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BRAIN CONNECTIVITY AND COMPENSATORY PROCESSES IN AGING: STUDIES FOCUSED ON LANGUAGE ABILITIES

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Supervised by:

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'Above all, don't fear difficult moments. The best comes from them'

Rita Levi-Montalcini

A mi madre y mi padre,
que lo dejaron todo para que yo tuviera una vida mejor.
A mi hermana y mis abuelos.

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LIST OF SCIENTIFIC PAPER INCLUDED IN THE THESIS

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2. **Gonzalez-Burgos L**, Barroso J, Ferreira D. Cognitive reserve and network efficiency as compensatory mechanisms of the effect of aging on phonemic fluency. *Aging (Albany NY)*. 2020; 12:23351-23378.

3. **Gonzalez-Burgos L**; B. Pereira J.; Mohanty R, Barroso J, Westman E, Ferreira D. Cortical networks underpinning compensation of verbal fluency in normal aging. *Cerebral Cortex (New York, N.Y.: 1991)*. https://doi.org/10.1093/cercor/bhab052 *(Online ahead of print).*

4. Mohanty R, **Gonzalez-Burgos L**, Diaz-Flores L, Muehlboeck J-S, Barroso J, Ferreira D, Westman E. Functional Connectivity and Compensation of Phonemic Fluency in Aging. *Frontiers in Aging Neuroscience. (Manuscript under review).*

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AF	Action fluency
BDRS	Blessed Dementia Scale
BM	Brain maintenance
BNT	Boston Naming Test
BR	Brain reserve
BRAPH	BRain Analysis using graPH theory
BRC	Brain reserve capacity
COWAT	Controlled Oral Word Association Test
CR	Cognitive reserve
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
CTT	Color Trails Test
FAQ	Functional Activity Questionnaire
***f*MRI**	Functional magnetic resonance imaging
FSPGR	Fast Spoiled Gradient Echo
FWD	Framewise displacement
FWE	Family-wise Error
GENIC	Group of Neuropsychological Studies of the Canary Islands
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HighCR	High cognitive reserve
HighPF	High performance
HP	High performance
JLOT	Judgment of Line Orientation Test
LM	Logical Memory
LowCR	Low cognitive reserve
LowPF	Low performance
LP	Low performance
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination

MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NR	Neural reserve
OA	Older age
OA-HP	Older age with high phonemic fluency performance
OA-LP	Older age group with low phonemic fluency performance
PASA	Posterior-Anterior Shift in Aging
PASAT	Paced Auditory Serial Addition Test
PF	Phonemic fluency
RF	Random forest
SF	Semantic fluency
SPM	Statistical Parametric Mapping
STAC	Scaffolding Theory of Aging and Cognition
STAC-r	Scaffolding Theory of Aging and Cognition – revised
STROOP	Stroop Test
TAVEC	Test de Aprendizaje Verbal España-Complutense
TE	Echo time
TMT A	Trail Making Test-A
TR	Repetition time
VF	Verbal fluency
VR	Visual Reproduction Test
WAIS-III	Wechsler Adult Intelligence Scale, Third edition
WMS-III	Wechsler Memory Scale, Third Edition Technical Manual
YA	Younger age
YA-HP	Younger age group with high phonemic fluency performance
YA-LP	Younger age group with low phonemic fluency performance

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1. INTRODUCTION

1.1. Normal aging and language

Changes in normal cognitive performance have been well documented in earlier research. Some abilities such as executive functions, processing speed, memory, attention, visuoconstructive and visuospatial functions decline with age (Ferreira et al., 2015; Harada et al., 2013; Salthouse et al., 1995; Salthouse, 2009; Singh-Manoux et al., 2012). Other cognitive abilities, such as crystallized abilities and language remain stable or even improve with age (Park & Reuter-Lorenz, 2009; Salthouse, 2010; Singh-Manoux et al., 2012). Besides these cognitive changes, neuroanatomical changes have also been observed, such as lower total volume, cortical thickness, gray matter reduction and changes in synapses (Fjell & Walhovd, 2010).

Regarding language, this is one of the most complex cognitive functions in humans. This ability is essential to the communication between people and its alteration is considered as a sign of lower intelligence or pathology (la Tourette & Meeks, 2000). Language is overall robust to the effect of aging but there are differences across linguistic components. While some components such as comprehension, semantic abilities, and vocabulary remain relatively stable or even improve with age (Ansado et al., 2013; Shafto & Tyler, 2014), other language components such as verbal fluency (VF) and naming are among the most vulnerable cognitive functions to aging (Machado et al., 2018).

VF's cognitive tests assess the ability to produce as many words as possible following specific rules and within a timeframe, usually 60-seconds. Words produced must begin with a specified letter (e.g., letter "F"; phonemic fluency (PF)), belong to a specific category (e.g., "animals", semantic fluency (SF); "to run", action fluency (AF)) and similar words and repetitions are not permitted. Results in the literature regarding a decline in VF with age are controversial. Some authors have found the effect of age on SF performance (Gladsjo et al., 1999; Kempler, Teng, Dick, Taussig, & Daviss, 1998; Lezak et al., 2012; Tombaugh et al., 1999); and others on PF performance (Auriacombe et al., 2001; Bäckman & Nilsson, 1996; Bryan et al., 1997; Mathuranath et al., 2003; Rodriguez-Aranda & Martinussen, 2006). Researches focused on the differential effect of age on SF and PF performance found a decline in word production on SF but did not on PF (Elgamal et al., 2011; Foldi et al., 2003; Kemper & Sumner, 2001; Parkin & Java, 1999; Troyer et al., 1997). The opposite result was found by Bryan et al. (1997), Mathuranath et al. (2003), and Stolwyk et al. (2015). Despite of these different findings, there is certain agreement considering that SF declines with age, whereas PF shows more stability with age. Studies on AF in normal aging are less frequents, and most of these studies could be found in diseases with a movement disorder such as Parkinson's disease (Herrera et al., 2012; Piatt et al., 1999a; Signorini & Volpato, 2006). In the AF modality, the effect of age informed in previous studies is also divergent. Most of them did not find an effect of age (Correia, 2010; Molina, 2015; Piatt et al., 1999b; Piatt et al., 2004), whereas fewer found an effect of age (Ferreira, 2012; Lezak et al., 2012).

As well as age-related differences on VF, the association of different cognitive domains with the VF modalities have also been investigated. Previous studies have observed a relationship between performance in SF and performance in test of processing speed (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), lexical access (Kraan et al., 2013; Lezak et al., 2004; Stolwyk et al., 2015), executive functions (Amunts et al., 2021; Shao et al., 2014; Stolwyk et al., 2015), and working memory (Kraan et al., 2013). Performance in PF has been associated with performance in tests of processing speed (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), attention (Ruff et al., 1997; Troyer et al., 1997), lexical access (Lezak et al., 2004), executive functions (Bolla et al., 1990; Rodriguez-Aranda & Sundet, 2006; Ruff et al., 1997; Shao et al., 2014; Stolwyk et al., 2015), and memory (Ardila et al., 1998; Ruff et al., 1997). Studies on AF did not find any relationships with episodic memory nor picture naming (Piatt et al., 1999b; Piatt et al., 2004).

1.2. Neural correlate of VF

Studies on functional magnetic resonance imaging (*f*MRI) and PF tasks reveal that several frontal regions are involved in work production, such as the left superior frontal, the middle frontal and the left inferior frontal gyrus (including the Wernicke's area) (Birn et al., 2010; Costafreda et al., 2006; Marsolais et al., 2014, 2015; Methqal et al., 2019; Tomasi & Volkow, 2012; Zhang et al., 2013), and other regions such as bilateral superior parietal (Birn et al., 2010; Marsolais et al., 2015), right inferior parietal (Tomasi & Volkow, 2012), left inferior parietal (Marsolais et al., 2014); middle temporal (Methqal et al., 2019; Zhang et al., 2013), and bilateral inferior temporal (Marsolais et al., 2014; Methqal et al., 2019; Tomasi & Volkow, 2012). Further, other regions have been reported to a lesser extent such as occipital regions (Birn et al., 2010; Marsolais et al., 2014, 2015), cerebellum (Marsolais et al., 2014, 2015; Tomasi & Volkow, 2012); cingulate cortex (Halari et al., 2006; Marsolais et al., 2015; Methqal et al., 2019); bilateral insula (Marsolais et al., 2014), left thalamus (Halari et al., 2006; Marsolais et al., 2015; Methqal et al., 2019), left pallidum (Marsolais et al., 2014), left and caudate nucleus (Halari et al., 2006; Methqal et al., 2019). While some authors found association between SF and the temporal lobe, other authors highlighted a strong association between PF and frontal lobe functioning (Azuma, 2004; Dennis & Cabeza, 2008; Grogan et al., 2009; Henry & Crawford, 2004; Piatt et al., 1999b). Regarding AF, there has been less research investigating the neural mechanisms underlying AF tasks during aging (Kochhann et al., 2018). AF, considered as an indicator of executive functioning, has also been associated with frontal regions (Paek et al., 2020; Piatt et al., 1999b), including frontal-subcortical (frontal-striatal) circuits, possibly given the involvement of motor planning and sensorimotor systems related to action word processing (Bak, 2013; Horoufchin et al., 2018).

The reason for these divergent findings in VF, both in cognitive performance and neural substrate, is partially related to the univariate approach across most of the studies.

However, the aging process is complex and heterogeneous, and is influenced by biological differences (e.g., synapse count), life experiences (e.g., development, education), among other factors (Reuter-Lorenz & Park, 2014). As an alternative to univariate analyses, more recently, multivariate approaches have addressed the study of age-related cognitive changes considering these variables to disentangle why some individuals develop dementia while others have successful aging.

1.3. Compensatory brain changes and successful aging

One of the first proposals regarding brain changes in aging was the *"age differentiation hypothesis"* (Garrett, 1946). According to this hypothesis, the organizational structure of cognitive abilities changes with age (Balinsky, 1941). In particular, cognitive abilities shift from a differentiated condition at younger ages (abilities are separate systems: differentiation) into a dedifferentiated condition at older ages (abilities are more interrelated with each other: dedifferentiation) (Baltes et al., 1980). This higher intercorrelation proposed by the *"age dedifferentiation hypothesis"* is associated with reduced neural specificity to cognitive processes, due to biological brain aging and increased interhemispheric activations (Baltes & Lindenberger, 1997; Baltes et al., 1980; Hülür et al., 2015).

Several decades later, the concept of "reserve" emerged from the observation of the mismatch between the degree of brain pathology or brain damage and the clinical manifestation of that damage observed in some patients (Katzman et al., 1989; Stern, 2002, 2009). Initially, reserve models were divided into *"passive models"* and *"active models"*. Passive models might include brain size or synapse count. As previously proposed, are included: *Brain reserve* (BR) (Katzman, 1993), *neural reserve* (NR) (Mortimer et al., 1981), and the threshold model, associated with the construct of *brain reserve capacity* (BRC) (Satz, 1993). The passive reserve models suggest that there are individual differences in BRC, and a critical threshold that causes clinical or functional deficits once it is depleted. More BRC can be considered a protective factor, while less BRC would impart vulnerability. Contrary, active reserve models suggest that the brain actively attempts to compensate for brain damage (Stern, 2002, 2009). Two types of reserve have been proposed: *cognitive reserve* (CR) and *compensation*. CR refers to the use of brain networks or cognitive paradigms that are less susceptible to disruption, considered a normal process used by healthy individuals when coping with task demands. *Compensation* refers to the use of brain structures or networks that are generally not used by individuals with intact brains in order to compensate for brain damage (Stern, 2002, 2009).

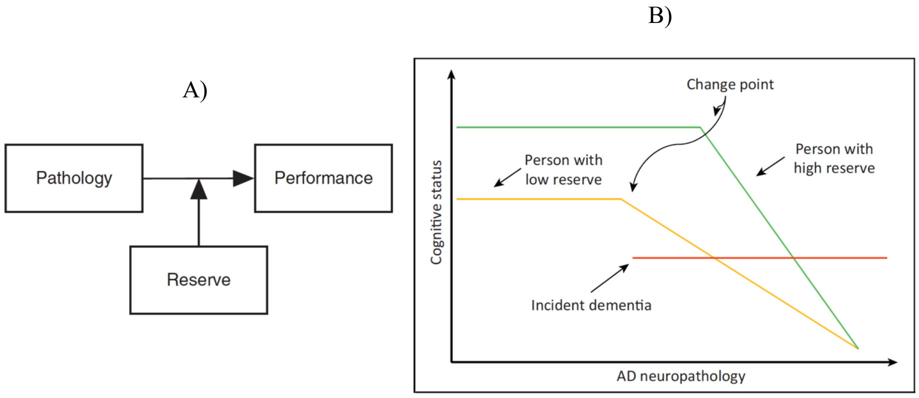
These concepts have evolved after more than 20 years of research (Stern et al., 2018a, 2020). Recently, CR has been redefined as “the adaptability (i.e., efficiency, capacity, flexibility) of cognitive processes that help to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult”. BR refers to the neurobiological capital at any point in time, conceived as neurobiological capital (numbers of neurons, synapses, ...). Then, some people are allowed to better cope with brain aging and pathology than others before clinical or cognitive changes emerge because of individual variation in the structural characteristics of the brain. Meanwhile, *brain maintenance* (BM) is defined as the preservation of neural resources (Cabeza et al., 2018; Nyberg et al., 2012) or reduced development of age-related brain changes and pathology over time based on genetics or lifestyle, and considered the brain is modifiable based on experience (Stern et al., 2018a, 2020). Then, CR can impact BM and lead to individual differences in morphologic brain decline associated with normal aging. The term *compensation* has been defined as the recruitment of brain structures or networks (and thus cognitive strategies) not generally used by individuals with intact brains in response to these brain changes, resulting in improvement or maintenance of performance (Stern et al., 2018a). Comparably, Cabeza et al. (2018)

defined compensation as the cognition-enhancing recruitment of neural resources in response to relatively high cognitive demand, enhancing cognitive performance. Figure 1 illustrates how CR may mediate between Alzheimer's disease (AD) pathology and its clinical expression, based on extensive epidemiological and experimental evidence.

Concerning VF performance, high CR level, usually measured as a high level of education, has been associated with a higher number of produced words in PF (Auriacombe et al., 2001; Balduino et al., 2019; Crossley et al., 1997; Roldán-Tapia et al., 2012; Tessaro et al., 2020; Tombaugh et al., 1999).

Figure 1

Mediation of CR between AD pathology and its clinical expression.



Note: Evidence from epidemiological and imaging studies. Figure A) extracted from Conceptual and measurement challenges in research on cognitive reserve (p. 594), by Jones et al., 2011, *Journal of the International Neuropsychological Society: JINS*, 17(4). Figure B) the x-axis represents AD pathology, and the y-axis represents cognitive function. Extracted from Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve (p. 503), by Barulli and Stern, 2013, *Trends in Cognitive Sciences*, 17(10); originally from Cognitive reserve (p. 2017), by Stern, 2009, *Neuropsychologia*, 47(10). AD: Alzheimer's disease.

Other two new concepts have arisen in the new field of preclinical AD to explain two distinct mechanisms of coping with pathology *vs.* avoiding pathology: *resistance vs. resilience* (Arenaza-Urquijo & Vemuri, 2018). *Resistance* refers to avoiding pathology (i.e., remaining cognitively normal with low AD pathology), whereas *resilience* refers to coping with pathology (i.e., remaining cognitively normal despite significant AD pathology). These two concepts have been used as an umbrella to define some concepts mentioned above. Brain resistance has been associated with brain maintenance, neural efficiency, CR (neural reserve) and (neuro)protection. Brain resilience has been associated with compensation, metabolic and structure maintenance, BR (the threshold model) and CR (neural compensation) (Arenaza-Urquijo & Vemuri, 2018).

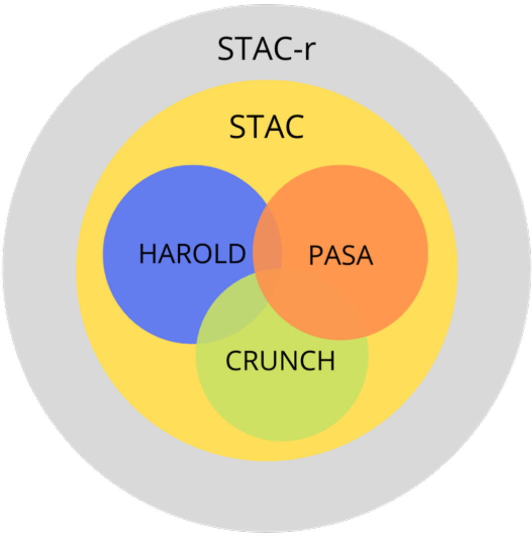
1.4. Theoretical perspective on compensatory processes

Higher activation of neural networks has been frequently reported in older adults in comparison with younger adults in neuroimaging studies. This overactivation has been associated with superior cognitive performance in older adults, suggesting compensatory processes of age-related decline and maintained cognitive performance. Several theories have been proposed to account for age differences in brain activation, with a distinctive explanatory scope with regard to compensatory processes (Festini et al., 2018): the Hemispheric Asymmetry Reduction in Older Adults model (HAROLD, Cabeza (2002)), the Posterior-Anterior Shift in Aging phenomenon (PASA, Davis et al. (2008); Dennis and Cabeza (2008)), the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH, Park and Reuter-Lorenz, (2009); Reuter-Lorenz and Cappell (2008); Reuter-Lorenz and Lustig, (2005); Reuter-lorenz and Mikels (2006)), the Scaffolding Theory of Aging and Cognition (STAC, Park and Reuter-Lorenz (2009)) and the STAC theory - revised (STAC-r, Reuter-Lorenz and Park (2014)).

The HAROLD model proposes that older adults show less lateralized prefrontal activity than younger adults while performing the same cognitive task. This asymmetry reduction was proposed to reflect either compensatory processes or dedifferentiation (Cabeza, 2002). The PASA phenomenon proposes that less activation of posterior brain regions (e.g., occipital) and greater activation of anterior brain regions (e.g., frontal) relative to younger adults compared to older adults is a compensatory mechanism, what reflects an attempt to increase performance and counterweight occipitotemporal sensory deficits (Davis et al., 2008; Dennis & Cabeza, 2008). The CRUNCH hypothesis suggests that age-related overactivation is a compensatory process, and this overactivation varies with the level of task demand at any age. Additional compensation is not possible once the older adults reach their capacity for compensatory recruitment (Banich, 1998; Park & Reuter-Lorenz, 2009; Reuter-Lorenz et al., 1999; Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Lustig, 2005; Reuter-lorenz & Mikels, 2006). The STAC theory proposes that older adults recruit compensatory neural scaffolding as an adaptive response to declining brain structure and brain function from a broader scope (Park & Reuter-Lorenz, 2009). In the context of older age, scaffolding implies the recruitment of additional/complementary neural resources to support specialized circuitry to preserve cognitive performance (Festini et al., 2018). Due to the prefrontal cortex’s flexible configuration and domain-general involvement, it is a frequent locus of scaffolding, although it may occur in any brain region (Badre, 2008; Miller et al., 2002). The STAC-r theory goes further and take as more comprehensive perspective, incorporating all characteristics of the STAC theory. It includes a longitudinal change in cognition and life-course experiences, which can serve as neural enrichment (e.g., education, physical fitness) or neural depletion (e.g., depression, vascular disease) factors (Reuter-Lorenz & Park, 2014) (See Figure 2). The level of cognition and rate of cognitive change may be predicted by brain structure, brain function, and compensatory scaffolding. At the same time, these factors can be directly influenced by enriching and depleting factors (See Figure 3) throughout the lifespan, even in the absence of brain pathology.

