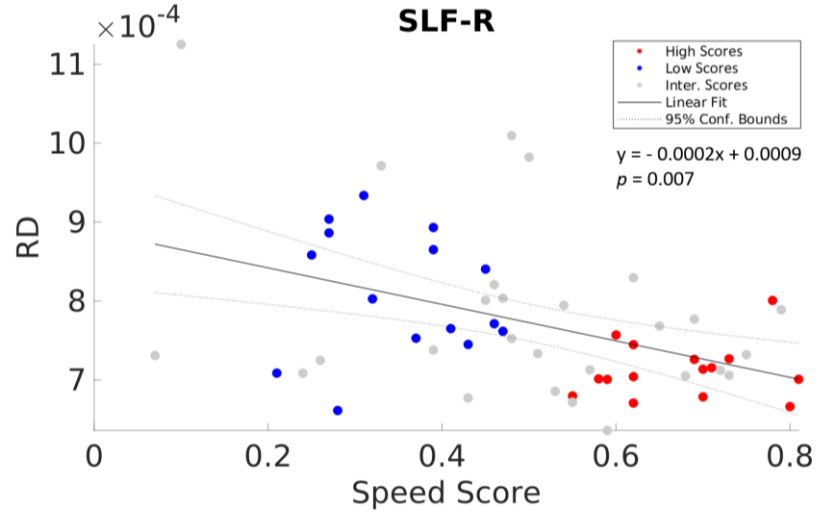
Parallelly, was also conducted a simple linear regression with the scores from the Processing Speed Index (independent variable) and the values from the DTI metrics for every WM fiber tract (dependent variable). As a result, twenty-seven cases were found in which the association between the two variables (the Processing Speed scores and DTI's metrics) expressed linearity. Nevertheless, only seven survived after correcting for multiple comparisons with Bonferroni correction, all of which can be consulted in Figure 3. The fornix presented significant results for all metrics (FA: p = .005; MA: p = .004; RD: p =.003). Regarding RD, in both left and right superior longitudinal fasciculus (p = .027 and p = .007, respectively), the metric's values were found to be linearly related to the Processing Speed scores. The same was found for the left and right uncinate fasciculus (p = .028 and p = .027, respectively).

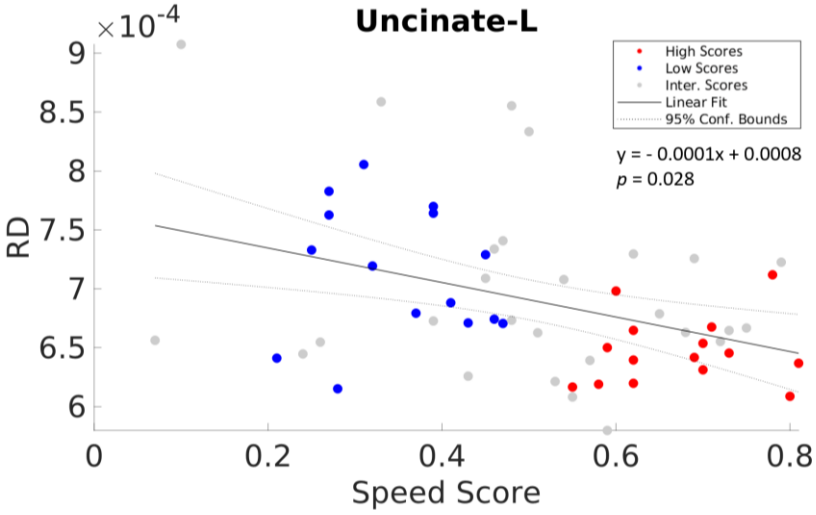
Figure 3

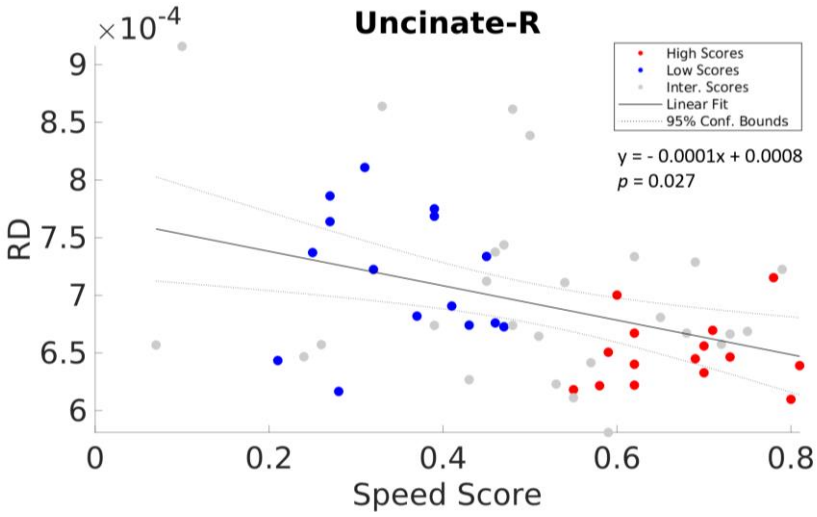
Association between Processing Speed scores and the values of the DTI's metrics (FA, MA, and RD) of the selected WM tracts




SLF-L
×10^-4
RD
Speed Score
High Scores
Low Scores
Inter. Scores
Linear Fit
95% Conf. Bounds
y = - 0.0001x + 0.0007
p = 0.027


SLF-R
×10^-4
RD
Speed Score
High Scores
Low Scores
Inter. Scores
Linear Fit
95% Conf. Bounds
y = - 0.0002x + 0.0009
p = 0.007


Uncinate-L
×10^-4
RD
Speed Score
High Scores
Low Scores
Inter. Scores
Linear Fit
95% Conf. Bounds
y = - 0.0001x + 0.0008
p = 0.028



Note. Scatter plots illustrating the associations between the scores obtained at the Processing Speed index ("Speed Score") and the DTI metrics' values. Each dot in the plots represents a participant. As described, each color corresponds to a different group of scores (red - high-processing speed group; blue - low-processing speed group; grey - intermediate scores group). In the scatter plots there is also information regarding the regression's equation and the level of significance.

4.2. ROI-to-ROI Connectivity (RRC)

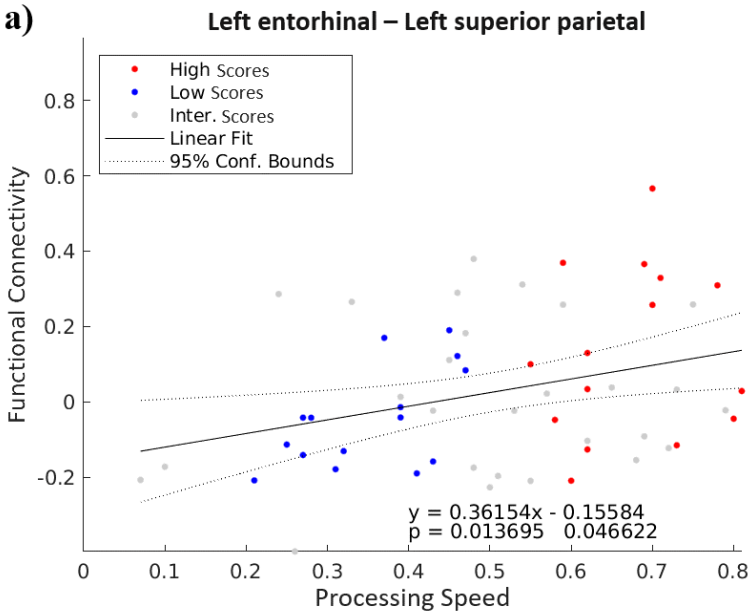
We performed unpaired two-sample t-tests to investigate group differences regarding functional connectivity between every possible pair made from the twelve selected ROIs, but none survived to FDR correction.