Figure 2

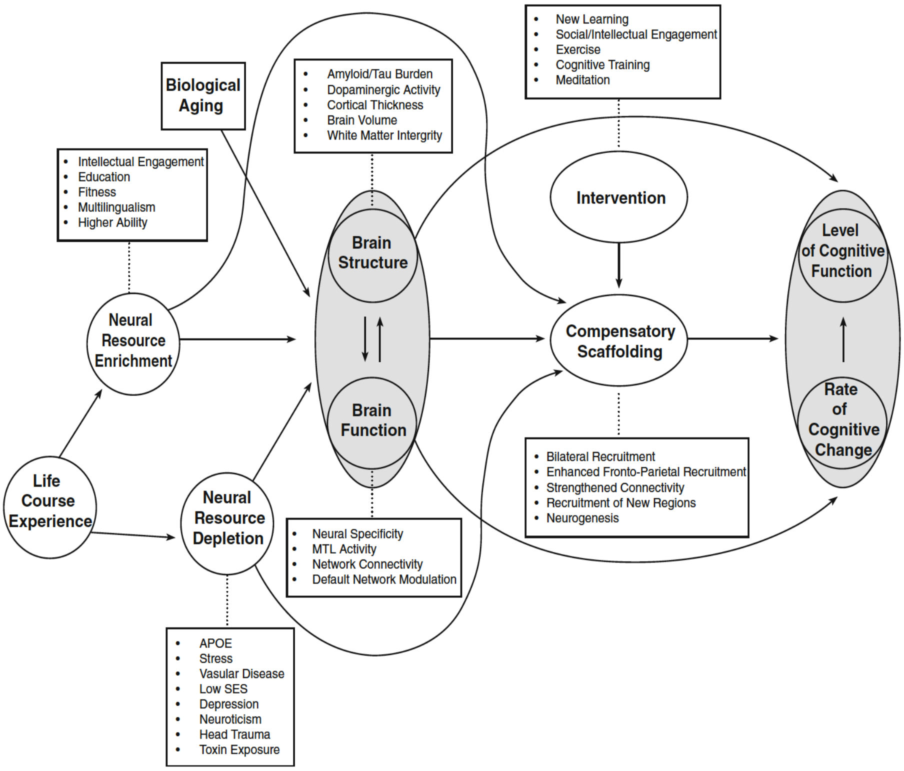
Depiction of the explanatory scope of the HAROLD, PASA, CRUNCH, STAC, and STAC-r models.



Note: HAROLD, PASA, and CRUNCH explain portions of the functional brain changes discussed within STAC and STAC-r. All the models converge on the idea that age-related differences in neural activation can be compensatory to support cognitive performance. Adapted from Theoretical Perspectives on Age Differences in Brain Activation: HAROLD, PASA, CRUNCH—How Do They STAC Up? (p. 8), by Festini et al., 2018, *Oxford Research Encyclopedia of Psychology*. HAROLD: Hemispheric Asymmetry Reduction in Older Adults; PASA: Posterior-Anterior Shift in Aging; CRUNCH: Compensation-Related Utilization of Neural Circuits Hypothesis; STAC: Scaffolding Theory of Aging and Cognition; STAC-r: Scaffolding Theory of Aging and Cognition, revised model.

Figure 3

A conceptual model of the Scaffolding Theory of Aging and Cognition-revised (STAC-r).



Note: The STAC-r model incorporates life-course variables that impact the structure and function of the aging brain. Extracted from How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition (p. 360), by Reuter-Lorenz and Park, 2014, *Neuropsychology Review*, 24(3).

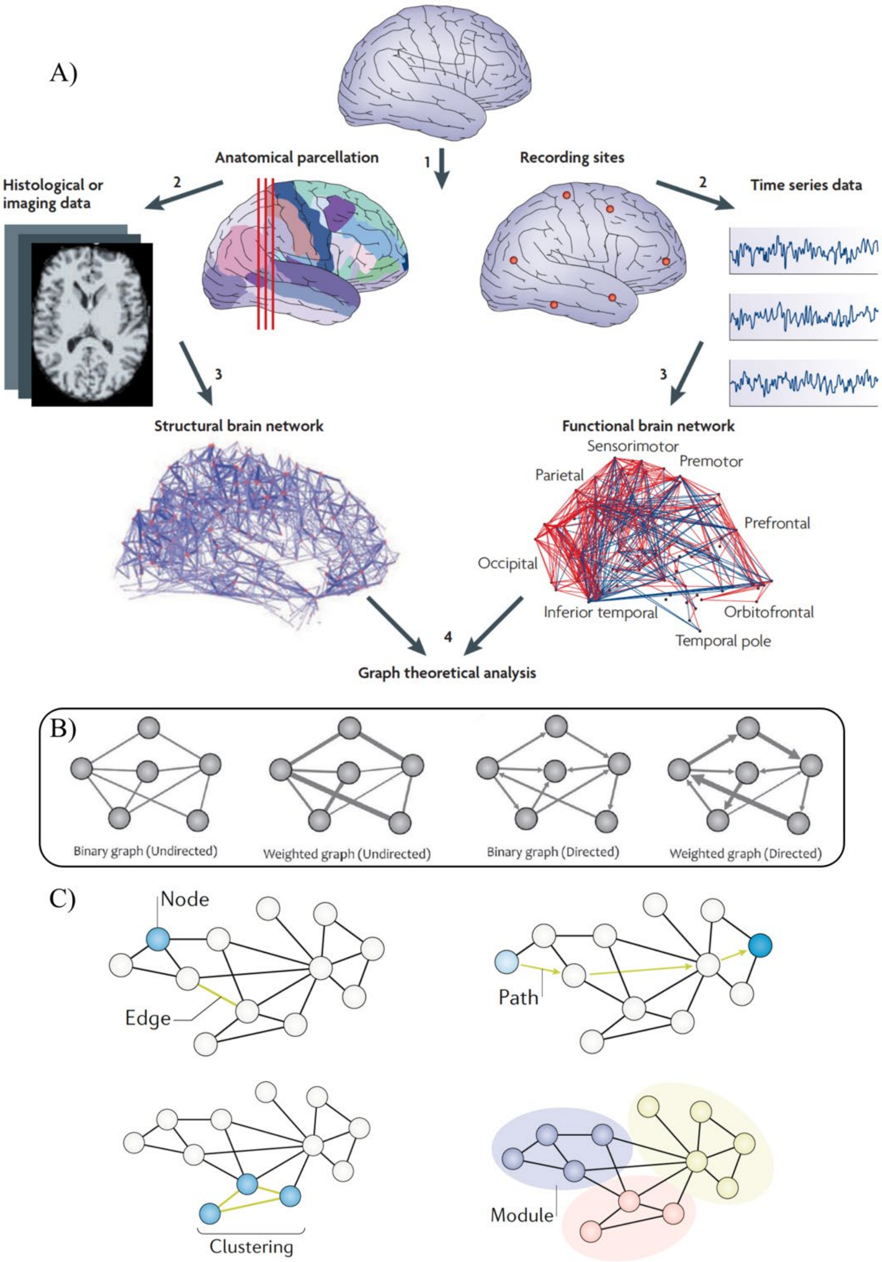
1.5. Brain connectivity and graph theory: a multivariate approach.

The study of brain connectivity and the role of network architecture have recently emerged in the field of connectomics (Sporns, 2012). This approach describes neural systems in terms of graphs or networks comprising neurons and/or brain regions as nodes, and synaptic connections, interregional pathways as edges (Sporns, 2013; van den Heuvel & Sporns, 2013). Figure 4 shows the fundamental components of graph theory. In neuroscience, the graph theory approach has been traditionally used to study networks and brain connectivity changes in normal aging (Achard & Bullmore, 2007; Dennis & Thompson, 2014; Meunier et al., 2009) and pathology (Ferreira et al., 2019; Pereira et al., 2018), using brain regions as nodes and the connection between them as edges. However, very few studies have applied graph theory on cognitive data (Garcia-Ramos et al., 2015, 2016; Jonker et al., 2019; Kellermann et al., 2015, 2016), using the cognitive functions as nodes and the connection between them as edges.

Three graph measures are relevant understanding of compensatory mechanisms, differentiation, and dedifferentiation processes: *efficiency, transitivity* and *strength. Efficiency* measures how efficiently information is exchanged over the network (Latora & Marchiori, 2001). *Transitivity* reflects how well the nodes are connected to nearby nodes forming cliques. *Strength* represents respective magnitudes of correlational or causal interactions (Rubinov & Sporns, 2010). Studies in brain connectivity using graph theory have found lower performance and reduced network efficiency, associated with decreased connectivity within the left hemisphere syntax network and widespread interhemispheric connectivity associated with age, consistent with the age-related dedifferentiation hypothesis (Meunier et al., 2014).

Figure 4

Brain networks, connectomics and network theory measures.



Note: A) Structural and functional brain networks. 1: Parcellation schemes can use prior anatomical criteria or the functional connectivity profiles of different regions. 2: measures of both functional and effective connectivity. 3: the choice of the threshold used to generate an adjacency matrix from the association matrix. 4: quantification of network parameters. B) Type of graph. C) Graph measures. Adapted from Complex brain networks: Graph theoretical analysis of structural and functional systems (p. 187), by Bullmore and Sporns, 2009, *Nature Reviews. Neuroscience,*10(3); Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks: A Systematic Review (p. 7), by Farahani et al., 2019, *Frontiers in Neuroscience*, *13*; and A cross-disorder connectome landscape of brain dysconnectivity (p. 2), by van den Heuvel and Sporns, 2019, *Nature Reviews Neuroscience*, 20(7).

1.6. Rationale

Despite extensive research on the effect of age on VF, findings are not entirely consistent. The reason for these contradictory findings is partly related to methodological differences across studies such as the use of different study designs (longitudinal *vs.* cross-sectional), the sample (size, selection criteria, age groups, age span, etc.), and the statistical approach (correlation *vs.* means comparison *vs.* covariance analysis, etc.), among others. The variation in the age span studied has implications beyond mere methodological differences because different compensatory mechanisms may be active and influence fluency performance differently at different ages.

Previous studies have reported an association of performance in VF with performance in other linguistic and non-linguistic cognitive functions such as processing speed, lexical access, executive functions, attention and memory (Amunts et al., 2021; Bolla et al., 1990; Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013; Rodríguez-Aranda & Sundet, 2006; Ruff et al., 1997; Shao et al., 2014; Stolwyk et al., 2015). However, whether these associations contribute to compensatory effects across age is unknown. Besides, these other cognitive domains also may decline due to the impact of age-related atrophy (Ferreira et al., 2014; Lowe et al., 2019; Raz & Rodrigue, 2006; Sungura et al., 2020). Due to the complexity of human cognition, an interesting approach is to investigate the contribution of different cognitive functions to VF performance by using multivariate methods for data analysis.

There has been an increasing interest in compensatory mechanisms that occur during aging (Cabeza, 2002; Fitzhugh et al., 2019; Grady, 2008; Morcom & Johnson, 2015). Previous studies have linked compensatory mechanisms to the concepts of CR and neural efficiency. Studies in PF have found that people with higher CR produce more words (Auriacombe et al., 2001; Balduino et al., 2019; Crossley et al., 1997; Roldan-Tapia et al., 2012; Tombaugh, 1999). Furthermore, people with higher CR have greater neural efficiency (Bartres-Faz et al., 2009; Fernández-Cabello et al., 2016). So far, to our knowledge, only few studies investigated efficiency on cognitive data, and these investigated individuals with epilepsy (Garcia-Ramos et al., 2015, 2016; Kellermann et al., 2015, 2016), and neurological patients with different aetiologies (Jonker et al., 2019), and did not focus on compensatory mechanisms. Very few studies have investigated differentiation and dedifferentiation processes on VF across the whole lifespan (Bolla et al., 1990; Ruff et al., 1997; Singh-Manoux et al., 2012). Further, inconsistent findings have been reported, probably due to differences in cognitive abilities assessed, age ranges of the included samples, and analytical techniques used across studies (La Fleur et al., 2018).

Besides the contribution of other cognitive functions to VF performance, similar results have been found using neuroimaging techniques. Recent resting-state functional connectivity and lesion studies have implicated the contribution of a more extended network in language processing (Birn et al., 2010; Costafreda et al., 2006; Marsolais et al., 2014, 2015; Methqal et al., 2019; Tomasi & Volkow, 2012; Zhang et al., 2013). In addition, limited neuroimaging studies have investigated the neural correlates of PF, specifically in the context of CR (Boyle et al., 2020; Rodríguez-Aranda et al., 2020).

Taken together, despite the divergent findings on the effect of age on VF, there is certain agreement considering that SF declines with age, whereas PF shows more stability with age. Studies on AF in normal aging are less frequent, and results are also divergent. This age trajectory of VF may be underlain by compensatory mechanisms that are particularly functional before the age of 60, when reduction in word production is more prominent.

Brain connectivity analysis and multivariate methods such as RF and graph theory may be helpful to characterize compensatory mechanisms by studying the contribution of different cognitive functions to VF performance and its association with CR. A novelty of our studies is that we applied graph theory to cognitive data in normal aging. Further, investigating how compensatory mechanisms in specific cognitive domains (e.g., language components) counteract the onslaught of aging may help disentangle the ongoing discussion on whether CR and compensation occur through a universal brain network or if their effects are task-dependent (Stern et al., 2018b).

Hence, advances in our understanding of compensatory mechanisms, differentiation, and dedifferentiation processes are expected to have significant implications. On the one hand, this knowledge may help to understand better the age-related processes of the human brain, and its dynamic responses to both negative and positive influences. On the other hand, in clinical practice, this knowledge could contribute to reach a more accurate diagnosis of cognitive disorders and facilitate early and personalized therapeutic interventions, improving older adults' everyday functioning.

2. AIMS AND HYPOTHESIS

2.1. Aims

This thesis aimed to study one of the main language components, VF, and its relationship with sociodemographic factors and other cognitive and neuroanatomic variables. This thesis also aimed to investigate the compensatory role of these variables in normal aging. The specific aims for each study were as follows:

- **Study I**: to investigate the association between performance in three components of VF (SF, PF, and AF) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly.
- **Study II**: to investigate how CR and efficiency levels contribute to PF differently in people with high *versus* low fluency performance and in younger *versus* older individuals.
- **Study III**: to investigate cortical brain networks potentially underpinning compensation of age-related differences in PF.
- **Study IV**: to study the neural functional substrates of PF and potential compensatory mechanisms facilitated by CR, which would contribute to high performance in PF across age groups.

2.2. Hypothesis

- The three fluency modalities (SF, PF, and AF) would decrease with increasing age. The association between fluency variables and non-fluency cognitive measures would be different between age groups spanning from the early middle-age to the late elderly, with predominance of dedifferentiation processes in the older groups.
- Older adults would perform worse than younger adults in VF, but this difference would be minimized by high CR levels and high efficiency of cognitive networks. In other words, high CR levels and network efficiency would help to maintain high

performance in older adults, thus contributing to compensate for the negative effect of age.

- Older individuals with high performance in PF would have a more efficient PF cortical network. More efficient semantic and executive-visuospatial cortical networks would be associated with higher performance in PF in older individuals, likely delineating compensatory processes in normal aging.
- Younger adults would show greater functional connectivity in the four modules previously related with PF than older adults. Functional connectivity, particularly in Broca's module (language production center), would be associated with performance in PF. CR would mediate the relationship between functional connectivity involving both linguistic and non-linguistic brain areas and performance in PF, especially in older adults, hence indicating compensation of the effect of age in PF.

3. PARTICIPANTS AND METHODS

3.1. Ethical considerations

Written informed consent was obtained from all participants according to the Declaration of Helsinki. All studies were approved by the ethics committee of the University of La Laguna (Spain).

3.2. Participants

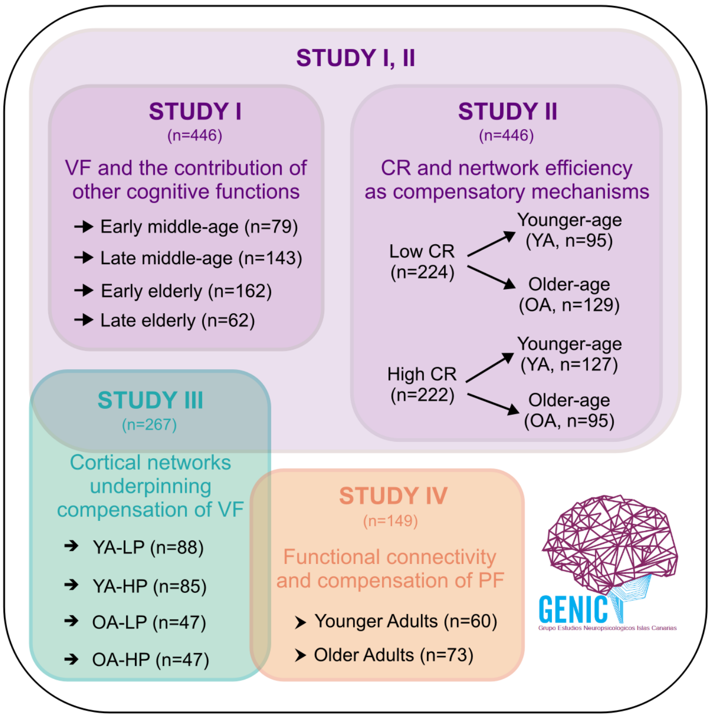
A general overview of the cohort and participants used in this thesis is presented in Figure 5. All participants were selected from the GENIC-database (Group of Neuropsychological Studies from the Canary Islands) (Ferreira et al., 2015; Machado et al., 2018). All participants were Spanish speakers.

Most of the participants were evaluated in the Unit of Neuropsychology at the Faculty of Psychology, at the University of La Laguna. Besides, other participants were evaluated in external building, in previously prepared offices, including the *Instituto de Enseñanza Secundaria (IES) Agustín de Betancourt* in Puerto de la Cruz, the *Centro de Educación Obligatoria (CEO) Príncipe Felipe* in La Victoria de Acentejo, and civic and cultural centers of Punta de Hidalgo’s neighborhoods. Data were collected between 2005 and 2019.

All the participants included in this thesis are cognitively normal. Participants were assessed with a comprehensive neuropsychological protocol applied by experienced neuropsychologists. Afterward, for each participant, cognitive profile and diagnosis were established at consensus by at least two qualified clinical neuropsychologists, using pertinent age-, sex-, and education-adjusted normative data. The diagnostic procedure consisted of a two-step process: Firstly, we excluded individuals with dementia based on the Blessed Dementia Scale (BDRS, Blessed et al., 1968) cut-point of ≥4, the Functional Activity Questionnaire (FAQ, Pfeffer et al., 1982) cut-point of >5, and the Mini-Mental State Examination (MMSE, Folstein et al., 1975) score cut-point of <24. Secondly, we further

Figure 5

Overview of the participants used in this thesis.



Note: VF: verbal fluency; CR: cognitive reserve, PF: phonemic fluency. YA-LP: younger-age with low PF performance. YA-HP: younger-age with high PF performance. OA-LP: older-age with low PF performance. OA-HP: older-age with high PF performance.

excluded individuals with Mild Cognitive Impairment (MCI) based on Winblad's et al. (2004) criteria. Inclusion criteria were: (1) normal cognitive performance in comprehensive neuropsychological assessment (2) no neurologic, psychiatric or systemic diseases; and (3) no history of substance abuse, (4) no abnormal findings (e.g., stroke, tumours, hippocampal sclerosis, etc.) in Magnetic Resonance Imaging (MRI), as assessed by an experienced neuroradiologist. An exception was made for the BDRS. Although the BDRS scale cut-off for abnormality is frequently established at ≥4 points (Blessed et al., 1968; Erkinjuntti et al., 1988), the ‘changes in personality, interests and drive’ subscale may influence the BDRS total score and does not necessarily reflect functional impairment. Intending to exclude only individuals with functional impairment, we included those participants with total BDRS scores ≥4 (n=24) if: a) 70% or higher percentage of the BDRS total score resulted from the ‘changes in personality, interests and drive’ subscale; and b) if a score ≤1.5 was obtained in the other two subscales (‘changes in performance of everyday activities’ and ‘changes in habits’).

3.2.1. Study I and II participants

A total of 446 participants were selected for Studies I and II, aged between 32 and 84 years, and a balanced distribution of sex across age (54.9% females) (Tables 1 and 2).

Table 1

Demographic characteristics of the study sample used in Study I.

	Early middle-age (n=79)	**Late middle-age (n=143)**	**Early elderly (n=162)**	**Late elderly (n=62)**	*p-value*
Age, years (min-max)	41.4 (2.8) [a,b,c] (32-45)	51.0 (3.9) [b,c] (46-58)	65.6 (3.4) [c] (59-71)	74.9 (2.3) (72-84)	<0.001
Sex (female, count (%))	43 (54.4%)	79 (55.2%)	91 (56.2%)	32 (51.6%)	0.943
Education level					
Illiteracy	0	0	6	1	<0.001
Unfinished primary studies	0	3	32	18	
Completed primary studies	34	52	52	24	
Completed secondary studies	25	39	24	13	
University studies	20	49	48	5	
WAIS-III Information	15.1 (5.9) [a,c]	17.3 (5.8) [b,c]	14.5 (6.3) [c]	12.4 (5.9)	<0.001
MMSE	29.20 (1.2) [b,c]	29.0 (1.1) [b,c]	28.1 (1.5) [c]	27.6 (1.5)	<0.001

Note: [a] Significantly different from Late middle-age. [b] Significantly different from Early elderly. [c] Significantly different from Late elderly. All continuous variables are reported as mean (standard deviation). WAIS-III: Wechsler Adult Intelligence Scale, Third edition.