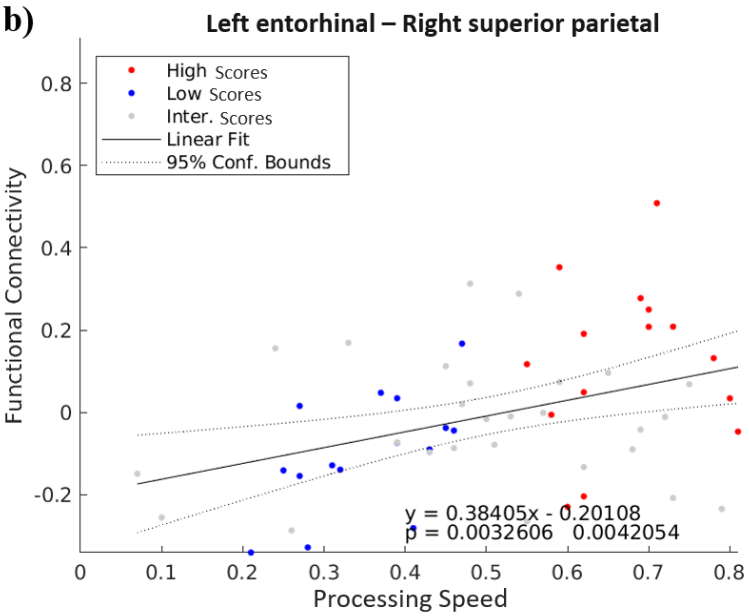
Moreover, simple linear regressions were performed considering the functional connectivity of the pairs of ROIs as dependent variable, and the scores of all fifty-seven participants at the Processing Speed measure as independent variable. This aimed to comprehend how the two variables were related. As a result, the functional connectivity of five pairs of ROIs demonstrated to be significantly linearly related to the Processing Speed scores: left entorhinal – left superior parietal ($t(55) = 2.547$; $p = .014$), left entorhinal – right superior parietal ($t(55) = 3.077$; $p = .003$), posterior cingulate – anterior cingulate ($t(55) =$

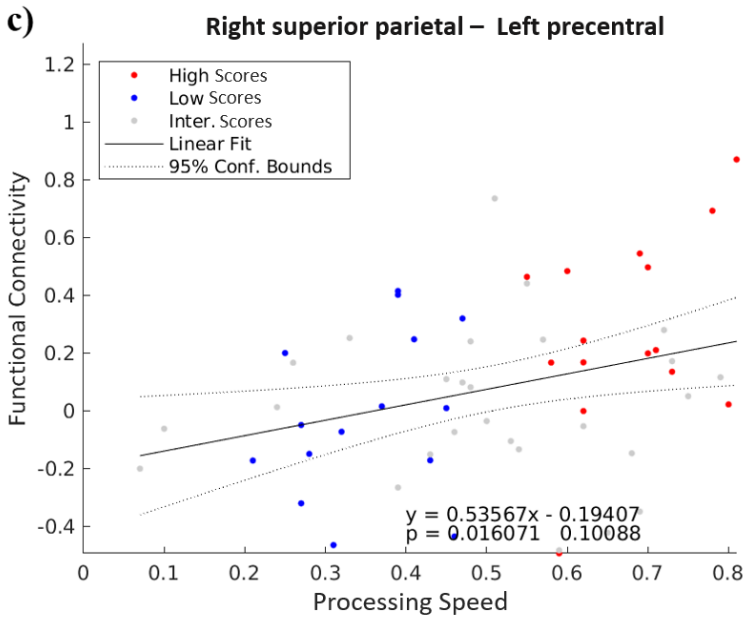
3.649; $p < .001$), precuneus - posterior cingulate ($t(55) = 2.263$; $p = .028$), and right superior parietal – left precentral ($t(55) = 2.184$; $p = .016$). This reveals that higher functional connectivity between all pairs of ROIs are associated with better cognitive performance, as can be consulted in Figure 4. Note that all *p* values are FDR-corrected.