Table 2

Demographic characteristics of the study sample used in Study II

	Low Cognitive Reserve (lowCR)				High Cognitive Reserve (highCR)				
	Younger-age (YA, n=95)		Older-age (OA, n=129)		Younger-age (YA, n=127)		Older-age (OA, n=95)		
	Low PF	High PF	Low PF	High PF	Low PF	High PF	Low PF	High PF	*p*-value
n	50	45	68	61	64	63	50	45	
Age, years (min-max)	46.9 (5.7) (37-58) ^{b,c,f,g}	46.6 (5.7) (34-58) ^{b,c,f,g}	68.8 (4.8) (59-79) ^{d,e}	69.3 (4.6) (60-80) ^{d,e,g}	48.0 (5.7) (38-58) ^{f,g}	48.5 (6.0) (32-58) ^{f,g}	67.8 (5.3) (59-79)	66.1 (6.0) (59-84)	p<0.001
Sex (female, (%))	39 (78%) $^{d\text{-}g}$	31 (69%) ^{d,f}	42 (62%) ^{d}	41 (67%) ^{d,f}	22 (34%)	30 (48%)	19 (38%)	21 (47%)	p<0.001
Education level									p<0.001
Illiteracy	0	0	5	2	0	0	0	0	
Unfinished primary studies	1	2	27	20	0	0	3	0	
Completed primary studies	38	26	28	29	14	8	12	7	
Completed secondary studies	8	12	7	8	26	18	15	7	
University studies	3	5	1	2	24	37	20	30	
WAIS-III Information	10.1 (3.1) $^{d\text{-}g}$	11.3 (2.8) $^{b,d\text{-}g}$	8.8 (2.8) $^{d\text{-}g}$	9.7 (3.2) $^{d\text{-}g}$	20.4 (2.8)	21.4 (3.1)	19.8 (2.8)	20.9 (3.0)	p<0.001
MMSE (min-max)	28,7 (1,2) ^{b} 25 - 30	28,9 (1,4) ^{b,c} 25 - 30	27,1 (1,6) $^{c\text{-}e}$ 24 - 30	27,9 (1,4) 25 - 30	29,2 (0,9) 27 - 30	29,3 (0,9) 27 - 30	28,5 (1,5) 25 - 30	28,7 (1,1) 25 - 30	p<0.001

Note: ^{a} Significantly different from YA+highPF+lowCR, ^{b} Significantly different from OA+lowPF+lowCR, ^{c} Significantly different from OA+highPF+lowCR, ^{d} Significantly different from YA+lowPF+highCR, ^{e} Significantly different from YA+highPF+highCR, ^{f} Significantly different from OA+lowPF+highCR, ^{g} Significantly different from OA+highPF+highCR. All continuous variables are reported as mean (standard deviation). PF: phonemic fluency, Low PF: low PF performance. High PF: high PF performance. MMSE: Mini-Mental State Examination, WAIS-III: Wechsler Adult Intelligence Scale, Third edition.

3.2.2. Study III participants

A total of 267 participants were selected, aged between 32 and 79, and balanced sex distribution across age (53% females). Since language is strongly left-lateralized, only right-handed participants were included in this study (Table 3).

Table 3

Demographic characteristics of the study sample used in Study III.

	YA-LP (n=88)	**YA-HP (n=85)**	**OA-LP (n=47)**	**OA-HP (n=47)**	***p*-value**
Age	47.7 (5.5) ^{b,c}	48.5 (6.3) ^{b,c}	68.4 (5.5) ^{c}	65.5 (4.9)	<0.001
(range)	(37 – 58)	(32 – 58)	(59 – 79)	(59 – 76)	
Sex (Female, men)	55 (62.5%)	39 (45.9%)	26 (55.3%)	22 (46.8%)	0.12
Education level					<0.001
Illiteracy	0	0	0	0	
Unfinished primary studies	1	0	9	1	
Completed primary studies	48	16	24	13	
Completed secondary studies	23	24	9	6	
University studies	16	45	5	27	
WAIS-III Information	14.4 (5.4) ^{a,c}	19.3 (5.4) ^{b}	12.5 (5.3) ^{c}	19.9 (4.4)	<0.001
MMSE	29.0 (1.1) ^{b}	29.1 (1.2) ^{b}	28.1 (1.5)	28.6 (1.2)	<0.001

Note: ^{a} Significantly different from YA-HP. ^{b} Significantly different from OA-LP. ^{c} Significantly different from OA-HP. All continuous variables are reported as mean (standard deviation). YA-LP: younger age group with low PF performance; YA-HP: younger age group with high PF performance; OA-LP: older age group with low PF performance; OA-HP: older age group with high PF performance; MMSE: Mini-Mental State Examination; WAIS-III: Wechsler Adult Intelligence Scale, Third Edition.

3.2.3. Study IV participants

A total of 149 cognitively normal healthy individuals were selected cross-sectionally from a community-based cohort, aged between 40 and 82. Since language is strongly left-lateralized, only right-handed participants were included in this study (Table 4).

Table 4

Demographics characteristics of the study sample used in Study IV.

	Full Cohort (n=133)	**Younger Adults (n=60)**	**Older Adults (n=73)**	***p*-value**
Age, years (min-max)	60.7 (9.3) (40 – 82)	52.1 (4.6) (40 – 59)	67.7 (5.5) (60 – 82)	<0.001
Sex (female, count (%))	75 (56.4%)	34 (56.7%)	41 (56.2%	1
Education level				0.049
Illiteracy	0	0	0	
Unfinished primary studies	8	0	8	
Completed primary studies	38	16	22	
Completed secondary studies	33	16	17	
University studies	54	28	26	
WAIS-III Information	17.1 (5.8) (5 – 27)	17.4 (5.2) (7 – 25)	16.7 (6.3) (5 – 27)	0.486
MMSE	29.4 (1.1) (25 – 30)	29.8 (0.6) (27 – 30)	29.1 (1.3) (25 – 30)	<0.001

Note: All continuous variables are reported as mean (standard deviation). MMSE: Mini-Mental State Examination; WAIS-III: Wechsler Adult Intelligence Scale, Third edition.

3.3. Methods

3.3.1. Neuropsychological assessment

The neuropsychological protocol includes tests of language, processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, and visuoconstructive, visuoperceptive and visuospatial functions (Table 5).

The assessment was performed in two section on different days. Each section lasted around 3 hours, with a 30-minute break in between each one. Assessments since 2017 were performed in only a 3-hours section in one day, with a 30-minute break in between. To counterbalance the task administration, the protocol was administered following two alternated orders (Form A and B).

Among all the tests included in the neuropsychological protocol, three tests of VF are of special relevance for the thesis:

- *Phonemic fluency*: The *Controlled Oral Word Association Test* (COWAT, Benton et al., 1989) was administrated. Participants had to recall words that begin with the letters F, A, and S, taking one minute on each of the letters. Proper nouns, numbers, and derived words were considered intrusion errors. A total score (F+A+S) was calculated as the number of correct words produced, excluding intrusions and perseverations (repetitions of correct words).
- *Semantic fluency*: Instructions were given following the administration procedures described in the Multilingual Aphasia Examination (Benton et al., 1989). Participants had to recall the names of animals for one minute. The total number of words, perseverations, and intrusions were registered.
- *Action fluency:* Participants had to recall verbs in the infinitive form (e.g., "to reflect"). Verbs included as part of a sentence (e.g., "to dance the tango") and repetitions of the same verb were considered errors (Piatt et al., 1999b). The total number of correct verbs, intrusions, and perseverations were counted.

Table 5

List of neuropsychological tests and cognitive components.

Neuropsychological test	Abbreviation	Reference	Cognitive component
Boston Naming Test	BNT	(Kaplan et al., 1983)	Lexical access by visual confrontation
Choice Reaction Time – Motor and Reaction times	PC-Vienna System	(Schuhfried, 1992)	Cognitive and motor reaction times
Paced Auditory Serial Addition Test	PASAT	(Gronwall, 1977)	Maintenance of attention
Stroop Test	STROOP	(Golden, 1978)	Processing speed and executive function (Inhibition)
Trail Making Test-A	TMT A	(Reitan, 1958)	Focusing/visual tracking
Color Trails Test - Part 1 and 2	CTT – 1 CTT – 2	(D'Elia & Saltz, 1989)	Focusing/visual tracking, Mental flexibility/ executive control
Facial Recognition Test (brief version)	FRT	(Benton et al., 1983)	Visuoperceptive abilities
Judgment of Line Orientation Test (H form)	JLOT	(Benton et al., 1983)	Visuospatial abilities
Digit Span – forward and backwards (WMS-III)	Digit Span	(Wechsler, 1997b)	Working memory: amplitude, manipulation
Visuospatial Span – forward and backwards (WMS-III)	Spatial Span	(Wechsler, 1997b)	Working memory: amplitude, manipulation
Logical Memory (WMS-III)	LM	(Wechsler, 1997b)	Verbal memory: immediate recall, delayed recall, recognition subtests
Test de Aprendizaje Verbal España-Complutense	TAVEC	(Benedet & Alejandre, 1998)	Verbal memory: immediate recall, delayed recall, recognition subtests
Visual Reproduction Test (WMS-III)	VR	(Wechsler, 1997b)	Visual memory: Immediate recall, Delayed recall, 2-D visuoconstructive abilities, Recognition subtests, Visuoperceptive abilities
Luria's Premotor Functions	Luria's	(Christensen, 1979)	hand alternative movements, motor coordination
Block Design (WAIS-III)	Block Design	(Wechsler, 1997a)	3-D visuoconstructive abilities

Note. WMS-III: Wechsler Memory Scale, Third Edition Technical Manual; WAIS-III: Wechsler Adult Intelligence Scale, Third edition.

3.3.2. MRI image acquisition and image processing (Study III and IV)

MRI image acquisition: MRI protocol

Participants were scanned using a 3T General Electric imaging system (General Electric, Milwaukee, WI, USA) with an eight-channel high-resolution head coil located at *Hospital Universitario de Canarias (HUC)* in Tenerife, Spain.

A three-dimensional T1-weighted FSPGR (Fast Spoiled Gradient Echo) sequence was acquired in the sagittal plane with the following parameters: repetition time (TR)/echo time (TE) = 8.73/1.74 ms., inversion time = 650 ms., field of view 250 x 250 mm, matrix 250 x 250 mm, flip angle 12°, slice thickness = 1 mm, voxel resolution = 1 x 1 x 1 mm^3. Six minutes of resting-state functional MRI were collected using single-shot echo-planar T2-weighted imaging with the following parameters: TR = 2000 ms, 179 time-points, TE = 22.1 ms, field of view = 24 × 24 mm, flip angle = 90°, matrix = 64 × 64, voxel dimensions 3.75 × 3.75 × 4 mm^3 and 36 slices on AC-PC orientation. Participants were instructed to relax with their eyes closed while staying awake, and head padding was provided to prevent head motion during scanning. Full brain and skull coverage was required for the MRI datasets. Detailed quality control was carried out on all MR images according to previously published criteria (Simmons et al., 2009, 2011): Full brain coverage; Wrap-around artifact affecting the brain; Motion artifacts; Intensity inhomogeneity; and Adequate grey/white matter contrast throughout the image.

Automated Image processing

TheHiveDB Database system (Muehlboeck et al., 2014) was used to automatically preprocess the T1-weighted images with FreeSurfer 6.0.0 (https://surfer.nmr.mgh.harvard.edu/) following standard procedures (See Figure 6). Resting-state *f*MRI volumes were processed with Statistical Parametric Mapping software version 12 (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) (See Figure 7).

Structural image processing: FreeSurfer pipeline

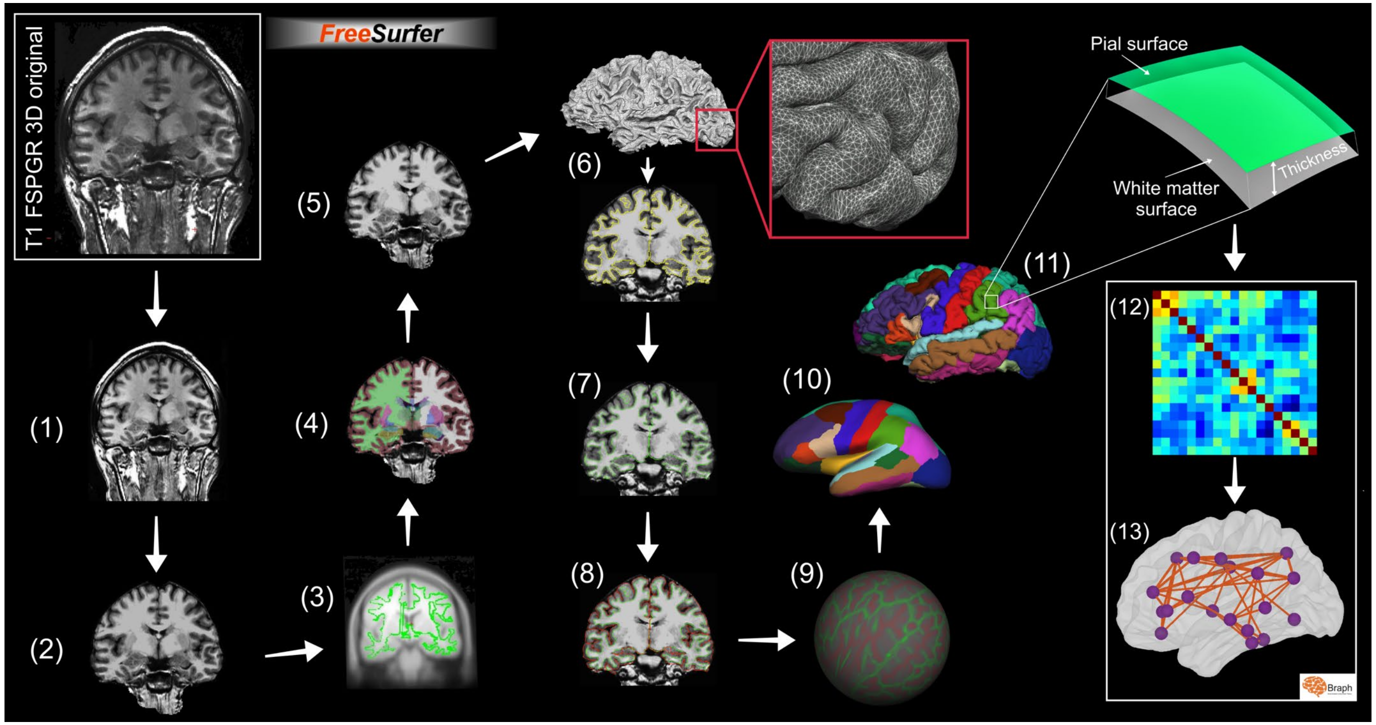
Visual quality control was performed on the original T1-weighted images (Simmons et al., 2009) and the FreeSurfer output. All steps involving brain extraction, automated Talairach transformation, tessellation, surfaces reconstruction, and subcortical segmentation were carefully checked. After image processing, among the different measures provided by FreeSurfer, we selected regional estimations of cortical thickness for the thesis (Study III). Cortical thickness measures include the same 34 regions for both hemispheres (Desikan et al., 2006).

Functional image processing: SPM

Functional MRIs were preprocessed with the following steps: the initial six functional volumes were discarded, slice time corrected, realigned to the mean of all functional volumes, motion correction, the mean functional volume was realigned and linearly co-registered to the structural MRI, the structural MRI was segmented into tissue classes (gray matter, white matter, and cerebrospinal fluid), the structural MRI was normalized to the standard Montreal Neurological Institute (MNI) space, the motion-corrected functional MRI volumes were normalized to the MNI space, and spatially smoothed with 8 mm full width at half maximum Gaussian kernel using SPM12. Then, functional MRIs were temporally filtered (Gaussian band-pass between 0.01 - 0.1 Hz, implemented with Oxford Centre for Functional MRI of the Brain Laboratory Software Library, version 5.0.9, https://fsl.fmrib.ox.ac.uk/fsl/). All scans were assessed visually (raw and registered images), and quality control was based on motion parameters (cases with motion >3 mm or 3° were excluded) and framewise displacement (FWD).

Figure 6

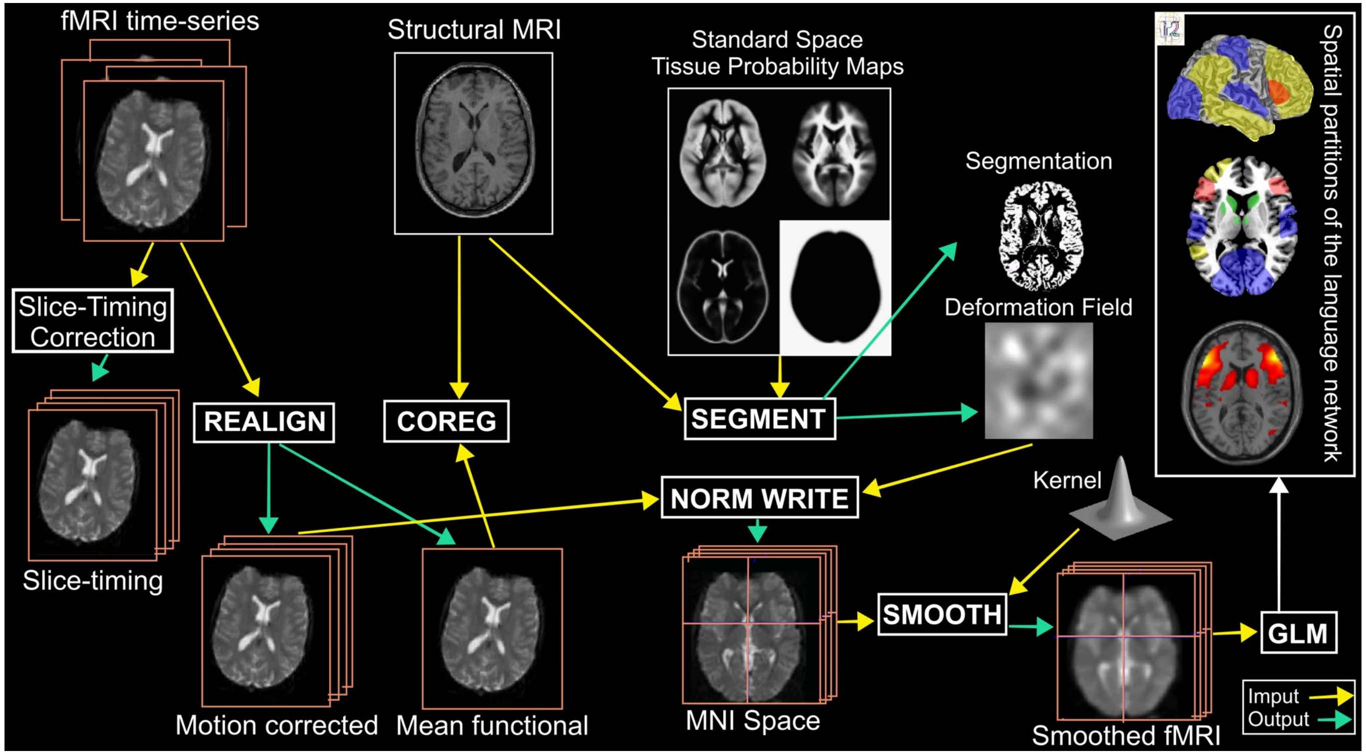
FreeSurfer methods for processing of T1-weighted MRI data and brain graphs estimation using Braph.



Note: FreeSurfer: (1) motion correction (Reuter et al., 2010); (2) removal of nonbrain tissue (Ségonne et al., 2004); (3) automated Talairach transformation; (4) segmentation of the subcortical structures (Fischl et al., 2002; Ségonne et al., 2004); (5) intensity normalization (Sled et al., 1998); (6) tessellation of the gray matter white matter boundary; (7) automated topology correction (Ségonne et al., 2007); (8) surface deformation following intensity gradients to optimally place the gray and/or white and gray and/or cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Fischl & Dale, 2000); (9) Surface inflation (Dale et al., 1999), registration to a spherical atlas (Fischl et al., 1999); (10) parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al., 2006); and (11) creation of a variety of surface based data. Braph: (12) Weighted correlation matrices of cortical regions included as nodes; (13) Brain graphs of the cortical network; nodes are depicted as purple spheres and edges as orange lines.

Figure 7

Preprocessing of fMRI data using Statistical Parametric Mapping (SPM).



Note: Functional MRI volumes were preprocessed with the following steps: the initial six functional volumes were discarded, slice time corrected, realigned to the mean of all functional volumes, motion correction, the mean functional volume was realigned and linearly co-registered to the structural MRI, the structural MRI was segmented into tissue classes, the structural MRI was normalized to the standard MNI space, the motion-corrected functional MRI volumes were normalized to the MNI space, and spatially smoothed. Then, functional MRI volumes were temporally filtered. Adapted from Resting functional connectivity of language networks: Characterization and reproducibility (p. 850), Tomasi and Volkow, 2012, *Molecular Psychiatry*, 17(8); and *Preprocessing of fMRI data (basic)- Practical session, SPM Course*, by Diaconescu et al., 2016.

Table 6

Overview of study design, subject cohort and methodology.

	STUDY I	STUDY II	STUDY III	STUDY IV
Main theme	Cognitive performance and compensation		Magnetic resonance image and connectivity	
Number of participants	446	446	267	149
Specific theme	VF and the contribution of other cognitive functions	CR and network efficiency as compensatory mechanisms on PF	Cortical network underpinning compensation of VF	Functional connectivity and compensation of PF
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Groups, number of participants	Early middle-age: 79 Late middle-age: 143 Early elderly: 162 Late elderly: 62	Low CR, YA: 95 Low CR, OA: 129 High CR, YA: 127 High CR, OA: 95	YA-LP: 88 YA-HP: 85 OA-LP: 47 OA-HP: 47	Younger adults: 60 Older adults: 73
Cognitive variables of interest	PF (F-A-S) SF (Animals) AF (Verbs)	PF (F-A-S)	PF (F-A-S)	PF (F-A-S)
Demographic variables of interest	Age Educative level (WAIS-III Information)	Age Educative level (WAIS-III Information)	Age Handedness	Age Educative level (WAIS-III Information) Handedness
MRI sequence and processing	-	-	3D T1-weighted FSPGR, FreeSurfer	3D T1-weighted FSPGR, T2-weighted, SPM12

Note: VF: Verbal fluency; PF: phonemic fluency; SF: semantic fluency; Action fluency; CR: cognitive reserve; WAIS-III: Wechsler Adult Intelligence Scale, Third edition; FSPGR: Fast Spoiled Gradient Echo.

3.4. Data analysis

Statistical analyses were performed using the R programming environment (Core, 2016), MATLAB R2014b (The MathWorks, Inc., Natick, Massachusetts, United States), and the BRAPH software (BRain Analysis using graPH theory, www.braph.org, Mijalkov et al., 2017). A detailed description of statistical analyses applying according to specific aims and type of data are provided in respective papers.

Previous to statistical analysis, an exploratory analysis of missing values was performed for all cognitive variables included in Study I. Two percent of the values were missing across the 48 cognitive variables. The non-parametric test of homoscedasticity showed a non-random distribution pattern of missing data ($p<0.05$). The missing values were imputed using the multivariate method of Random Forest (RF) (Buuren & Groothuis-Oudshoorn, 2011; Liaw & Wiener, 2002). This imputed dataset was saved and used in subsequent analyses: RF analyses in Study I and ANCOVA, RF, and graph analyses in Study II. The cognitive variables of interest (PF, SF, and AF) were not imputed.

3.4.1. Analysis of Covariance (ANCOVA)

The ANCOVA was used in Study I to test the association between age (between-subject factor, three or four age groups) and performance in VF (within-subject factor, three fluency modalities), including WAIS-III Information as a covariable to control for between-subjects variability in the level of crystallized intelligence. In Study II, ANCOVA was used to test the effects of CR level, performance level, and age over PF, including sex as a covariate.

Besides, in Study I, the mixed ANCOVA was used to investigate potential non-linear associations between age and performance in VF. To do this, we tested for linear, quadratic, and cubic associations by applying the technique “trend analysis”, which is a way of decomposing the variance explained by the factor that accompanies an ANOVA using specially chosen linear weights called “orthogonal polynomials”. The polynomial contrast will test for trends in the data depending on the numeric factor levels. Since we have more than two levels in our independent variable, the polynomial contrast will examine other trends in the data, such as quadratic and cubic trends.

3.4.2. Random forest regression analyses

RF regression analyses were used in Study I and II to investigate the multivariate association between VF measures and 45 cognitive variables. In RF models, the contribution of the predictors in the models is reported as *Imp* (from Importance), which reflects the relative error in the prediction when a predictor is excluded from the model. *Imp* values higher than zero denote that a given variable contributes to the prediction of the outcome. The larger the *Imp* value, the greater the contribution. *Imp* values do not have an upper limit, and they can rather be interpreted by considering the obtained values concerning the variable yielding the highest *Imp* value in the model.

3.4.3. Structural network construction and graph analysis

Network construction, measures calculation, and graph analyses were performed using BRAPH (Mijalkov et al., 2017). The formulae used to calculate all these graph measures are provided by Barrat et al. (2004), Latora & Marchiori (2001), and Rubinov & Sporns (2010).

Networks were constructed using cognitive variables as nodes in Study II, and the average cortical thickness from selected regions of the Desikan atlas (Desikan et al., 2006) in Study III. Performance in cognitive measures was corrected for the effect of sex using multiple linear regression, and the resulting residual values were used to substitute the raw values for network analysis (Voevodskaya et al., 2014). The edges between the nodes were calculated through group-specific association matrices of Pearson correlation coefficients from each pair of nodes. The matrices were binarized by thresholding the correlation coefficients at a range of network densities: min = 20% to max = 40%, in steps of 1% in Study II, and min. = 10% to max. = 45%, in steps of 1% in Study III. That is, ensuring the exclusion of disconnected networks (densities below 20% in Study II, and below 10% the Study III) and random topologies (densities above 40% in Study II, and above 45% in Study III, small-world index close to 1). Network topologies were compared across this range of densities. Both self-connections and negative correlations were excluded.

Once the networks were constructed, different global measures were calculated: the *average global efficiency,* the *transitivity* and the *average strength* (Study II and III), and the *average local efficiency* (Study III) (Rubinov & Sporns, 2010). The following nodal measures were calculated in Study III: the *global nodal efficiency*, the *local nodal efficiency* (Latora & Marchiori, 2001), and the *nodal strength* (Barrat et al., 2004). Nodal measures refer to each specific node, whereas global measures refer to the average across all the nodes. Table 7 shows a description of these measures. *Global efficiency, local efficiency, and transitivity* measures were calculated from the binary networks across the different densities. *Strength* was calculated from the weighted network (before binarization). Between-group comparisons of graph measures were conducted through 1000 nonparametric permutations over a range of network densities mentioned above. The 95% confidence intervals of each distribution were used as critical values for testing the null hypothesis at p≤0.05 (two-tailed). Modular analyses were conducted by applying the Louvain algorithm (Blondel et al., 2008) on weighted undirected networks with a gamma value of 1.

Table 7

Graph theory measures.

Measure/Authors		Definition
Global efficiency	***Nodal global efficiency*** (Latora & Marchiori, 2001)	Average of the inverse shortest path length between a specific node and the rest of the network.
	Average global efficiency (Latora & Marchiori, 2001)	Average of the global efficiencies of all nodes. It measures how efficiently information is exchanged throughout the network.
Local efficiency	***Nodal local efficiency*** (Latora & Marchiori, 2001)	Global efficiency of a node calculated on the subgraph created by the node's neighbors.
	Average local efficiency (Rubinov & Sporns, 2010)	Average of the local efficiencies of all nodes. Conceptually, it is also related to the clustering coefficient, which can be regarded as a measure of the local efficiency of information transfer or the network's robustness to deletion of individual nodes (Bullmore & Sporns, 2009).
Transitivity	(Rubinov & Sporns, 2010)	Fraction of a node's neighbours that are also neighbours of each other in the whole network, normalized by the entire network. It reflects how well the nodes are connected to nearby nodes forming cliques.
Strength	***Nodal strength*** (Barrat et al., 2004)	Sum of the weights of all edges connected to a node.
	Average strength (Rubinov & Sporns, 2010)	Average of the strengths of all nodes.

3.4.4. Functional networks and connectivity analysis

Voxelwise multiple linear regression was performed in Study IV to investigate the association between functional connectivity and PF performance. We examined functional connectivity in the functional language network, previously identified in healthy individuals (Tomasi and Volkow 2012). The significance of the obtained clusters was based on whether they achieved an extent threshold corresponding to a whole-brain Family-wise Error (FWE)-corrected $p \leq 0.05$ and a cluster-forming threshold of uncorrected $p \leq 0.001$. The association between functional connectivity and PF performance was verified with a non-parametric approach (SnPM13.1.08). Here, permutation testing (5000 permutations) determined the significance of the obtained clusters that achieved an extent threshold corresponding to FWE-corrected $p \leq 0.05$ and a cluster-forming threshold of FWE-corrected $p \leq 0.05$. Cluster-level functional connectivity was computed as the first eigenvariate over the whole significant cluster and was used for subsequent post hoc analyses.

The total sample was divided into two age groups, with a threshold at 60 years: a reference control group with younger adults (40 – 59 years) and a group with the older adults (60 – 82 years). Functional connectivity patterns specific to each module and age group were identified through a voxelwise one-sample t-test, revealing brain regions with functional connectivity greater than the global mean value. Multiple comparison correction was performed with FWE $p \leq 0.001$. Sex was included as a potential covariate, and the whole procedure was repeated for each of the four modules of the language network. Differences in functional connectivity between the younger adults and older adults were tested using a voxelwise two-sample t-test at the group level. Multiple comparison correction was performed with FWE $p \leq 0.05$. This whole procedure was repeated for each of the four modules of the language network.

3.4.5. Mediation analysis

In Study IV, mediation analyses were performed to examine potential mediation effects of CR on the association between functional connectivity and PF performance. We tested the direct involvement of functional connectivity and the indirect involvement of functional connectivity mediated by CR (WAIS-III Information subtest) in relation to PF performance (Baron & Kenny, 1986). We implemented the mediation model through a series of linear regression models comprising four tests. Path *a*: association of functional connectivity with CR; path *b*: association of CR with PF; direct path *c*: association of functional connectivity with PF, and indirect path *c'*: association of functional connectivity and CR with PF.

4. RESULTS

The following section describes the main findings of the studies included in this thesis. More detailed results and discussion are reported in the respective publications/manuscripts. Study I and Study II, and Study III and Study IV are discussed together, respectively.

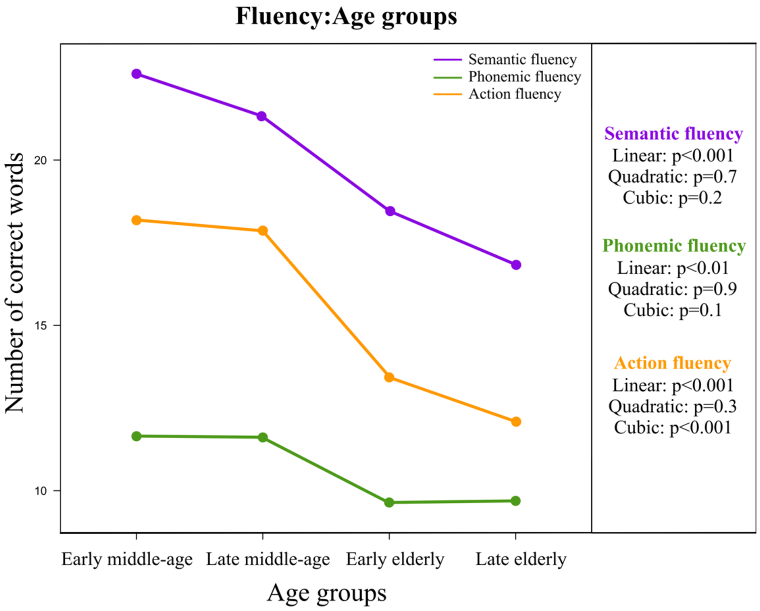
4.1. Study I

Study I (Paper I) aimed to investigate the association between performance in three components of VF (SF, PF, and AF) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly. A total of 446 participants were divided into four equidistant age groups based on the own sample age distribution: early middle-age (32 - 45 years), late middle-age (46 - 58 years), early elderly (59 - 71 years), and late elderly (72 - 84 years). These four groups were compared in VF performance (SF, PF, and AF), and the association between VF performance and other cognitive measures was analyzed within each age group.

A mixed ANCOVA model was conducted to examine the interaction between age and VF performance. The four age groups served as the between-subject factor, the three VF tasks served as the within-subject factor, and the WAIS-III Information was included as a covariate. This model showed a significant interaction ($F_{(6, 882)} = 7.8$; $p < 0.001$) (See Figure 8). The fluency modality modulates the association between age and VF performance. The two middle-age groups do not differ from each other in performance on PF and AF ($p > 0.05$) and perform rather similarly on SF ($p = 0.048$). However, the two middle-age groups always outperform the two elderly groups ($p < 0.01$). The early-elderly group outperformed the late-elderly group, but only on SF ($p < 0.05$). Due to this finding, the two middle-age groups were combined, and only three age groups were used for subsequent analyses (i.e., middle-age, early elderly, and late elderly).

Figure 8

The mixed ANCOVA model for age-related differences on VF performance.

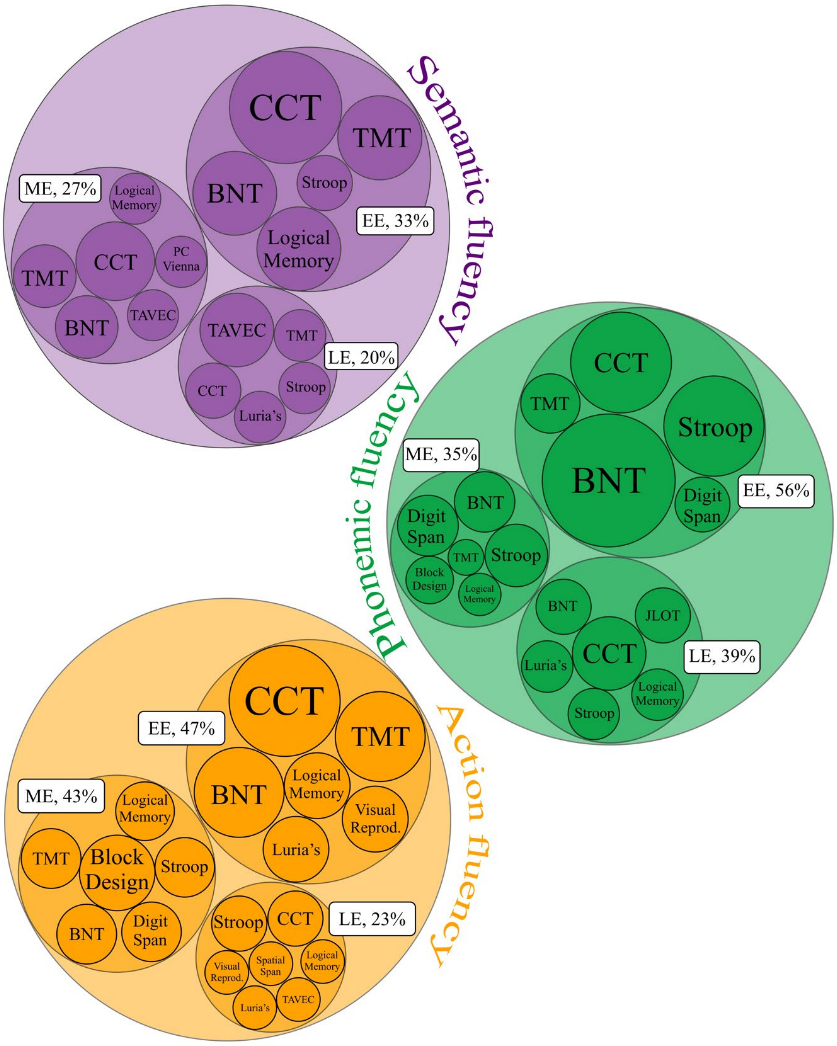


Note. The x-axis represents the age groups. The y-axis represents the number of words produced. The total number of words produced on PF (F+A+S) was divided by three to allow comparability among the three fluency modalities (1 minute). P-values are reported to estimate linear, quadratic, and cubic effects from the trend analysis tested through the ANCOVA model. The lines represent the outcome from the mixed ANCOVA for age (between-subjects factor) and fluency modality (within-subjects factor) using cross-sectional data.

The RF regression model was performed to assess whether the contribution of numerous non-fluency cognitive variables to VF performance differs across age. Figure 9 shows a summary of the most important variables in predicting performance in each of the three age groups (i.e., middle-age, early elderly, and late elderly).

Figure 9

Contribution of non-fluency cognitive variables to VF by age groups in Study I - RF regression models.



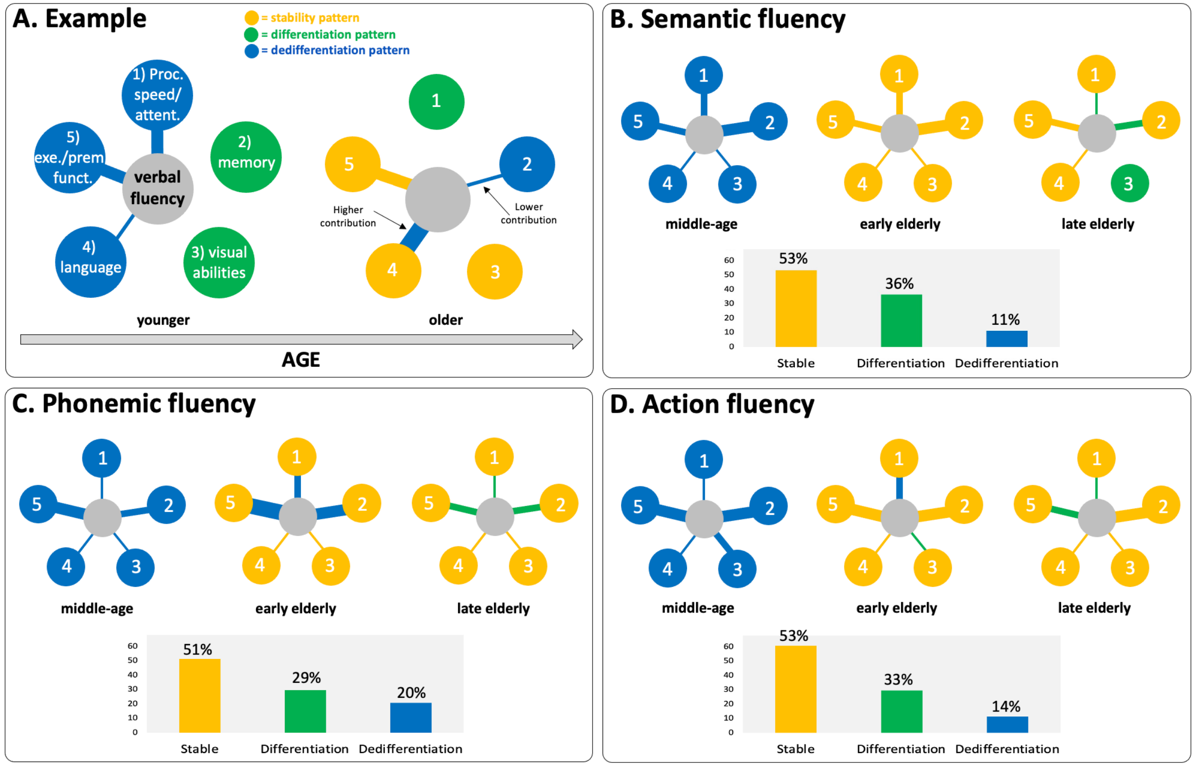
Note. Big circle: VF modality (SF (purple color), PF (green color), AF (yellow color)). Medium circle: age groups (ME: Middle-age; EE: Early elderly; LE: Late elderly). Small circle: the most important variables in predicting performance in each of the three age groups

(ME, EE, and LE). The medium and small circle size is in line with the explained variance and important values, respectively, where the higher the value the higher the circle size. Values 27%, 33%, 20%, 35%, 56%, 39%, 43%, 47%, and 23% represent the explained variance of the model in each group. The explained variance is the total cumulative variance explained by all the predictors in the model. The importance of each variable in predicting the outcome variable is calculated as the relative error in the prediction when a given predictor is excluded from the model. BNT: Boston Naming Test (spontaneous responses); PCV: PC-Vienna System; TMT: Trail Making Test; CTT, Color Trails Test; JLOT: Judgment of Line Orientation Test; Visual Reprod.: Visual Reproduction Test; Luria's: Luria's Premotor Functions. Only the most important variables in predicting performance are represented in this figure (Importance ≥ 10). For further information, see Table 3 in Paper I).

Three different patterns can be observed regarding the contribution of cognitive abilities to VF performance with increasing age in the RF models: Differentiation, dedifferentiation, and stability patterns. A differentiation pattern can be observed when cognitive variables stop contributing with increasing age. The dedifferentiation pattern is observed when variables start contributing with increasing age. A stability pattern is seen when the contribution of the variables remains stable across age. In some cases, a combination of these patterns can also be observed in the same variable. We classified as stable/differentiation and stable/dedifferentiation those variables that, despite mainly showing a stability pattern, stop or start contributing with increasing age, respectively. Figure 10 summarizes the three patterns in each of the three age groups and VF modality.