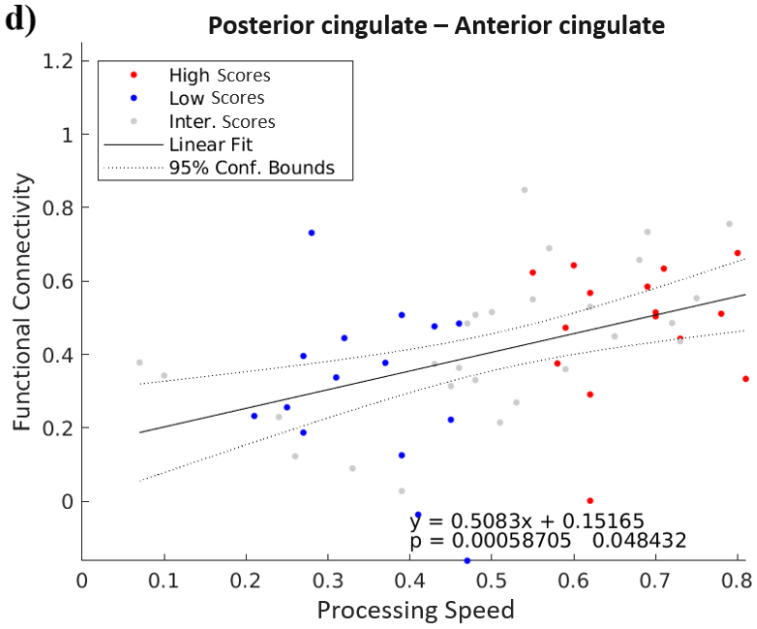
Figure 4

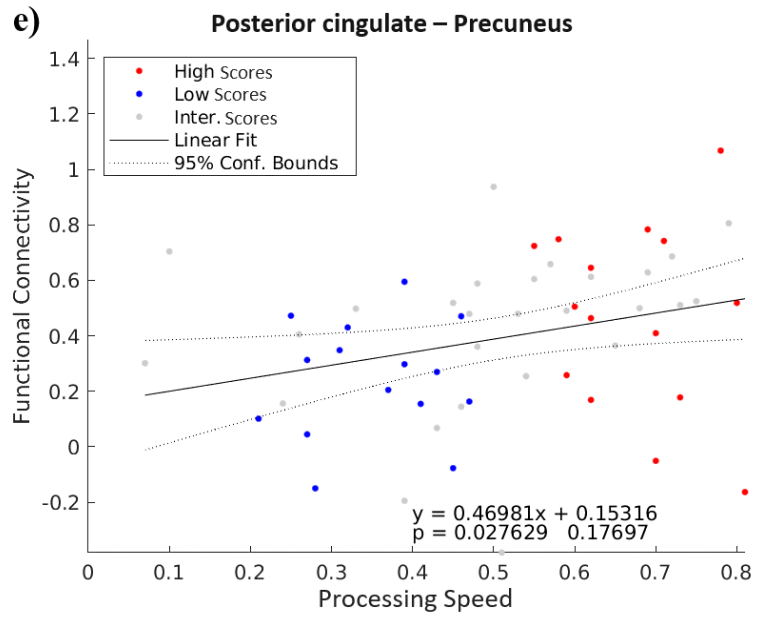
Association between Processing Speed scores and the functional connectivity between the different pairs of ROIs




b)
Left entorhinal – Right superior parietal
High Scores
Low Scores
Inter. Scores
Linear Fit
95% Conf. Bounds
Functional Connectivity
Processing Speed
y = 0.38405x - 0.20108
p = 0.0032606 0.0042054


c)
Right superior parietal – Left precentral
High Scores
Low Scores
Inter. Scores
Linear Fit
95% Conf. Bounds
Functional Connectivity
Processing Speed
y = 0.53567x - 0.19407
p = 0.016071 0.10088





Note. From a) to e) the scatter plots illustrate the significant associations between the functional connectivity of pairs of ROIs and the Processing Speed scores. Each dot in the plots represents a participant. Each color corresponds to a different group of scores (red - high-processing speed; blue - low-processing speed; grey - intermediate scores). The scores from the Processing Speed index concern the composite measure calculated from all three neuropsychological tests administered. The

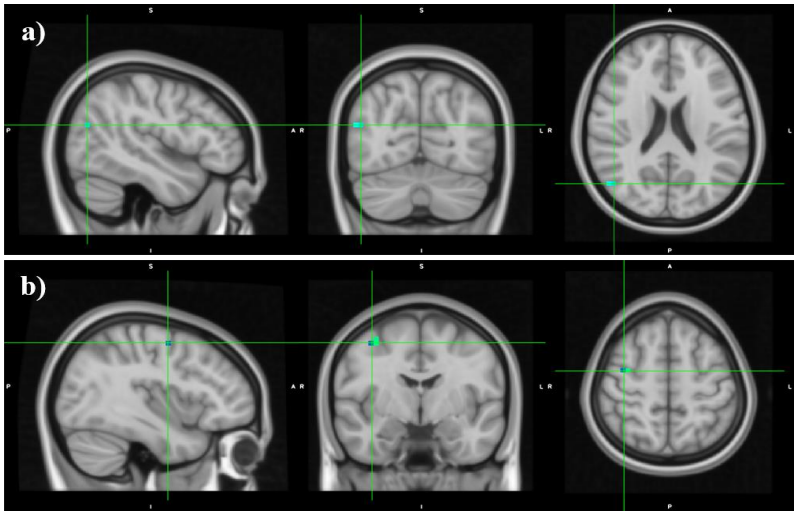
functional connectivity was calculated by correlating the time-series of the two correspondent ROIs. On the lower right of each plot can be consulted the regression's function, as well as the level of significance, FDR-corrected.