Figure 10

Differentiation, dedifferentiation, and stability patterns across age.



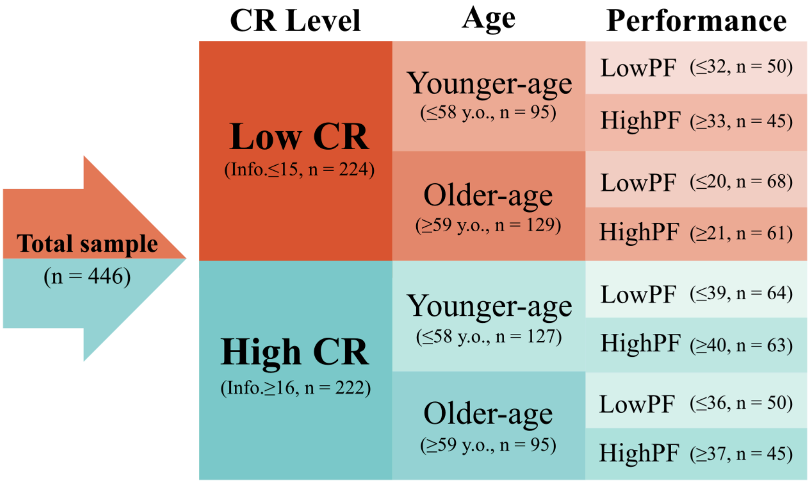
Note. Patterns are represented with different colors (differentiation in green color, dedifferentiation in blue color, stability in yellow color). Cognitive functions are represented with circles. The connecting lines show the contribution of the cognitive function towards VF performance. The presence of a line denotes contribution, whereas the absence of a line denotes no contribution. The thickness of the lines represents the strength of the contribution as measured by the importance parameter from the RF models (the thicker the line, the higher the value of the importance parameter). VF is differentiated from other functions in the youngest group when no connecting lines exist (in green). Contrarily, VF is dedifferentiated from other functions when connecting lines exist (in blue). Stability patterns cannot be seen in the youngest group because they entail comparison with a younger group. In older groups, the yellow color denotes that the relationship between VF performance and the other functions is the same as in the previous age group. The thickness and color of the lines can change depending on the contribution. If the function contributes more than in the previous age group, the line becomes thicker, and it is represented in blue color because a stronger contribution reflects a dedifferentiation process. If the function contributes less than in the previous age group, the line becomes thinner, and it is represented in green color because a weaker contribution reflects a differentiation process. The circle of the function remains yellow because only the strength of the contribution changes, but not its status (contribution *vs.* no contribution). The bar charts in the lower rows of each panel show the percentage of associations (i.e., how many variables contributed to VF divided by the total number of variables across the three age groups) (y-axis) separately for each pattern (x-axis). An explanation of how these associations are computed is given in Table S2 in Paper I. Proc. Speed/attent.: processing speed/attention; exe./prem. funct.: executive functions, premotor functions.

4.2. Study II

Study II (Paper II) aimed to investigate how CR and efficiency levels contribute to PF differently in people with high *versus* low fluency performance and younger *versus* older individuals. A total of 446 participants were stratified the cohort into groups of CR, performance in PF, and age using the median values for these variables, as detailed in Figure 11. These groups were compared in PF performance (F-A-S). The association between PF performance and other non-fluency cognitive measures was analyzed within each age and performance group.

Figure 11

Cohort stratification of the Study II.

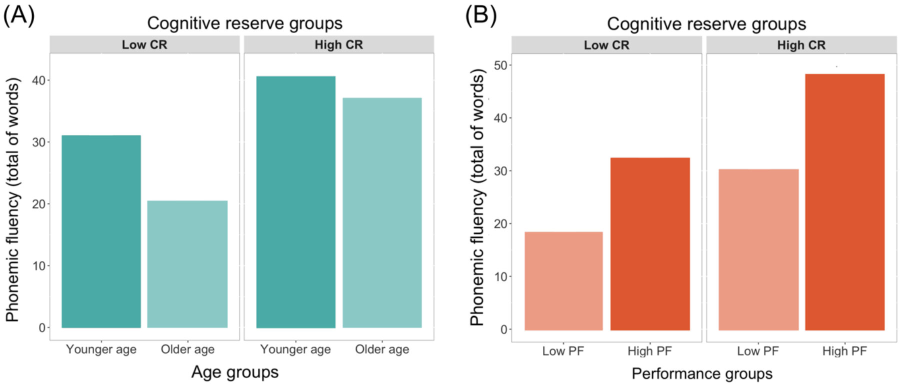


Note: The cohort was stratified into groups of CR, performance in PF, and age, using the median values for these variables. CR: cognitive reserve; Info.: WAIS-III Information Subtest; y.o.: years old; LowPF: low phonemic fluency performance; HighPF: high phonemic fluency performance.

The ANCOVA model showed a significant interaction between CR and age groups ($F_{(3, 442)} = 38.68$; $p < 0.001$) (See Figure 12A), and between CR and performance groups ($F_{(3, 442)} = 10.34$; $p < 0.01$) (See Figure 12B). The younger age (YA) group outperformed the older age (OA) group ($p < 0.001$), but this difference was smaller in the high CR (highCR) group than in the low CR (lowCR) group (See Figure 12A). Hence, higher CR reduces age-related differences. The difference between low PF (lowPF) and high PF (highPF) performance groups was greater in the highCR group than in the lowCR group (See Figure 12B). Hence, higher CR increases performance on PF, irrespectively of the age (the partial effect of age was controlled for in the ANCOVA).

Figure 12

*Interaction between CR levels and age (**A**), and between CR levels and performance groups (**B**), in the prediction of PF (ANCOVA).*

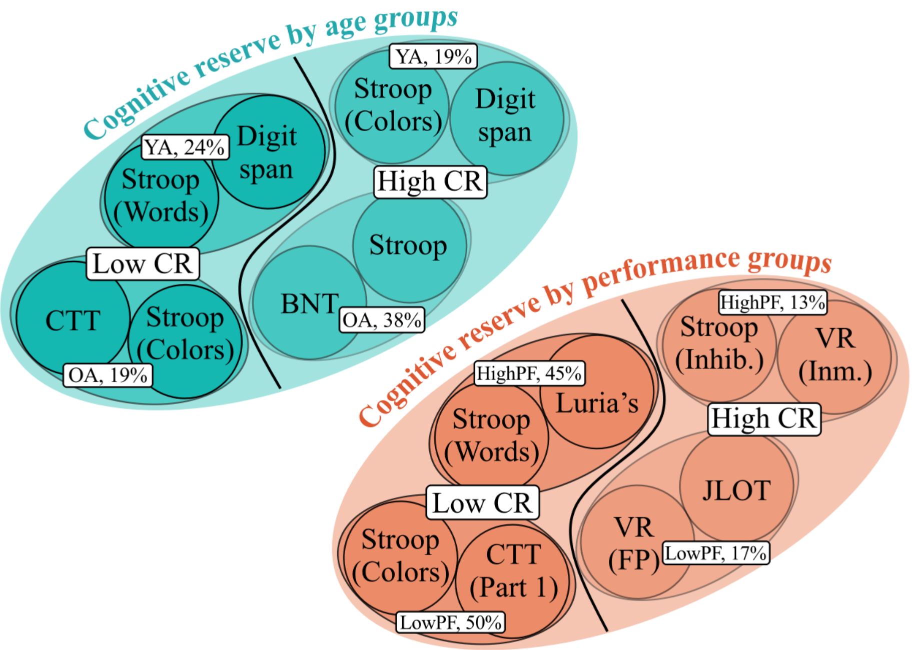


Note: Bars represent the mean of words produced. Panel A depicts the interaction between CR and age. Panel B represents the interaction between CR and performance groups. CR: cognitive reserve; YA: younger age; OA: older age; PF: phonemic fluency; Low PF: low PF performance; High PF: high PF performance.

RF regression models were performed separately within each age group (YA+lowCR, OA+lowCR, YA+highCR, and OA+highCR) and within each performance group (lowPF+lowCR, highPF+lowCR, lowPF+highCR, and highPF+highCR) to assess the contribution of numerous non-fluency cognitive variables to PF performance. Figure 13 summarizes of the most important variables in predicting performance in each of the age and performance groups.

Figure 13

Contribution of non-fluency cognitive variables to PF performance (RF regression models) in Study II



Note: CR by age groups (blue color, big oval). CR by performance groups (orange color, big oval). Medium oval: age and performance groups (YA, OA, Low PF, High PF). Small circle: the most important variables in predicting performance in each of the groups. Values 24%, 19%, 19%, 38%, 50%, 45%, 17%, and 13% represent the explained variance of the model in each group. The explained variance is the total cumulative variance explained by all the predictors in the model. The importance of each variable in predicting the outcome variable is calculated as the relative error in the prediction when a given predictor is excluded from the model. CR: cognitive reserve; YA: younger age; OA: older age; PF: phonemic fluency; LowPF: low PF performance; HighPF: high PF performance; BNT: Boston Naming Test (spontaneous responses); CTT: Color Trails Test; Stroop (Inhib.): Stroop test – Inhibition; VR: Visual Reproduction Test, VR (Inm.): Visual Reproduction – Immediate; VR (FP): Visual Reproduction – False Positives; JLOT: Judgment of Line Orientation Test; Luria's: Luria's Premotor Functions - motor coordination.

Graph theory analysis revealed that, when comparing the age groups, there were no significant differences in the average strength of the OA+highCR group as compared to the OA+lowCR and YA+lowCR groups (*p*>0.05). Global efficiency was increased in the OA+highCR group as compared to both OA+lowCR and YA+lowCR groups. There were no significant differences in transitivity (*p*>0.05). When comparing the performance groups, the highPF+highCR group showed lower average strength than the highPF+lowCR (p<0.001) but comparable average strength than the lowPF+highCR group (p=0.246). Global efficiency was increased in highPF+highCR compared with the highPF+lowCR group and tended to be increased compared with the lowPF+highCR group. Transitivity was decreased in the highPF+highCR group as compared with both highPF+lowCR and lowPF+highCR groups. When comparing the highPF+lowCR and lowPF+lowCR groups, we did not observe any significant difference in the average strength, global efficiency, or transitivity. All these analyses were controlled for the effect of sex.

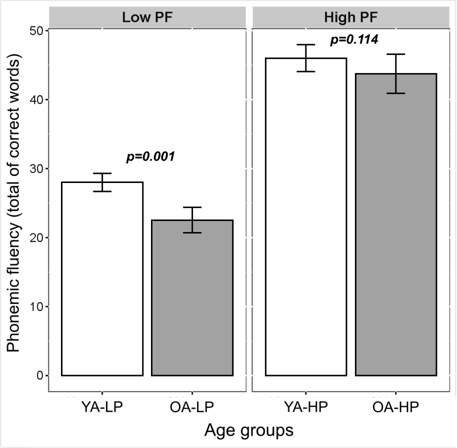
4.3. Study III

Study III (Paper III) aimed to investigate cortical brain networks potentially underpinning the compensation of age-related differences in PF. A total of 267 cognitively healthy participants were divided into younger age (YA, 38 - 58 years) and older age (OA, 59 - 79 years) groups with low performance (LP) and high performance (HP) in PF as follows: YA-LP, YA-HP, OA-LP, OA-HP. These four groups were compared in cognitive variables and in global and nodal graph measures in the three cortical networks.

The two-way ANOVA for PF as the outcome variable showed that the older age group performed worse than the younger age group in PF. However, this effect was only observed within the low performance groups (YA-LP *vs.* OA-LP, $p = 0.001$), but not within the high performance groups (YA-HP *vs.* OA-HP, $p = 0.114$) (See Figure 14).

Figure 14

Interaction between age and performance groups with PF as the outcome measure (ANOVA).



Note. Bars represent the mean of correct words produced, and the jack-knifes the 95% confidence intervals. The older age group performed worse than the younger age group in PF, but only within the low performance groups (younger adults with low PF performance, YA-LP *vs.* older adults with low PF performance, OA-LP, $F_{(3,263)} = 136.93$, $p = 0.001$). PF: phonemic fluency; Low PF: low PF performance groups; High PF: high PF performance groups.

Graph theory analysis on structural MRI revealed that brain regions associated with PF performance, semantic and executive-visuospatial abilities, respectively, comprise a cortical network associated with performance only in PF and semantic abilities, but not in executive-visuospatial abilities. Therefore, these networks are likely underpinning PF performance and semantic abilities. However, the executive-visuospatial cortical network does not seem to be involved in executive-visuospatial abilities investigated in this study.

We investigated the compensation of age-related differences in PF performance in the older group (59 – 79 years) by investigating features of the PF cortical network and the semantic cortical network. To do this, we compared the older groups (OA-LP and OA-HP) *versus* the reference group YA-LP. To disentangle the effect of age from compensation effects, we tested for potential differences between the OA-HP and YA-HP groups (age) and between the OA-LP and OA-HP groups (compensation). In the PF cortical network, the same pattern of reduced efficiency and increased transitivity was associated with high performance in PF and older age. However, the OA-HP group reached a higher PF performance than the OA-LP group and equaled the performance of the YA-HP group, likely by keeping a more segregated PF network with greater participation of frontal nodes as compared to temporal or posterior nodes in the OA-LP group, and by keeping a high strength in its correlations. In the semantic cortical network, as demonstrated for the PF cortical network, the same pattern of reduced efficiency and increased transitivity was associated with high performance in semantic abilities and older age. However, in contrast to the OA-LP group, individuals in the OA-HP group tended to have a more segregated semantic cortical network. (See Figure 15).

Figure 15

Comparison of the age and PF performance groups across global graph measures.

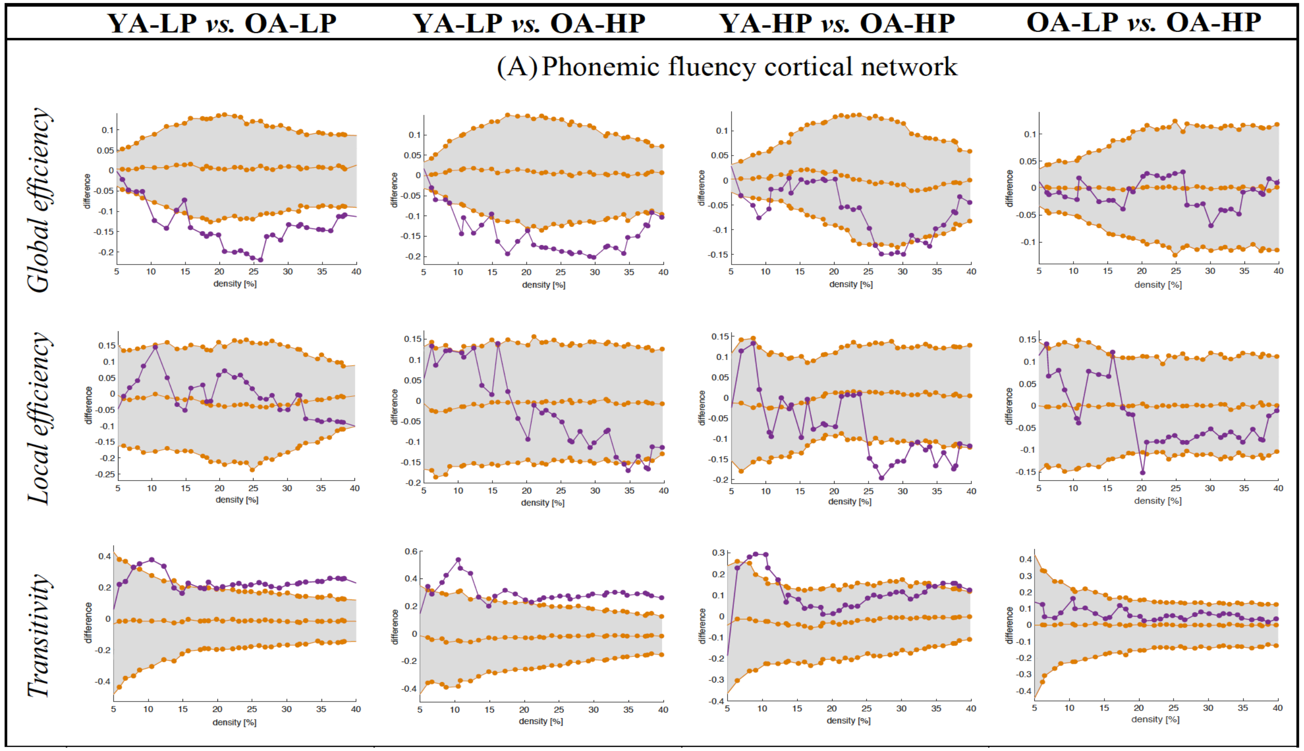
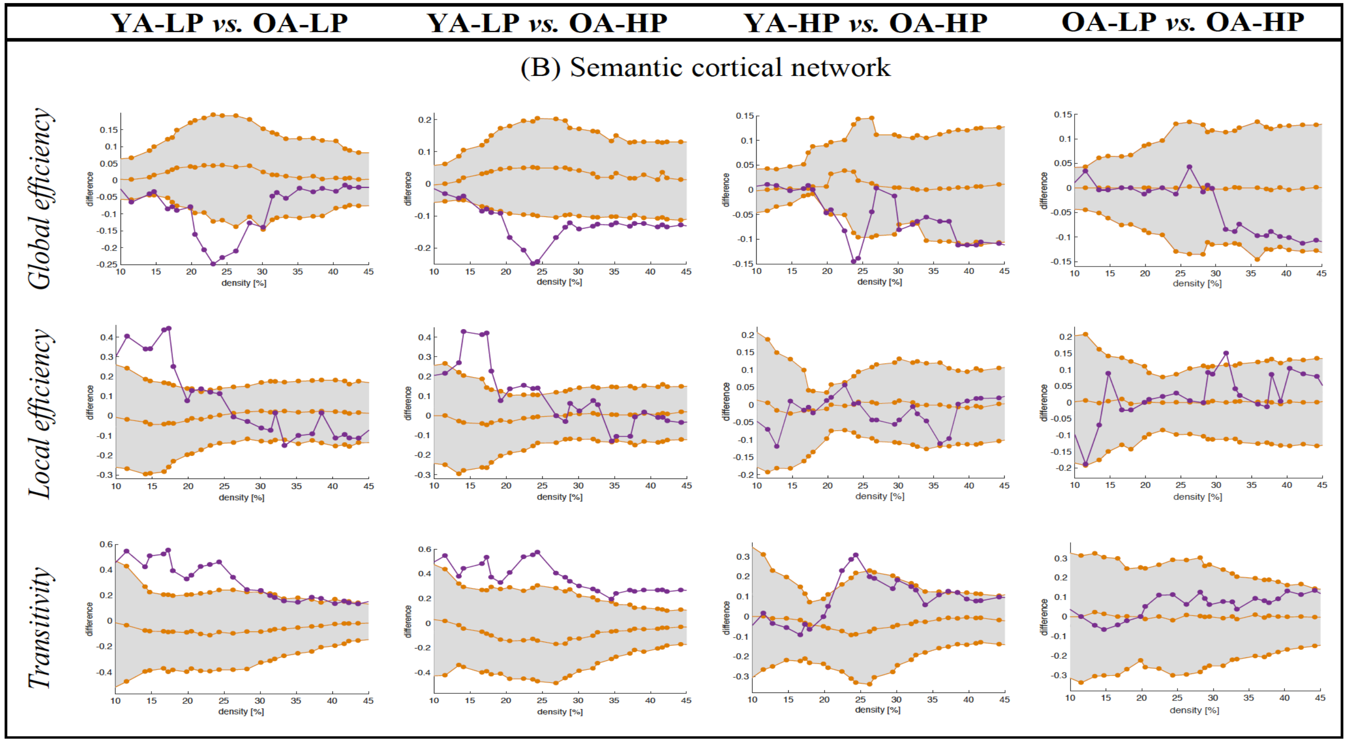


Figure 15 *(Continuation)*

Comparison of the age and PF performance groups across global graph measures.



Note. (A) Comparison between PF performance and age groups across global graph measures in the PF cortical network. (B) Comparison between the PF performance and age groups across global graph measures in the semantic cortical network. Network densities are displayed on the x-axis from min = 10% to max = 45%, in steps of 1%. Between-group differences in the global graph measures are displayed on the y-axis. The 95% confidence intervals were used as critical values for testing the null hypothesis at p≤0.05 (two-tailed), however, graphs show the one-tailed t-test results. YA-LP: younger-age with low PF performance; YA-HP: younger-age with high PF performance; OA-LP: older-age with low PF performance; OA-HP: older-age whit high PF performance.