4.3. Functional Connectivity of the Resting-State Networks

In order to determine whether the two experimental groups (high- and low-processing speed) differ in terms of the functional connectivity concerning two well-known resting-state networks - the DMN and the FPN - independently for each RSN we performed voxel-wise two-samples t-tests. Regarding the DMN, the analysis yields a statistically significant difference in a small cluster (2 voxels, totaling 16 mm^3) located in the right superior occipital cortex. The low-processing speed group presented higher values of functional connectivity when compared with the high-processing speed group. Likewise, for the FPN, we also found a statistically significant difference in the right precentral gyrus (3 voxels, totaling 24 mm^3), in which the group of high-processing speed showed greater values of functional connectivity than the low-processing speed group. The clusters obtained for each RSN can be seen in Figure 5.

Figure 5

Clusters of voxels that significantly differed between groups in DMN and FPN



Note. Clusters of voxels whose functional connectivity differed between the high- and low-processing speed in both a) DMN and b) FPN. These results were obtained after TFCE and FWE-correction ($p < .05$). The images presented correspond to the sagittal, coronal and axial views, respectively.

5. Discussion

Processing speed is a cognitive function highly susceptible to the aging processes (Salthouse & Ferrer-Caja, 2003) that underpins a wide range of higher-order cognitive abilities (Kail & Salthouse, 1994; Magistro et al., 2015; Waiter et al., 2008). Therefore, its relevance for understanding, predicting, and delaying age-related cognitive deterioration is undeniable. The present study proposed to investigate and unravel some of the neural mechanisms underlying differences in processing speed in older adults, focusing specifically on anatomical and functional connectivity. To achieve this purpose, two main imaging techniques were used - DTI and fMRI -, the first focusing on the microstructure of the WM, whereas the other in the conjoint engagement of different brain regions (with particular interest for processing speed), and the functional connectivity of well-known RSNs. Some main findings worth noting resulted from this. Firstly, although in the literature the majority of works focuses on FA, this study indicates RD as an important metric in what concerns cognitive processing speed, possibly indicating that demyelination is one of the deterioration processes with a higher impact on processing speed in the elderly. Also, results regarding both anatomical and functional connectivity suggest that some cognitive functions have a crucial role in processing speed performance. These correspond to memory (particularly episodic memory), attention, executive functions, and motor planning.

Microstructural disruption of the WM has been previously shown to be central for processing speed performance. This association has long been reported in the literature (e.g., Bennett & Madden, 2014;

Betjemann et al., 2010; Turken et al., 2008). Nevertheless, to the best of our knowledge, only a few studies address it focusing on other metrics besides FA, as is the case of RD. Interestingly the current study presented results consistently highlighting the importance of this measure of diffusivity to processing speed in several main fiber bundles. According to the data, the groups of low- and high-processing speed at the Processing Speed index differed significantly in RD within the splenium of the corpus callosum, the left and right inferior fronto-occipital fasciculus, and the fornix. Likewise, it was found that the same metric is linearly related to the scores obtained at the composite measure of processing speed in the fornix, the superior longitudinal fasciculus, and the uncinate fasciculus. In both cases, lower RD corresponded to faster processing speed in all fiber tracts that presented significant results, which corroborates what was described already in the literature (Jacobs et al., 2013; Kerchner et al., 2012).

Considering that this metric potentially mirrors the level of (de)myelination of the WM structures and, consequently, membrane permeability (Bender et al., 2016; Hong et al., 2015), the results might indicate that poor processing speed performance is associated with the disruption of the fiber bundles by the loss of myelin. This would suggest that neural transmission of information along the tracts is affected, leading to malfunctioning of cognitive processes essential for the processing speed ability (Bender et al., 2016; Turken et al., 2008).