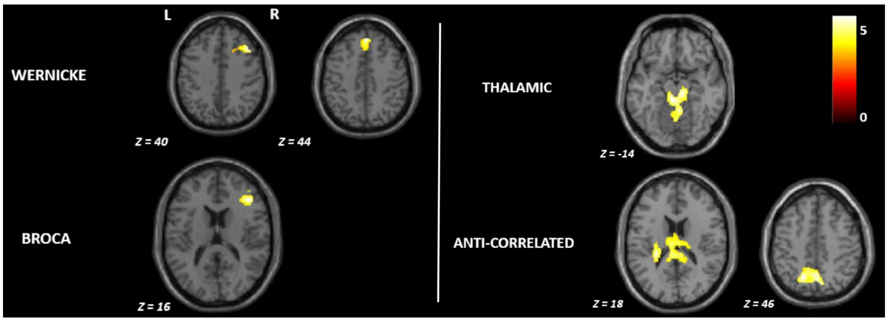
4.4. Study IV

Study IV (Manuscript paper IV) aimed to study the functional neural substrates of PF and potential compensatory mechanisms facilitated by CR, which would contribute to high performance in PF across age groups. A total of 149 cognitively normal healthy participants were divided into two age groups: younger adults (40 – 59 years) and older adults (60 – 82 years). These groups were compared in functional connectivity in a language network, and mediation effects of CR were used to investigate compensation.

The voxelwise two-sample *t*-test at the group level showed higher functional connectivity in younger than older adults (Family-Wise Error corrected $p \leq 0.05$) in all four modules. In the younger group, higher functional connectivity was observed in: (a) the right middle and superior frontal gyrus for the Wernicke module; (b) the right middle frontal gyrus for the Broca module; (c) the brainstem for the thalamic module; and (d) the left parietal operculum and superior parietal lobule for the anti-correlated module. We did not find any significant effects for brain regions showing higher functional connectivity in older adults than in younger adults in any module. (See Figure 16).

Figure 16

Group differences in functional connectivity between younger and older adults in the language network.



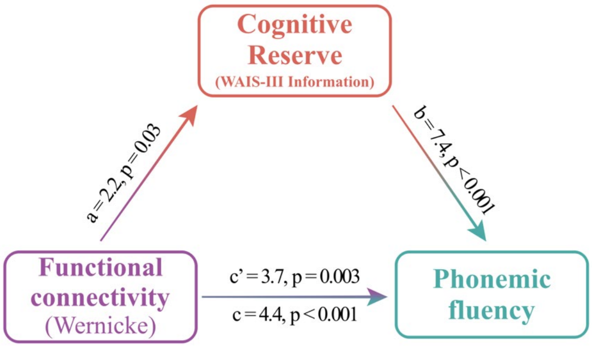
Note: All brain maps are visualized at familywise error corrected $p \leq 0.05$. R: right; L: left.

Greater functional connectivity of the Wernicke module involving ipsilateral and contralateral cuneus and extending to precuneus, calcarine cortex, and lingual gyrus, was significantly associated with higher PF at the cluster-level ($r = 0.35$, $p < 0.001$). Older adults with lower functional connectivity presented poorer PF performance compared to the younger adults. We did not observe any significant associations between functional connectivity and PF performance for the Broca, thalamic or anti-correlated modules.

We conducted a mediation analysis to demonstrate that CR mediates the association between functional connectivity of the Wernicke module and performance in PF. This analysis was performed in the combined cohort (younger and older groups pooled together). Figure 17 presents the mediation model for the Wernicke module within the significant cluster that correlated with PF. CR was a partial mediator between functional connectivity of the Wernicke module and PF in the combined cohort.

Figure 17

Mediation effects of CR.



Note: Mediation model testing CR as a mediator between cluster-level functional connectivity of the Wernicke module and PF performance. a: association of functional connectivity with CR; b: association of CR with PF; direct path c’: association of functional connectivity with PF; and indirect path c: association of functional connectivity and CR with PF.

Once demonstrated that CR mediates the association between the cluster-level functional connectivity and PF performance, we investigated whether this effect is differential in younger and older adults, with a greater mediation effect in older adults, hence delineating compensation. CR was a partial mediator between functional connectivity of the Wernicke module and PF performance only in older adults. Older adults with low CR and low functional connectivity showed the poorest PF performance than all other groups. However, older adults with high CR showed PF performance comparable to their younger counterparts, suggesting compensation for the effect of aging in PF.

4. DISCUSSION

The overall aim of this thesis was to study one of the main language components, VF, and its relationship with sociodemographic factors and other cognitive and neuroanatomic variables. This thesis also aimed to investigate the compensatory role of these variables in normal aging. We addressed these aims in four studies. The Study I's overall purpose was to investigate the association between performance in three components of VF (SF, PF, and AF) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly. Therefore, delineating how differentiation and dedifferentiation processes in VF are organized across the lifespan (32 to 84 years old). We found a lower word production with increasing age in the three fluency modalities, mainly in SF. The most prominent reduction in performance was observed between the middle-age and the early elderly in the three modalities, when a high number of cognitive variables stopped contributing, especially to SF and AF. Despite potentially compensatory dedifferentiation patterns in the three modalities, a stronger differentiation process was observed in the three modalities. In Study II, we focused on PF performance, and we investigated how CR and efficiency levels contribute to PF performance differently in people with high *versus* low performance and younger *versus* older individuals. We found that older adults performed worse than younger adults in PF, but this difference was minimized by high CR levels and high efficiency of cognitive networks. We investigated cortical networks underpinning compensation of PF performance in Study III. We observed a similar pattern of segregation associated with both HP and OA. Hence, two completely opposed levels of PF performance seem to share a common pattern of cortical connectivity. These similar patterns may underlie different brain mechanisms, suggesting a successful compensation in individuals with HP and an aberrant network organization in individuals with OA and LP. Overall, older adults who performed high in PF had the most segregated PF and semantic cortical networks, involved frontal nodes more strongly, and had a high average strength in the correlations among cortical regions. In Study IV, using functional MRIs, we demonstrated the association of functional connectivity with PF performance and how CR mediates this association, likely reflecting compensation in normal aging. We tested the hypothesis that older individuals with high CR can possibly maintain PF performance by recruiting both linguistic and non-linguistic networks, as hypothesized in Study II. We validated this hypothesis by showing that greater functional connectivity of the Wernicke module with non-Wernicke structures (ipsilateral and contralateral cuneus, precuneus, calcarine cortex and lingual gyrus) was associated with higher performance in PF. Further, this association was not mediated by CR in the younger adults but was mediated by CR in the older adults, thus, presumably representing compensation in the elderly.

The three VF modalities showed a decrease in performance with increasing age. However, the pattern of decline was different. SF showed a lineal and progressive reduction throughout the whole age range (32 – 84 years). PF was rather stable during the middle-age (32 – 58 years), followed by a drop during the early elderly (59 – 71 years) that seems to get stabilized in the late elderly (72 – 84 years). Regarding AF, it showed a cubic trend, with a plateau of high performance during the middle-age, a drop during the early elderly, and a trend for stability in performance during the late elderly. Other studies have also reported relative stability until the age of 60 in SF performance (Daigneault et al., 1992; Elgamal et al., 2011; Ferreira et al., 2015; Foldi et al., 2003; Tombaugh, 1999) and PF performance (Daigneault et al., 1992; Ferreira et al., 2015; Rodriguez-Aranda & Martinussen, 2006; Tombaugh, 1999), followed by a decline in performance (SF (Auriacombe et al., 2001; Bryan et al., 1997; Crossley et al., 1997; Foldi et al., 2003; Kempler et al., 1998; Ravdin et al., 2003; Rodriguez-Aranda & Martinussen, 2006; Singh-Manoux et al., 2012; Tombaugh, 1999), PF (Auriacombe et al., 2001; Bolla et al., 1998; Bryan et al., 1997; Kavé & Knafo-Noam, 2015; Rodriguez-Aranda & Martinussen, 2006)).

The contribution of various cognitive functions to VF performance was also different depending on the fluency modality and the age group. Regarding SF, the contribution of executive functions was observed in the range of age with a greater reduction in word production. When several relevant cognitive functions stop contributing (differentiation), performance drops, but new executive components emerge (dedifferentiation), likely being recruited as a compensatory mechanism. This suggests that both differentiation and dedifferentiation patterns can co-occur from young ages and not only at the oldest ages, as previously suggested (Hülür et al., 2015; La Fleur et al., 2018; Wilson et al., 2012). New brain networks or new parts of the same networks may be involved in this process, extending from the original differentiated function or network, in line with the CRUNCH hypothesis (Reuter-Lorenz & Cappell, 2008). The STAC theory suggests a generalized increased frontal activation with age as a compensatory response (Park & Reuter-Lorenz, 2009), as supported by the emergence of premotor functions as a new contributor in the late elderly. The differentiation process was more prominent than the dedifferentiation process, suggesting that executive functions cannot wholly compensate for the onslaught of aging, or this compensation coexists with the overall executive dysfunction observed in normal aging (Dempster, 1992), or both explanations at the same time. Regarding PF, the contribution of premotor and visuospatial abilities emerged in the late elderly. Thus, new brain regions seem to be recruited for SF (dedifferentiation) but possibly extending more to the posterior cortex in PF. The visuoconstructive and visuospatial component of the tasks suggests a greater participation of the right hemisphere with increasing age, in line with the hemispheric asymmetry reduction postulated by the HAROLD model (Cabeza, 2002). Our results suggest that this potential reorganization of the brain is somewhat effective, minimizing the negative onslaught of aging. Regarding AF, visual functions (visual memory and visuospatial functions) started contributing to the older age strata (dedifferentiation). This suggests that new brain networks or parts of the same networks are recruited, including more posterior and right hemispheric regions (Cabeza, 2002). The same as for SF, this finding emerged in the age range with a greater reduction in word production, possibly as a compensatory response.

To further understand the differential contribution of cognitive functions to VF depending on the fluency modality and the age group, we studied the contribution of CR and network efficiency in Study II. Older participants produced fewer words than younger participants, as previously reported (Rodriguez-Aranda & Martinussen, 2006; Singh-Manoux et al., 2012). Nevertheless, this reduction in words with increasing age was buffered by high CR levels. In this study, we demonstrate that high CR levels minimize the differences in PF between younger and older individuals. The RF analyses showed that the contribution of various cognitive functions to performance in PF differed depending on the age, as in Study I, and also depending on the CR levels. The strength of this contribution was clearly the greatest in older individuals with high CR levels, despite the number of variables contributing to performance was essentially the same in high and low CR groups. The signature contribution to VF associated with CR and age, i.e., lexical access and a strong contribution of executive functions, allows for older individuals with high CR to maintain their high performance on VF. CR is frequently considered as a factor that contributes to maintaining cognitive performance in the presence of increasing age or pathology (Stern et al., 2020). The graph theory analyses showed that the average global efficiency was increased in older participants with high CR levels. In the context of our study, this measure reflects how the performance in non-fluency tasks contributes to performance in PF. High CR may enable older individuals to access the lexical storage to retrieve more words rapidly (BNT had a high contribution), perhaps supported by better executive capacities such as using better strategies, inhibiting distractions, etc. (executive functions also had a high contribution). Our findings suggest that CR and age groups differ in integration features (global efficiency) rather than in segregation features (transitivity) or the magnitude of the associations among cognitive functions (average strength). Altogether, our findings show that despite largely the same number of cognitive functions contributing to fluency performance in older individuals with high CR levels, they predict a much higher variance of VF as compared to the other groups. The healthy nature of our cohort seems to highlight the role of integration features in cognitive compensation, rather than segregation features, which are likely to be related to the reorganization of brain networks seen in neurodegenerative diseases as a consequence of more overt brain pathology (Ferreira et al., 2019; Pereira et al., 2015).

We observed variability in performance within high CR participants. Although individuals with high CR levels performed better, some individuals achieving very high performance, and some achieving a lower performance. Individuals with high CR levels need a lower number of contributing variables in order to achieve high performance. Among these, individuals with high CR who achieved lower performance needed a greater number of contributing variables and had less efficient networks (as reflected by higher transitivity values, i.e., a more fragmented cognitive network). This finding may suggest that fluency performance partly relies on the number of contributing variables but also on the efficiency of the cognitive networks (a lower number of contributing variables and lower predicted variance would suggest more efficient cognitive networks). Interestingly, individuals with high CR levels recruited networks involved in visual abilities (immediate visual memory and JLOT). The difference between high CR individuals who achieved very high performance and those who achieved lower performance is that the former recruited executive functions, suggesting the recruitment of right fronto-parietal networks, which are contralateral to the language networks of the left hemisphere. The more outstanding contribution of executive functions and the possible involvement of the right fronto-parietal network suggest an increased frontal activation and greater participation of the right hemisphere with increasing age, respectively. This is supported by the STAC theory (Park & Reuter-Lorenz, 2009), the HAROLD model (Cabeza, 2002), and the CRUNCH hypothesis (Reuter-Lorenz & Cappell, 2008), respectively. The signature feature of high CR levels is the lower average strength, and the signature feature of individuals performing better is the less segregated (or fragmented) cognitive networks (lower transitivity). We interpret the finding on lower average strength as a highly efficient network in high CR individuals who are able to achieve high performance by involving the right fronto-parietal network and integrating information in a very efficient manner. In contrast, low CR individuals are much less efficient, and their VF strongly relies on processing speed. In Study II, we confirmed the hypothesis of compensatory processes at the bases of differential contribution of cognitive functions to VF performance across age groups, postulated in Study I. We also showed that efficiency levels could be at the base of this compensatory mechanisms.

Using cortical thickness measures and graph theory analyses in Study III, we demonstrated that isolated brain areas that have been associated with PF performance (Birn et al., 2010; Costafreda et al., 2006; Marsolais et al., 2014, 2015; Methqal et al., 2019; Tomasi & Volkow, 2012; Zhang et al., 2013) and semantic abilities (Budisavljevic et al., 2017; Nakajima et al., 2019) in previous studies do comprise cortical networks underpinning PF and semantic abilities. In contrast, the right fronto-parietal cortical network was not associated with performance in the executive-visuospatial cognitive tests investigated in our study. A possible explanation for this is the use of slightly different tests of executive and visuospatial abilities, different age groups or the exclusion of regions of the left hemisphere also belonging to the right executive-visuospatial network (Bagarinao et al., 2019; Budisavljevic et al., 2017; Nakajima et al., 2019). However, we limited our network to the right hemisphere to force the distinction between ipsilateral (semantic network) and contralateral (right executive-visuospatial) compensation.

Compensation can occur in different ways: as a more efficient use of a specific brain network, which in our study was illustrated by network characteristics within the PF cortical network, and through recruitment of other brain networks, which in our study was illustrated by network characteristics of an ipsilateral language network, i.e., the semantic cortical network. The recruitment of a network with shared brain regions could be explained by the association between PF and other linguistic functions (Gonzalez-Burgos et al., 2019; Lezak et al., 2004). The main finding in this study is that the same pattern of reduced efficiency and increased transitivity in PF and semantic cortical networks was associated with both high performance and older age. Hence, interpreting network features in combination with level of cognitive performance is thus essential. The pattern of reduced efficiency and increased transitivity associated with lower performance in older individuals is in line with our hypothesis and suggests that this pattern of network organization is aberrant or inefficient (Cabeza et al., 2018; Grady, 2008; Logan et al., 2002; Meunier et al., 2014; Park et al., 2004; Reuter-Lorenz & Cappell, 2008; Vaqué-Alcázar et al., 2020). However, many older individuals managed to maintain a high level of performance in PF (the OA-HP group), which was as high as the level of performance in the YA-HP group. Hence, reduced efficiency and increased transitivity associated with high performance in older individuals suggests that this network organization pattern can also be effective, possibly underlying compensatory mechanisms.

Despite the overall network similarities, several findings allowed us to discriminate between compensation and aberrant network organization: the topological organization (modular analyses) and the greater participation of frontal nodes (nodal measures). We identified two modules in each of our four groups; however, the groups had distinct topological organizations. The Broca area, Wernicke area, and the supramarginal gyri were clustered in two separate modules in the groups with high performance, while in the groups with low performance, these regions were clustered in one single module. These two clusters in conjunction with a greater participation of frontal nodes and a higher average strength in the OA-HP group, suggests that the Broca area's close connectivity with neighboring frontal regions favor the high performance in PF. In contrast, long-distance connectivity of the Broca area seems to be less efficient and is associated with low performance in PF. Although long-distance connections can transfer information quickly and noiselessly by reducing the path length (Bullmore & Sporns, 2012; Buzsáki et al., 2004), the cost of long-distance connections can exceed its value (Achard & Bullmore, 2007; Bullmore & Sporns, 2012; van den Heuvel & Sporns, 2013, 2019). The frontal lobe has been postulated as a scaffold in compensatory processes (Park & Reuter-Lorenz, 2009). The interaction among neighboring brain regions to reduce metabolic and wiring cost is greater in individuals with high CR (Bullmore & Sporns, 2012; Franzmeier et al., 2018; Lee et al., 2019; Marques et al., 2016), who have more efficient compensatory mechanisms (Gonzalez-Burgos et al., 2020). Hence, high performance in PF seems to be underpinned by a highly intra-connected sub-network with short-distance connections, primarily including the Broca and other frontal areas.

Given the healthy cognitive nature of our cohort, compensatory mechanisms underlying PF may not be understood entirely by using structural data. Then, in Study IV, using resting-state *f*MRI, we tested the hypothesis that older individuals with high CR can maintain PF possibly by recruiting both linguistic and non-linguistic networks, as postulated in Study III. We investigated an extended language network beyond the classically identified Wernicke's and Broca's areas by including the Wernicke's, Broca's, thalamic and anti-correlated modules (Tomasi & Volkow, 2012). Across these four modules, we observed four spatially distinct functional connectivity patterns with involvement of frontal, temporal, parietal, and subcortical brain regions, therefore extending beyond traditional Wernicke's and Broca's areas. This is consistent with the notion that language processing is supported by multiple and distributed sub-networks (modules) rather than individual specialized brain regions (Fedorenko & Thompson-Schill, 2014). Functional connectivity patterns in each of these modules also differed between age groups. On the one hand, we found the involvement of additional brain regions in older adults relative to younger adults within the Wernicke and Broca modules. On the other hand, we found the involvement of fewer brain regions in older adults relative to younger adults in the thalamic and anti-correlated modules. Such a differential pattern has often been attributed to aging (Cabeza & Dennis, 2012; Logan et al., 2002) and observed in other brain networks, including visual (Geerligs et al., 2014; Park et al., 2004) and motor (Carp et al., 2011) networks. Irrespective of the module, we found that older adults had diminished functional connectivity compared to younger adults, what implies that older brains are more vulnerable to a breakdown of within-module connectivity (Damoiseaux, 2017; Ferreira & Busatto, 2013; Sala-Llonch et al., 2015), thus, increasing the likelihood of a need for compensation at an older age.

In the combined cohort, we identified a significant correlation between PF performance and functional connectivity of the Wernicke module. However, this finding is incongruent with our hypothesis that functional connectivity involving the Broca's area (inferior frontal gyri) would be associated with PF. The Broca's area, part of the Broca module in our study, has been implicated in language production (Meinzer et al., 2009). In contrast, Wernicke's area (superior temporal gyri), part of the Wernicke module in this study, is traditionally known to be involved in language comprehension. This discordance could have three explanations: (a) the Wernicke module comprises additionally temporal, parietal, and frontal brain regions. Frontal regions have been implicated in PF task activation (Perani et al., 2003; Wagner et al., 2014). (b) the involvement of the Wernicke's area in PF, and its pervasive semantic facilitation (Schwartz et al., 2003). (c) the possible role of Wernicke's area in enabling the knowledge needed to articulate motor movements prior to production

(Binder, 2015). Altogether, we suggest that in our cohort of cognitively normal individuals with normal PF performance, variability in PF is related to the efficient recruitment of non-Broca areas belonging to Wernicke and anti-correlated modules. We also observed a significant correlation between PF and the functional connectivity of the Wernicke module with non-Wernicke regions. We observed the engagement of regions such as the cuneus, calcarine cortex, and lingual gyrus core to visual processing, and precuneus that is key for the default mode network, hence involved in attention and memory. This implies that PF elicited connectivity of task-positive (Wernicke module) and concomitantly task-negative (anti-correlated module) networks, suggesting the dichotomized functional organization in the brain (Fox et al., 2005).

CR was a partial mediator of the relationship between functional connectivity (of Wernicke with anti-correlated module) and PF performance in the combined cohort. Older adults with low CR and low functional connectivity exhibited significantly lower PF. In contrast, older adults with high CR performed significantly better and comparable to the younger adults regardless of functional connectivity, thus demonstrating compensation in older age. Neuroanatomically, these effects were localized in the calcarine cortex, lingual gyrus and precuneus. The contributions of structures from the anti-correlated module (calcarine cortex, lingual gyrus, precuneus) have been shown to be part of the network topography expressing differential deactivation in aging (Stern et al., 2005).

5. CONCLUSIONS

- VF declines with increasing age. SF seems to be more vulnerable to the effect of aging than PF and AF.
- Lexical access, processing speed, and executive functions are among the most contributing functions to performance in VF. The most striking contribution of new cognitive functions takes place during the transition from the middle-age to the early elderly.
- Differentiation processes (functions stop contributing with increasing age) coexist with dedifferentiation processes (new functions start contributing with increasing age). Compensatory mechanisms are postulated to underlie these patterns.
- PF declines less with age in individuals with higher CR levels, probably due to their greater capacity to recruit contralateral fronto-parietal networks, and efficiently use ipsilateral language networks, integrating information in a rapid way across less fragmented networks. In terms of functions, these networks are represented by executive/visual abilities and access to the lexicon, respectively.
- Graph theory-based modular analyses complemented with nodal network analyses and measures of network strength may help to disentangle compensation from the aberrant network organization associated with older age.
- More segregated cortical networks with a strong involvement of frontal nodes seems to allow older adults to maintain their high performance in PF.
- Functional connectivity involving brain areas shared by the Wernicke (linguistic) and anti-correlated (non-linguistic) modules was associated with PF in aging. This association was mediated by CR in the older adults but not in the younger adults, indicating compensation of the effect of aging in PF in the elderly.
- A balance among structure, function and CR most likely regulates an individual's ability to compensate lower cognitive performance in the face of aging and pathology.

6. ABSTRACT

BACKGROUND

Changes in normal cognitive performance have been well documented in earlier research. Some abilities such as executive functions, processing speed, memory, attention, visuoconstructive and visuospatial functions decline with age (Ferreira et al., 2015; Harada et al., 2013; Salthouse et al., 1995; Salthouse, 2009; Singh-Manoux et al., 2012). Other cognitive abilities, such as crystallized abilities and language remain stable or even improve with age (Park & Reuter-Lorenz, 2009; Salthouse, 2010; Singh-Manoux et al., 2012).

Regarding language, this is one of the most complex cognitive function in humans. Language is overall robust to the effect of aging but there are differences across linguistic components. While some components such as comprehension, semantic abilities, and vocabulary remain rather stable or even improve with age (Ansado et al., 2013; Shafto & Tyler, 2014), other language components such as verbal fluency (VF) and naming are among the most vulnerable cognitive functions to aging (Machado et al., 2018).

Cognitive tests of VF asses the ability to produce as many words as possible following specific rules and within a timeframe, usually 60-seconds. Words produced must begin with a specified letter (e.g., letter “F”; phonemic fluency (PF)), belong to a specify category (e.g., “animals”, semantic fluency (SF); “to run”, action fluency (AF)), and similar words and repetitions are not permitted. Results in literature regarding decline in VF with age are controversial. Some authors have found effect of age on SF (Gladsjo et al., 1999; Kempler et al., 1998; Lezak et al., 2012; Tombaugh et al., 1999), and others on PF (Auriacombe et al., 2001; Bäckman & Nilsson, 1996; Bryan et al., 1997; Mathuranath et al., 2003; Rodriguez-Aranda & Martinussen, 2006). Despite these different findings, there is certain agreement considering that SF declines with age, whereas PF shows more stability with age. Studies on AF in normal aging are less frequent, and most of these studies could be found in diseases with movement disorder such as Parkinson’s disease (Herrera et al., 2012;

Piatt et al., 1999a; Signorini & Volpato, 2006). In the AF modality, the effect of age informed in previous studies is also divergent. Most of them did not find an effect of age (Correia, 2010; Molina, 2015; Piatt et al., 1999b; Piatt et al., 2004), whereas fewer found an effect of age (Ferreira, 2012; Lezak et al., 2012).

The association of different cognitive domains with the VF modalities have also been investigated. Previous studies have observed a relationship between performance in SF and performance in tests of processing speed (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), lexical access (Kraan et al., 2013; Lezak et al., 2004; Stolwyk et al., 2015), executive functions (Amunts et al., 2021; Shao et al., 2014; Stolwyk et al., 2015), and working memory (Kraan et al., 2013). Performance in PF has been associated with performance in tests of processing speed (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), attention (Ruff et al., 1997; Troyer et al., 1997), lexical access (Lezak et al., 2004), executive functions (Bolla et al., 1990; Rodriguez-Aranda & Sundet, 2006; Ruff et al., 1997; Shao et al., 2014; Stolwyk et al., 2015), and memory (Ardila et al., 1998; Ruff et al., 1997). Studies on AF did not find any relationships with episodic memory or picture naming (Piatt et al., 1999b; Piatt et al., 2004).

While some authors found associations between SF and the temporal lobe, other authors highlighted a strong association between PF and frontal lobe functioning (Azuma, 2004; Dennis & Cabeza, 2008; Grogan et al., 2009; Henry & Crawford, 2004; Piatt et al., 1999b). Regarding AF, there has been fewer research investigating the neural mechanisms underlying AF tasks during aging (Kochhann et al., 2018), but some syudies have linked AF with frontal regions (Paek et al., 2020; Piatt et al., 1999b).

These divergent findings in VF, both in cognitive performance and neural substrate, are partially related to the univariate approach across most of the studies. However, the aging process is complex and heterogeneous and is influenced by biological differences (e.g., synapse count), life experiences (e.g., development, education), among other factors (Reuter-Lorenz & Park, 2014). As an alternative to univariate analyses, more recently, multivariate approaches have addressed the study of age-related cognitive changes considering these variables to disentangle why some individuals develop dementia while others have successful aging.

One of the first proposals regarding brain changes in aging is the *"age differentiation hypothesis"* (Garrett, 1946). According to this hypothesis, the organizational structure of cognitive abilities changes with age (Balinsky, 1941). Several decades later, the concept of reserve emerged from the observation of the mismatch between the degree of brain pathology or brain damage and the clinical manifestation of that damage observed in some patients (Katzman et al., 1989; Stern, 2002, 2009). *Cognitive reserve* (CR) refers to the use of brain networks or cognitive paradigms that are less susceptible to disruption, considered a normal process used by healthy individuals when coping with task demands. *Compensation* refers to the use of brain structures or networks not normally used by individuals with intact brains in order to compensate for brain damage (Stern, 2002, 2009). Concerning VF performance, high CR level, usually measured as a high level of education, has been associated with a higher number of produced words in PF (Auriacombe et al., 2001; Balduino et al., 2019; Crossley et al., 1997; Roldán-Tapia et al., 2012; Tessaro et al., 2020; Tombaugh et al., 1999).

Higher activation of neural networks has been reported frequently in older adults in comparison with younger adults in neuroimaging studies. This overactivation has been associated with superior cognitive performance in older adults, suggesting compensatory processes of age-related decline and maintained cognitive performance. Several theories have been proposed to account for age differences in brain activation (Festini et al., 2018): the Hemispheric Asymmetry Reduction in Older Adults model (HAROLD, Cabeza (2002)), the Posterior-Anterior Shift in Aging phenomenon (PASA, Davis et al. (2008); Dennis and

Cabeza, (2008)) theory, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH, Park and Reuter-Lorenz (2009); Reuter-Lorenz and Cappell (2008); Reuter-Lorenz and Lustig (2005); Reuter-lorenz and Mikels (2006)), and the Scaffolding Theory of Aging and Cognition (STAC, Park and Reuter-Lorenz (2009)) and the STAC theory - revised (STAC-r, Reuter-Lorenz and Park, (2014)).

The study of brain connectivity and the role of network architecture have recently emerged in the field of connectomics (Sporns, 2012). The graph theory approach has been used to study changes in brain connectivity and networks in both normal aging (Achard & Bullmore, 2007; Dennis & Thompson, 2014; Meunier et al., 2009) and pathology (Ferreira et al., 2019; Pereira et al., 2018), using brain regions as nodes and the connection between them as edges. However, very few studies have applied graph theory on cognitive data (Garcia-Ramos et al., 2015, 2016; Jonker et al., 2019; Kellermann et al., 2015, 2016), using the cognitive functions as nodes and the connection between them as edges.

AIMS AND HYPOTHESIS

Aims

This thesis aimed to study one of the main language components, VF, and its relationship with sociodemographic factors and other cognitive and neuroanatomic variables. This thesis also aimed to investigate the compensatory role of these variables in normal aging. The specific aims for each study were as follows:

- **Study I**: to investigate the association between performance in three components of VF (SF, PF, and AF) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly.

- **Study II**: to investigate how CR and efficiency levels contribute to PF differently in people with high *versus* low fluency performance and in younger *versus* older individuals.
- **Study III**: to investigate cortical brain networks potentially underpinning compensation of age-related differences in PF.
- **Study IV**: to study the neural functional substrates of PF and potential compensatory mechanisms facilitated by CR, which would contribute to high performance in PF across age groups.

Hypothesis

- The three fluency modalities (SF, PF, and AF) would decrease with increasing age. The association between fluency variables and non-fluency cognitive measures would be different between age groups spanning from the early middle-age to the late elderly, with predominance of dedifferentiation processes in the older groups.
- Older adults would perform worse than younger adults in VF, but this difference would be minimized by high CR levels and high efficiency of cognitive networks. In other words, high CR levels and network efficiency would help to maintain high performance in older adults, thus contributing to compensate for the negative effect of age.
- Older individuals with high performance in PF would have a more efficient PF cortical network. More efficient semantic and executive-visuospatial cortical networks would be associated with higher performance in PF in older individuals, likely delineating compensatory processes in normal aging.
- Younger adults would show greater functional connectivity in the four modules previously related with PF than older adults. Functional connectivity, particularly in

Broca's module (language production center), would be associated with performance in PF. CR would mediate the relationship between functional connectivity involving both linguistic and non-linguistic brain areas and performance in PF, especially in older adults, hence indicating compensation of the effect of age in PF.

MATERIAL AND METHODS

All participants were selected from the GENIC-database (Group of Neuropsychological Studies from the Canary Islands) (Ferreira et al., 2015; Machado et al., 2018). All the individuals included in this thesis are cognitively normal. Individuals were assessed with a comprehensive neuropsychological protocol applied by experienced neuropsychologists. A total of 446 participants were selected for Study I and II (32 – 84 years, 54.9% females). A total of 267 right-handed participants were selected for Study III (32 – 79 years, 53% females), and 149 right-handed participants for Study IV (40 – 82 years, 56.4% females).

The neuropsychological protocol includes tests of language, processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, and visuoconstructive, visuoperceptive and visuospatial functions. Among all the tests included in the neuropsychological protocol, three tests of VF are of special relevance for the thesis:

- *Phonemic fluency*: The *Controlled Oral Word Association Test* (COWAT; Benton et al., 1989) was administrated. Participants had to recall words that begin with the letters F, A, and S, taking one minute on each of the letters. Proper nouns, numbers, and derived words were considered intrusion errors. A total score (F+A+S) was calculated as the number of correct words produced, excluding intrusions and perseverations (repetitions of correct words).

- *Semantic fluency*: Instructions were given following the administration procedures described in the Multilingual Aphasia Examination (Benton et al., 1989). Participants had to recall the names of animals for one minute. The total number of words, perseverations, and intrusions were registered.
- *Action fluency:* Participants had to recall verbs in the infinitive form (e.g., "to reflect"). Verbs included as part of a sentence (e.g., "to dance the tango") and repetitions of the same verb were considered errors (Piatt et al., 1999b). The total number of correct verbs, intrusions, and perseverations were counted.

Participants were scanned using a 3T General Electric imaging system (General Electric, Milwaukee, WI, USA) with an eight channel high resolution head coil located at *Hospital Universitario de Canarias (HUC)* in Tenerife, Spain. TheHiveDB Database system (Muehlboeck et al., 2014) was used to automatically preprocess the T1-weighted images with FreeSurfer 6.0.0 (https://surfer.nmr.mgh.harvard.edu/), following standard procedures. Resting-state functional magnetic resonance imaging (*f*MRI) volumes were processed with Statistical Parametric Mapping software version 12 (SPM12).

Statistical analyses were performed using the R programming environment (Core, 2016), the BRAPH software (BRain Analysis using graPH theory, www.braph.org, Mijalkov et al., 2017), and MATLAB R2014b (The MathWorks, Inc., Natick, Massachusetts, United States). Previous to statistical analysis, an exploratory analysis of missing values was performed for all cognitive variables included in Study I. Two per cent of the values were missing across the 48 cognitive variables. The non-parametric test of homoscedasticity showed a non-random distribution pattern of missing data ($p<0.05$). The missing values were imputed using the multivariate method of Random Forest (RF) (Buuren & Groothuis-Oudshoorn, 2011; Liaw & Wiener, 2002). This imputed dataset was saved and used in subsequent analyses: RF analyses in Study I, and ANCOVA, RF, and graph analyses in Study II. The cognitive variables of interest (PF, SF and AF) were not imputed. RF regression analyses were used in Study I and II to investigate the multivariate association between the measures of VF and a total of 45 cognitive variables.

In the graph theory analysis, networks were constructed using cognitive variables as nodes in Study II and the average cortical thickness from selected regions of the Desikan atlas (Desikan et al., 2006) in Study III. For functional connectivity analysis, voxelwise multiple linear regression was performed in Study IV to investigate the association between functional connectivity and PF. Functional connectivity patterns specific to each module and age group were identified through voxelwise one-sample t-test, revealing brain regions with functional connectivity greater than the global mean value. In Study IV, mediation analyses were performed to examine potential mediation effects of CR on the association between functional connectivity and PF. We tested the direct involvement of functional connectivity as well as the indirect involvement of functional connectivity mediated by CR (WAIS-III Information subtest) in relation to PF (Baron & Kenny, 1986).

RESULTS

In Study I, a mixed ANCOVA model was conducted to examine the interaction between age and VF. This model showed a significant interaction, indicating that the association between age and VF is modulated by the fluency modality. All modalities declined with increasing age, but SF was the most vulnerable to aging. Then, RF regression models were performed to assess whether the contribution of numerous cognitive variables to VF differs across age and VF modality. Lexical access, processing speed, and executive functions were among the most contributing functions. The most prominent reduction in performance was observed during the transition from middle-age to early elderly, when cognitive variables stopped contributing (differentiation), and new cognitive variables started contributing (dedifferentiation).

In Study II, ANCOVA was used to investigate the interaction between CR, age, and performance in PF. The ANCOVA model showed a significant interaction between CR and age groups, and between CR and performance groups. The younger age (YA) group outperformed the older age (OA) group, but this difference was smaller in the high CR (highCR) group than in the low CR (lowCR) group. Hence, higher CR reduces age-related differences. The difference between low PF (lowPF) and high PF (highPF) performance groups was greater in the highCR group than in the lowCR group. Hence, higher CR increases performance on PF, irrespectively of the age (the partial effect of age was controlled for in the ANCOVA). RF and graph theory analyses on cognitive data were conducted to study the contribution of non-fluency cognitive variables and efficiency measures to performance in PF, respectively. Higher CR increased performance in PF and reduced age-related differences in PF. A slightly higher number of cognitive functions contributed to performance in high CR groups. Networks were more integrated in high CR individuals, both in the older age and high-performance groups. The strength and segregation of the networks were decreased in high-performance groups with high CR.

In Study III, the two-way ANOVA for PF showed that the older age group performed worse than the younger age group in PF, but this effect was only observed within the low performance groups (YA-LP *vs.* OA-LP), but not within the high performance groups (YA-HP *vs.* OA-HP). Graph theory analysis on structural magnetic resonance imaging revealed the same pattern of reduced efficiency and increased transitivity was associated with both high performance (compensation) and older age (aberrant network organization) in the PF and semantic cortical networks. Compared with the OA-LP group, the higher PF performance in the OA-HP group was associated with more segregated PF and semantic cortical networks, greater participation of frontal nodes, and stronger correlations within the PF cortical network.

In Study IV, using resting-state functional magnetic resonance imaging, we evaluated functional connectivity in an established and extended language network comprising Wernicke, Broca, thalamic and anti-correlated modules. We conducted voxel-wise multiple linear regression to identify the brain areas associated with PF. We found that greater functional connectivity between the Wernicke module and brain areas within the anti-correlated module was associated with better performance in PF. We tested for mediation effects of CR, measured by the Wechsler Adult Intelligence Scale – Information subtest, upon the association between functional connectivity and PF tested to investigate compensation. We found that CR was an unlikely mediator in younger adults. In contrast, CR was a partial mediator of the association between functional connectivity and PF in older adults, likely representing compensation to counter the effect of aging.

CONCLUSIONS

- VF declines with increasing age. SF seems to be more vulnerable to the effect of aging than PF and AF.
- Lexical access, processing speed, and executive functions are among the most contributing functions to performance in VF. The most striking contribution of new cognitive functions occurs during the transition from the middle-age to the early elderly.
- Differentiation processes (functions stop contributing with increasing age) coexist with dedifferentiation processes (new functions start contributing with increasing age). Compensatory mechanisms are postulated to underlie these patterns.
- PF declines less with age in individuals with higher CR levels, probably due to their greater capacity to recruit contralateral fronto-parietal networks and efficiently use

ipsilateral language networks, integrating information in a rapid way across less fragmented networks. In terms of functions, these networks are represented by executive/visual abilities and access to the lexicon, respectively.

- Graph theory-based modular analyses complemented with nodal network analyses and measures of network strength may help to disentangle compensation from the aberrant network organization associated with older age.
- More segregated cortical networks with a strong involvement of frontal nodes seems to allow older adults to maintain their high performance in PF.
- Functional connectivity involving brain areas shared by the Wernicke (linguistic) and anti-correlated (non-linguistic) modules was associated with PF in aging. This association was mediated by CR in the older adults but not in the younger adults, indicating compensation of the effect of aging in PF in the elderly.
- A balance among structure, function and CR most likely regulates an individual’s ability to compensate lower cognitive performance in the face of aging and pathology.

7. RESUMEN EN CASTELLANO

MARCO TEÓRICO

Los cambios en el rendimiento cognitivo normal han sido ampliamente informados en investigaciones anteriores. Algunas funciones cognitivas como las funciones ejecutivas, velocidad de procesamiento, memoria, atención, funciones visoperceptivas y visoespaciales se deterioran con la edad (Ferreira et al., 2015; Harada et al., 2013; Salthouse et al., 1995; Salthouse, 2009; Singh-Manoux et al., 2012). En cambio, otras funciones como las habilidades cristalizadas y el lenguaje permanecen estables o incluso mejoran con la edad (Park & Reuter-Lorenz, 2009; Salthouse, 2010; Singh-Manoux et al., 2012).

Con relación al lenguaje, es una de las funciones cognitivas más complejas en los humanos. En general, el lenguaje es resistente al efecto de la edad, pero hay diferencias entre los distintos componentes de este. Mientras algunos componentes como la comprensión, habilidades semánticas y el vocabulario permaneces relativamente estables, o incluso mejoran con la edad (Ansado et al., 2013; Shafto & Tyler, 2014), otras funciones como la fluidez verbal (FV) y la denominación son más vulnerables al efecto envejecimiento (Machado et al., 2018).

Los tests cognitivos de FV evalúan la habilidad de producir tantas palabras como sea posible de acuerdo con unas reglas específicas en un tiempo determinado, comúnmente 60 segundos. Las palabras producidas deben comenzar con una letra específica (p. ej., la letra "F", fluidez fonética (FF)), o pertenecer a una categoría específica (p.ej., "animales", fluidez semántica (FS); "acciones" (p. ej., "correr", fluidez de acciones (FA)). Las palabras derivadas o repeticiones no están permitidas. Los resultados en la literatura en relación con el deterioro de la FV con la edad son controvertidos. Algunos autores han encontrado efecto de la edad en FF (Auriacombe et al., 2001; Bäckman & Nilsson, 1996; Bryan et al., 1997; Mathuranath et al., 2003; Rodriguez-Aranda & Martinussen, 2006), y otros en FS (Gladsjo et al., 1999; Kempler et al., 1998; Lezak et al., 2012; Tombaugh et al., 1999). A pesar de las diferencias en los resultados encontrados, hay una gran convergencia en que la FF es más estable, mientras que la FS se deteriora con la edad. Los estudios en FA en el envejecimiento normal son menos frecuentes, la mayoría de ellos se han realizado en enfermedades con trastornos del movimiento como la Enfermedad de Parkinson (Herrera et al., 2012; Piatt et al., 1999a; Signorini & Volpato, 2006). En esta modalidad, estudios anteriores también han encontrado resultados divergentes en cuanto al efecto de la edad. La mayoría de los estudios no han encontrado efecto de la edad (Correia, 2010; Molina, 2015; Piatt et al., 1999b; Piatt et al., 2004), solamente algunos lo han encontrado, observándose un descenso en el rendimiento (Ferreira, 2012; Lezak et al., 2012).