In line with this, the splenium is a posterior part of the corpus callosum that due to its projections to the occipital lobe (Anstey et al., 2007; Fabri et al., 2014), is responsible for interhemispheric communication related to visual processing (Fabri et al., 2014; Imperati et al., 2011), a cognitive process required for the fast and correct execution of most neuropsychological tests used to assess processing speed, since they strongly rely on visual stimuli. For instance, concerning the tests from the Processing Speed index, performing the Symbol Digit Coding and the Symbol Search subtests from WAIS-III

rely on the quick identification of abstract symbols (Crowe et al., 1999), whereas the Stroop test demands fast recognition and discrimination of words and colors. In addition, this fiber tract also underlies visual search (Bennett et al., 2012; Burzynska et al., 2017), a cognitive process inherent to the execution of the Symbol Search, and, to a lesser extent, to the Symbol Digit Coding subtests from WAIS-III. Thus, it seems logical that individuals with faster information transmission along the streams that ensure this cognitive processing as a consequence of better "isolation" (i.e., myelination), present better cognitive performance in tasks highly demanding in terms of processing speed, in comparison to the ones who don't.

The absence of significant results concerning the other callosal regions (i.e., the genu and body of the corpus callosum) might be explained by their different fiber compositions: regions connecting sensorimotor areas, such as the splenium, are characterized by larger (higher caliber) and more myelinated fibers crossing the commissure which benefit the speed of information exchange (Aboitiz & Montiel, 2003). By hypothesis, these different fibers composition might accrue from how the brain is structured so that fiber bundles underlying cognitive processes with the biggest impact on processing speed present the most favorable characteristics to the information transfer. Therefore, the loss of myelin in the splenium could be a better biomarker of cognitive impairments regarding processing speed, when compared to the genu and body of the corpus callosum, which would explain the results obtained.

Another fiber tract whose RD significantly differed between the high- and low-processing speed groups was the inferior fronto-occipital fasciculus, a long-range association fiber bundle that anatomically connects the occipito-temporal (and parietal) areas to the frontal lobe (Rollans & Cummine, 2018). According to the literature, the dorsal pathway of this fiber bundle, which connects the superior frontal and parietal areas, might be involved in the frontoparietal network (Rollands & Cummine, 2018), a functional network known for being

recruited during the execution of tasks requiring top-down attentional control (e.g., visual search) and response selection (Corbetta & Shulman, 2002). Thus, since all those cognitive processes are implicated in processing speed related tasks (such as those included in the Processing Speed index), it would be expected, as was confirmed by the results, that the integrity of the inferior fronto-occipital fasciculus would be relevant to achieve a good level of processing speed performance.

With respect to the fornix, the results clearly show that its integrity, as measured by FA and RD metrics, is a distinguishing factor between the high- and low-processing speed groups. Concretely the results indicate that the diffusion along the fornix, in the group of individuals with a worse performance at the Processing Speed index, is less directional and the tract less myelinated. Additionally, the fornix's values of FA, MA, RD from all participants were found to be linearly related to the results obtained by the same subjects at the Processing Speed index. More specifically, our findings indicate that in faster individuals, besides the fornix's diffusion being more directional and the fiber more myelinated, the anisotropy is also more linear (less planar). This means that the loss of the fornix's integrity, whether due to myelination or other deterioration processes, such as axonal damage, is associated with poorer processing speed performance. Although these are strong results that corroborate those already reported by other studies (e.g., Alexander et al., 2014; Burzynska et al., 2017; Yallampalli et al., 2013), it is still not fully understood why the integrity of the fornix is as relevant for processing speed. One possible hypothesis may rely on the fact that processing speed tasks may recruit memory functions related to the fornix (Ly et al., 2016), such as episodic memory (Syc et al., 2013), visual short-term memory and working memory (Crowe et al., 1999; Zahr et al., 2009). Thus, high (fast) processing speed may be dependent on optimal use of memory systems. Nevertheless, to fully comprehend this question, further investigation is required.

Additionally, other WM tracts revealed a linear relationship with processing speed: the left and right superior longitudinal fasciculus and the left and right uncinate fasciculus. These fasciculi were analyzed separately for each hemisphere, but the results were similar, indicating that, independently of the hemisphere, the lower the RD of the superior longitudinal fasciculus or the uncinate fasciculus, the faster is the processing speed of an individual.

The superior longitudinal fasciculus corresponds to a bidirectional association tract connecting the occipital lobe to the superior frontal cortex (Salami et al., 2012), with projections to the temporal regions (Turken et al., 2008). The association between this tract and processing speed was also found by Turken et al. (2008) that reported that the interplay between anterior and posterior areas is essential for the set of operations performed during the execution of the Symbol Digit Coding subtest from WAIS-III. Like the inferior fronto-occipital fasciculus, this fiber bundle is part of the WM tracts underlying the frontoparietal network, ensuring its correct functioning. As a result, the integrity of the superior longitudinal fasciculus, besides being crucial for attention and executive functioning (Makris et al., 2005), is also relevant for visual search (Bennett et al., 2012) - processes that are important for maintaining high levels of cognitive processing speed.

Regarding the uncinate fasciculus, this association fiber links the anterior temporal lobe to the inferior frontal gyrus (Catani & Mesulam, 2008; Rollans et al., 2017). Until now studies have been associating this fiber bundle to the capability of learning visual associations (according to an animal study; Eacott & Gaffan, 1992), executive functioning (Borghesani et al., 2013), and lexical retrieval and naming (Rollans et al., 2017). The fact that executive functions and processing speed rely on the same tracts (i.e., the superior longitudinal and the uncinate fasciculi) to correctly function might indicate that the disruption of these WM structures is what is underlying the strong relationship

between age-related differences in both cognitive functions (Albinet et al., 2012). Moreover, according to Rémy et al. (2015) the uncinate fasciculus, like the fornix, is associated with episodic memory, which seems to support the already inferred association between episodic memory and processing speed.

The ROI-to-ROI functional analysis presented interesting results pointing out that the increase in functional connectivity in five pairs of ROIs is associated with faster processing speed. This suggests that the exchange of information between those regions that subserve specific cognitive functions is somehow beneficial for processing speed. From this set of pairs makes part the left entorhinal with the left and the right superior parietal, the posterior cingulate with the anterior cingulate and the precuneus, and the right superior parietal with the left precentral.

The first two pairs describe the functional connectivity between the left entorhinal - a region involved in memory-related processes, in particular, associative and episodic memory (Burggren et al., 2011; Devanand et al., 2007; Rodrigue & Raz, 2004) -, and bilateral superior parietal regions which, in turn, are related to higher functions, such as attention, working memory, and language processing (Cabeza & Nyberg, 2000). As such, the fact that processing speed depends on the same regions as memory and attention possibly explains why literature reports that age-related deficits in processing speed are associated with age-related declines in those higher-order abilities (Kail & Salthouse, 1994; Waiter et al., 2008). Additionally, these significant results involving the entorhinal reinforce our previous conclusion that fast-processing speed may depend on the efficient use of memory systems, particularly, episodic memory.

Interestingly, the connection between the left entorhinal and left superior parietal is possibly ensured by the left inferior fronto-occipital fasciculus since it has projections to the medial temporal lobe and the superior parietal (Cabeza & Nyberg, 2000; Hau et al., 2016), whereas the interhemispheric connection (left entorhinal - right superior

parietal) might be partially assured by the splenium, considering it is the callosal region with projections to posterior brain areas (Jang & Kwon, 2014). Hence, these results and the significant DTI findings regarding the referred tracts might be related.

Regarding the posterior cingulate - precuneus pair, it is important to note that the two regions are involved in episodic memory retrieval (Lou et al., 2004; Lundstrom et al., 2005). The significant result concerning this pair points out that, for some reason, the better the communication among the referred regions, the faster the processing speed of an individual. Thus, considering these regions are associated with episodic memory retrieval, once more we speculate that processing speed benefits from the correct functioning of memory processes. Moreover, this result appears to be in line with those described by Genova et al. (2009) that reported the posterior cingulate and the precuneus as part of a network activated during challenging tasks in terms of the processing speed ability. However, the cerebellum that was included in the referred network, in the current study did not present any significant result.

Another pair whose functional connectivity was positively associated with processing speed was the posterior cingulate - anterior cingulate. As already described, the posterior cingulate has an important role for episodic memory retrieval (Lou et al., 2004), whereas the anterior cingulate is associated with response selection (Mansouri et al., 2009) and attentional control (Posner, 1994). According to Madden et al. (2012), one of the hallmarks of the aging effect on functional resting-state activity is the reduction of the functional connectivity between the regions above-mentioned. Thus, considering our finding indicates that processing speed benefits from a better exchange of information between the posterior and anterior cingulate, it is plausible to think that the disruption in the functional connectivity between both regions might be underlying the occurrence of processing speed deficits with advancing age. In addition, we can also interpret that this result

corroborates some of the findings previously reported which indicate the processing speed as a cognitive function that strongly relies on memory and attentional processes.

Since both the posterior and anterior cingulate, as well as the precuneus correspond to some of the DMN's regions, our results may be considered as in line with studies referring the functional connectivity within DMN is associated with processing speed (Bonavita et al., 2014; Savini et al., 2019; Staffaroni et al., 2018; Sumowski et al., 2010).

Lastly, the functional connectivity between the right superior parietal and the precentral gyrus also linearly related to the processing speed results at the Processing Speed index. This pair represents the communication between an area responsible for the multimodal sensory information (Cabeza & Nyberg, 2000) and a primary motor area (Ugur et al., 2005), which correspond to cognitive processes expected to be implicated during the execution of processing speed tasks and to be working alongside, continuously exchanging information. Furthermore, both areas are associated with motor imagery, that is, the conscious mental representation of a movement without performing it (Fleming et al., 2009). Speculating, this possibly means that processing speed benefits from a previous "internal rehearsal" and planning of actions that the tasks underlying processing speed might request.

According to Wolpert et al. (2013), parietal regions and precentral motor areas communicate so that the first ones receive input regarding intended actions and ongoing movements and, hence, predict possible mistakes to correct them rapidly. Therefore, this supports the idea that the superior parietal and the precentral gyrus are implicated in motor planning, making the motor function more efficient and contributing to a faster processing speed performance, which is also congruent with the positive correlation found by Stöckel et al. (2017) between anticipatory motor planning and processing speed.

It should be noted that the number of participants might explain

some discrepancies (in both the DTI and ROI-to-ROI analyses) between the results obtained for the comparisons between the high- and low-processing speed groups and for the simple linear regression, since the first only included thirty subjects, instead of fifty-seven as occurred in the regression.

Relatively to the ICA analysis, it revealed that the experimental groups (high- and low-processing speed) differ, in relation to the DMN's functional connectivity, in a small cluster (two voxels) located in the right superior lateral occipital cortex. More precisely, the high-processing speed group presented less functional connectivity than the low-processing speed group, regarding that cluster. However, according to the dedifferentiation phenomena, it would be expected that higher functional connectivity would be associated with higher cognitive processing speed (Geerligs et al., 2015; Nashiro et al., 2017), in opposition to what was found. Nevertheless, given the cluster's size, this result has to be interpreted cautiously, once this could simply represent an artifact. The same stands for the FPN's results that only showed a significant cluster of three voxels in the precentral gyrus. As would be expected, the high-processing speed group presented a greater mean value of functional connectivity in this primary motor area.

Additionally, one limitation can be pointed out and it accrues from the fact that the sample is highly educated and non-representative of the Portuguese population. We can hypothesize this resulted from having recruited the majority of the participants at senior universities where people tend to be more educated. On the other hand, another explanation might rely on the fact that highly educated individuals generally are more cognitively preserved and thus, more easily fulfil all the inclusion criteria. Nevertheless, it is worth noting that this work presents a considerable sample size, considering it reports to a study with MRI data. This added value to the study which has stronger statistical power comparatively to other studies with a smaller sample size.

Concerning future directions, we think it would be interesting to conduct a new study in which the participants perform similar tasks to the ones included in the Processing Speed index inside the MRI scanner. This would enable the study of other neural aspects underlying the processing speed ability, for instance, it would make it possible to determine which regions and networks are being recruited during highly demanding tasks regarding this cognitive function and verify if the obtained results corroborate the findings from the current study.

6. Conclusions

The current study aimed to evaluate, in older adults, how brain connectivity can influence processing speed. After employing different approaches focusing on anatomical and functional connectivity, some interesting findings arose.

Firstly, our results indicate that the loss of myelin has a preponderant role in processing speed performance. Furthermore, data revealed that both the fornix's integrity and the functional connectivity of the entorhinal, posterior cingulate, and precuneus are associated with processing speed, suggesting that this cognitive function might rely on the optimal functioning of memory systems, with particular emphasis on episodic memory. Still, regarding the entorhinal, our results point out that it has greater relevance for processing speed than it was thought until this moment. Likewise, based on our findings we consider that motor planning, attention, and executive functioning might have an important role in processing speed performance. Lastly, in what concerns the functional connectivity within the DMN and FPN, we did not find group differences that we considered of statistical relevance.

Taking all these findings together, we consider that this study brings us a step closer to understanding the processes behind differences in processing speed in the elderly and, therefore, to have a greater insight into the aging phenomena. Furthermore, the study presents novel findings that should be investigated in more detail in the future.

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