También se ha estudiado la asociación entre distintos dominios cognitivos y las modalidades de FV. Estudios anteriores han observado relación entre el rendimiento en FF y el rendimiento en tests de velocidad de procesamiento (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), atención (Ruff et al., 1997; Troyer et al., 1997), acceso al léxico (Lezak et al., 2004), funciones ejecutivas (Bolla et al., 1990; Rodriguez-Aranda & Sundet, 2006; Ruff et al., 1997; Shao et al., 2014; Stolwyk et al., 2015), y memoria (Ardila et al., 1998; Ruff et al., 1997). El rendimiento en FS se ha asociado con el rendimiento en test de velocidad de procesamiento (Elgamal et al., 2011; Kavé & Mashal, 2012; Kraan et al., 2013), acceso al léxico (Kraan et al., 2013; Lezak et al., 2004; Stolwyk et al., 2015), funciones ejecutivas (Amunts et al., 2021; Shao et al., 2014; Stolwyk et al., 2015) y memoria de trabajo (Kraan et al., 2013). Los estudios de FA no han encontrado relación con la memoria episódica ni con la denominación pictórica (Piatt et al., 1999b; Piatt et al., 2004).

En cuanto al sustrato neuroanatómico de la FV, algunos autores han encontrado una fuerte asociación entre la FF y el lóbulo frontal; otros autores asocian la FS con el lóbulo temporal (Azuma, 2004; Dennis & Cabeza, 2008; Grogan et al., 2009; Henry & Crawford, 2004; Piatt et al., 1999b). En relación con la FA, ha habido pocas investigaciones orientadas al estudio de los mecanismos neurales subyacentes a esta tarea en el envejecimiento (Kochhann et al., 2018), sin embargo, algunos estudios la han asociado con regiones del lóbulo frontal (Paek et al., 2020; Piatt et al., 1999b).

Esos resultados divergentes en FV, tanto en el rendimiento cognitivo como en el sustrato neuroanatómico, están parcialmente explicados por el enfoque univariado aplicado en la mayoría de los estudios. Sin embargo, el proceso del envejecimiento es complejo y heterogéneo y está afectado por diferencias a nivel biológico (p. ej., recuento sináptico), experiencias vitales (p. ej., el periodo de desarrollo, la educación), entre otros factores (Reuter-Lorenz & Park, 2014). Como alternativa a los análisis univariados, más recientemente, estas variables se han tenido en cuenta en aproximaciones multivariadas que han abordado el estudio de los cambios cognitivos relacionados con la edad para descifrar por qué algunas personas desarrollan demencia mientras que otros tienen un envejecimiento saludable y exitoso.

Una de las primeras propuestas relacionadas con los cambios cerebrales en el envejecimiento es la *"hipótesis de la desdiferenciación con la edad"* (Garrett, 1946). De acuerdo con esta hipótesis, la estructura organizativa de las funciones cognitivas cambia con la edad (Balinsky, 1941). Varias décadas después, se propuso el concepto de *"reserva"* para explicar la incongruencia observada entre el grado de patología o daño cerebral y su manifestación clínica en algunos pacientes (Katzman et al., 1989; Stern, 2002, 2009). El concepto de *Reserva Cognitiva* (RC) se refiere al uso de redes cerebrales o paradigmas cognitivos que son menos susceptibles de alteración, considerado un proceso normal usado por individuos sanos para hacer frente a las demandas de la tarea. La *Compensación* se refiere al uso de estructuras o redes cerebrales no usadas normalmente por individuos con cerebros sanos para compensar el daño cerebral (Stern, 2002, 2009). En relación con el rendimiento en FV, altos niveles de RC, comúnmente medido con el nivel alto de educación, se ha asociado con un mayor número de palabras producidas en FF (Auriacombe et al., 2001; Balduino et al., 2019; Crossley et al., 1997; Roldán-Tapia et al., 2012; Tessaro et al., 2020; Tombaugh et al., 1999).

En estudios de neuroimagen frecuentemente se ha observado niveles más altos de activación de redes cerebrales en los adultos mayores que en los adultos jóvenes. Esta sobreactivación se ha asociado con un nivel de rendimiento cognitivo superior en adultos mayores, sugiriendo procesos compensatorios frente al deterioro asociado a la edad y para el mantenimiento del rendimiento cognitivo. Se han propuesto varias teorías para explicar las diferencias en activación cerebral asociadas a la edad, con un enfoque explicativo distinto a los procesos compensatorios (Festini et al., 2018): el modelo de “*Reducción de la Asimetría Hemisférica en Adultos Mayores”* (HAROLD en inglés, Cabeza (2002)), la fenómeno del *“Cambio Postero-Anterior en el envejecimiento”* (PASA en inglés, Davis et al. (2008); Dennis y Cabeza (2008)), la *“Hipótesis de la Utilización de Circuitos Neurales Relacionado con la Compensación”* (CRUNCH en inglés, Park and Reuter-Lorenz (2009); Reuter-Lorenz y Cappell (2008); Reuter-Lorenz y Lustig (2005); Reuter-lorenz y Mikels (2006)), y la *“Teoría del Andamiaje del envejecimiento y la Cognición”* (STAC en inglés, Park and Reuter-Lorenz (2009)) y la teoría STAC revisada, (STAC-r en inglés, Reuter-Lorenz and Park (2014)). El estudio de conectividad cerebral y el papel de la arquitectura de las redes ha emergido recientemente en el campo del conectoma (Sporns, 2012). La teoría de grafos se ha aplicado para estudiar cambios en las redes neuronales y la conectividad tanto en el envejecimiento normal (Achard & Bullmore, 2007; Dennis & Thompson, 2014; Meunier et al., 2009) como patológico (Ferreira et al., 2019; Pereira et al., 2018), usando las regiones cerebrales como como nodos y las conexiones entre ellas como aristas. Sin embargo, pocos estudios han aplicado la teoría de grafos en datos cognitivos, usando las funciones cognitivas como nodos y las conexiones entre ellas como aristas (Garcia-Ramos et al., 2015, 2016; Jonker et al., 2019; Kellermann et al., 2015, 2016).

OBJETIVOS E HIPÓTESIS

Objetivos

El objetivo de esta tesis fue estudiar uno de los principales componentes del lenguaje, la FV, y su relación con factores sociodemográficos y otras variables cognitivas y neuroanatómicas. Además, otro objetivo fue investigar el papel compensatorio de estas variables en el envejecimiento normal. Los objetivos específicos de cada estudio fueron los siguientes:

- **Estudio I**: investigar la asociación entre el rendimiento en tres modalidades de FV (FF, FS y FA) y el rendimiento en numerosas variables cognitivas (distintas a la fluidez) dentro de diferentes grupos de edad, desde la mediana edad hasta la vejez tardía.
- **Estudio II**: investigar cómo la RC y el nivel de eficiencia contribuyen a la FF de forma diferente en personas con alto *versus* bajo rendimiento en fluidez, así como en participantes jóvenes *versus* viejos,
- **Estudio III**: investigar redes cerebrales corticales que potencialmente sustentan la compensación de las diferencias en el rendimiento en FF asociadas a la edad.
- **Estudio IV**: estudiar los sustratos neuronales funcionales de la FF y mecanismos compensatorios potenciales facilitados por la RC, los cuales contribuirían al alto rendimiento en FF en los distintos grupos de edad.

Hipótesis

- Las tres modalidades de fluidez verbal (FF, FS y FA) presentarán un descenso en el rendimiento con el aumento de la edad. La relación entre las variables de fluidez y las otras variables cognitivas (distintas a las de fluidez) será diferente entre los grupos de edad que van desde la mediana edad temprana hasta la vejez tardía, con predominio de procesos de desdiferenciación en los grupos de mayor edad.
- Los participantes de mayor edad rendirán peor que los jóvenes en FV, pero esta diferencia se vería minimizada por un nivel alto de RC y una alta eficiencia en las redes cognitivas. En otras palabras, los altos niveles de RC y la eficiencia de la red ayudarán a mantener un rendimiento alto en los participantes de mayor edad, por tanto, contribuyendo a compensar el efecto negativo de la edad.
- Los participantes de mayor edad con alto rendimiento en FF tendrán una red fonética cortical más eficiente. La eficiencia de las redes semántica y ejecutiva-visoespacial estará relacionada con un mayor rendimiento en FF en los participantes de mayor edad, probablemente delineando procesos compensatorios en el envejecimiento normal.
- Los participantes más jóvenes mostrarán una mayor conectividad funcional en los cuatro módulos previamente relacionados con FF que los participantes de mayor edad. La conectividad funcional, especialmente en el módulo de Broca (centro de producción del lenguaje), estará asociada con el rendimiento en FF. La RC mediará la relación entre conectividad funcional de regiones lingüísticas y no lingüísticas y el rendimiento en FF, especialmente en los participantes de mayor edad, por tanto indicando compensación del efecto de la edad en FF.

MATERIAL Y MÉTODO

Todos los participantes fueron seleccionados de la base de datos de GENIC (Grupo de Estudios Neuropsicológicos de las Islas Canarias) (Ferreira et al., 2015; Machado et al., 2018). Todos los participantes incluidos en esta tesis presentan un rendimiento cognitivo normal. Los participantes fueron evaluados con un protocolo neuropsicológico amplio aplicado por neuropsicólogos/as experimentados/as. En los Estudios I y II se incluyeron 446 participantes (32 – 84 años, 54.9% mujeres). En el Estudio III se incluyeron 267 participantes diestros (32 – 79 años, 53% mujeres), y en el estudio IV se incluyeron 149 participantes diestros (40 – 82 años, 56.4% mujeres).

El protocolo neuropsicológico incluye pruebas de lenguaje, velocidad de procesamiento, funciones ejecutivas, memoria verbal y visual, memoria procedimental, funciones visoconstructivas, visoperceptivas y visoespaciales. Entre todos los tests incluidos en el protocolo, tres tests fueron de especial relevancia para esta tesis:

- *Fluidez Fonética*: Se administró el *Test de Asociación Controlada de Palabras* (COWAT en inglés; Benton et al. (1989)). Los participantes deben decir palabras que comiencen por las letras F, A y S, durante un minute cada una. Los nombres propios, números y palabras derivadas se consideran errores de intrusión. Se calcula la puntuación total (F+A+S) según el número de palabras correctas evocadas, excluyendo intrusiones y perseveraciones (repetición de palabras correctas).
- *Fluidez Semántica*: Se dieron instrucciones siguiendo el procedimiento de administración descrito en el manual de Examen Multilingüe de las Afasia (Benton et al., 1989). Los participantes deben decir nombres de animales durante un minuto. Se registra el total de palabras correctas, intrusiones y perseveraciones.
- *Fluidez de Acciones:* Los participantes deben decir verbos en su forma infinitiva (p. ej., “reflexionar”). Los verbos incluidos como parte de una frase (p. ej., “bailar un

tango") y las repeticiones del mismo verbo se consideran errores (Piatt et al., 1999b). Se registra el total de verbos correctos, intrusiones y perseveraciones.

Las imágenes por resonancia magnética (IRM) de los participantes se obtuvieron usando un sistema de imagen de 3T General Electric (General Electric, Milwaukee, WI, USA) con bobina de cabeza de alta resolución con ocho canales localizada en el Hospital Universitario de Canarias (HUC) en Tenerife, España. El sistema de base de datos TheHiveDB (Muehlboeck et al., 2014) se usó para el procesamiento automático de las imágenes ponderadas en T1 mediante FreeSurfer 6.0.0 (https://surfer.nmr.mgh.harvard.edu/), siguiendo los procedimientos estándar, y para el procesamiento de los volúmenes de las IRM funcional (IRMf) en estado de reposo mediante el programa *Statistical Parametric Mapping,* versión 12 (SPM12).

Los análisis estadísticos se llevaron a cabo usando el entorno de programación R (Core, 2016), el programa BRAPH ("BRain Analysis using graPH theory" en inglés, www.braph.org, Mijalkov et al., 2017), y el programa MATLAB R2014b (The MathWorks, Inc., Natick, Massachusetts, United States). Antes de los análisis estadísticos se llevó a cabo un análisis exploratorio de los valores perdidos en todas las variables cognitivas incluidas en el Estudio I. En las 48 variables cognitivas se encontró un total de un 2% de valores perdidos. La prueba no paramétrica de homocedasticidad mostró un patrón de distribución no aleatorio de los valores perdidos ($p<0.05$). Los valores perdidos fueron imputados usando el método multivariado de *ranfom forest* (RF) (Buuren & Groothuis-Oudshoorn, 2011; Liaw & Wiener, 2002). La base de datos imputada se guardó y se usó en los análisis posteriores: análisis de RF en el Estudio I, ANCOVA, RF, y análisis de grafos en el Estudio II. Las variables cognitivas de interés (FF, FS y FA) no fueron imputadas. En los Estudios I y II se llevaron a cabo análisis de regresión de RF para investigar la asociación multivariada entre medidas de FV y las 45 variables cognitivas.

Para el análisis de la teoría de grafos, las redes se construyeron usando las variables cognitivas como nodos en el Estudio II y el grosor cortical medio de regiones seleccionadas del atlas de Desikan (Desikan et al., 2006) en el Estudio III. Para el análisis de conectividad funcional, se llevó a cabo una regresión lineal múltiple a nivel de voxel en el Estudio IV para investigar la asociación entre conectividad funcional y el rendimiento en FF. Los patrones específicos de conectividad funcional para cada modulo y grupo de edad se identificaron mediante prueba T de una muestra a nivel de voxel, revelando regiones cerebrales con mayor conectividad funcional que el valor medio global. En el Estudio IV, se llevaron a cabo análisis de mediación para examinar el efecto mediador potencial de la RC entre la conectividad funcional y el rendimiento en FF. Se probó la implicación de la conectividad funcional en relación con el rendimiento en FF, tanto de forma directa como indirecta, mediada por la RC (Test de Información del WAIS-III) (Baron & Kenny, 1986).

RESULTADOS

En el Estudio I, se llevó a cabo un modelo de ANCOVA mixto para examinar la interacción entre la edad y el rendimiento en FV. Este modelo mostró una interacción significativa, la asociación entre la edad y la FV está modulada por la modalidad de FV. Todas las modalidades de FV se deterioran con la edad, pero la FS fue la más vulnerable a la edad. El modelo de regresión de RF se aplicó para evaluar si la contribución de numerosas variables cognitivas (distintas a FV) al rendimiento en FV cambia con la edad. Entre las variables de mayor contribución se observó el acceso al léxico, la velocidad de procesamiento y las funciones ejecutivas. La reducción más prominente en el rendimiento en FV se observó durante la transición de la mediana edad a la vejez temprana, cuando algunas variables cognitivas dejaron de contribuir (diferenciación) y otras variables nuevas empezaron a contribuir (desdiferenciación).

En el Estudio II, se aplicó ANCOVA para investigar la interacción entre la RC, la edad y el rendimiento en FF. El modelo mostró una interacción significativa entre la RC y la edad, y entre la RC y los grupos de rendimiento. El grupo de menor edad (YA) rindió mejor que el grupo de mayor edad (OA), pero esa diferencia fue menor en el grupo de RC alta que en el de RC baja. Por tanto, la RC alta reduce las diferencias en el rendimiento asociadas a la edad. La diferencia entre los grupos de rendimiento bajo (LP) y alto (HP) en FF fue mayor en el grupo de RC alta que en el grupo de RC baja. Por tanto, la RC alta aumenta el rendimiento en FF, independientemente de la edad (el efecto parcial de la edad se controló en el ANCOVA). Se llevaron a cabo análisis de RF y medidas de la teoría de grafos para estudiar la contribución de la cognición al rendimiento en FF y medidas de eficiencia, respectivamente. La RC alta aumenta el rendimiento en FF y reduce las diferencias asociadas a la edad. Un número ligeramente mayor de funciones cognitivas contribuyó al rendimiento en los grupos de RC alta. Las redes estaban más integradas en los grupos de RC alta, tanto en los grupos de mayor edad como en los grupos de rendimiento alto.

En el Estudio III, el modelo ANOVA para la FF mostró que los grupos de mayor edad rindieron peor en FF que los grupos de menor edad, pero este efecto se observó solo en los grupos de rendimiento bajo (YA-LP *vs.* OA-LP), pero no en los grupos de rendimiento alto (YA-HP *vs.* OA-HP). Los análisis de la teoría de grafos revelaron el mismo patrón de eficiencia reducida y aumento en la transitividad asociado tanto con el rendimiento alto (compensación) como con la vejez (organización aberrante de la red) en las redes fonética y semántica. En comparación con el grupo OA-LP, el mayor rendimiento en el grupo OA-HP se asoció con unas redes fonética y semántica más segregada, mayor participación de nodos frontales y una correlación más fuerte dentro de la red cortical fonética.

En el Estudio IV, usando IRMf en estado de reposo, evaluamos la conectividad funcional en una red de lenguaje establecida y extensa que comprende módulos de Wernicke, Broca, tálamo y anti-correlacionado. Se aplicó regresión linear múltiple a nivel de voxel para identificar áreas cerebrales asociadas con la FF. Se encontró que la mayor conectividad funcional entre el módulo de Wernicke y las áreas cerebrales dentro del módulo anti-correlacionado estaba asociada con mejor rendimiento en FF. La compensación se investigó mediante los efectos de mediación de la RC sobre la asociación entre la conectividad funcional y el rendimiento en FF. No se observó un papel mediador de la RC en los adultos jóvenes. Por el contrario, la RC fue un mediador parcial en la asociación entre la conectividad funcional y el rendimiento en FF en los adultos mayores, sugiriendo una posible compensación para contrarrestar el efecto de la edad.

CONCLUSIONES

- El rendimiento en FV desciende con el aumento de la edad. La FS parece ser más vulnerable al efecto de la edad que la FF y la FA.
- El acceso al léxico, la velocidad de procesamiento y las funciones ejecutivas fueron de las funciones con mayor contribución al rendimiento en FV. La mayor contribución de nuevas variables cognitivas ocurrió durante la transición de la mediana edad a la vejez temprana.
- Los procesos de diferenciación (las funciones cognitivas dejan de contribuir con la edad) coexisten con procesos de desdiferenciación (nuevas funciones cognitivas empiezan a contribuir con la edad). Los mecanismos compensatorios parecen estar subyaciendo estos patrones.
- La FF disminuye menos con la edad en personas con niveles altos de RC, probablemente debido a su capacidad de reclutar redes fronto-parietales contralaterales y por un uso

eficiente de redes ipsilaterales de lenguaje, integrando la información de forma rápida a través de redes menos fragmentadas. En término de funciones, estas redes están representadas por funciones ejecutivas/visuales y el acceso al léxico, respectivamente.

- Los análisis de modularidad basados en la teoría de grafos en combinación con los análisis nodales y medidas de fuerza pueden ayudar a diferenciar procesos de compensación de la organización aberrante de las redes asociadas a la edad.
- Las redes corticales más segregadas con una fuerte participación de nodos frontales parecen permitir a los participantes de mayor edad mantengan su alto rendimiento en FF.
- La conectividad funcional en áreas cerebrales compartidas del módulo de Wernicke (lingüístico) y el módulo anti-correlacionado (no lingüístico) se asoció con el rendimiento en FF en el envejecimiento. Esta asociación estuvo mediada por la RC en los participantes de mayor edad, pero no en los de menor edad, indicando compensación del efecto de la edad en el rendimiento en FF en la vejez.
- Un equilibrio entre la estructura cerebral, su funcionalidad y la RC parece regular la capacidad individual para compensar el efecto del envejecimiento y la patología.

8. REFERENCES

Achard, S., & Bullmore, E. (2007). Efficiency and Cost of Economical Brain Functional Networks. *PLoS Computational Biology*, *3*(2), e17. https://doi.org/10.1371/journal.pcbi.0030017

Amunts, J., Camilleri, J. A., Eickhoff, S. B., Patil, K. R., Heim, S., von Polier, G. G., & Weis, S. (2021). Comprehensive verbal fluency features predict executive function performance. *Scientific Reports*, *11*(1), 6929. https://doi.org/10.1038/s41598-021-85981-1

Ansado, J., Marsolais, Y., Methqal, I., Alary, F., & Joanette, Y. (2013). The adaptive aging brain: Evidence from the preservation of communication abilities with age. *European Journal of Neuroscience*, *37*, 1887–1895. https://doi.org/10.1111/ejn.12252

Ardila, A., Galeano, L. M., & Rosselli, M. (1998). Toward a model of neuropsychological activity. *Neuropsychology Review*, *8*(4), 171–190. https://doi.org/10.1023/A:1021618218943

Arenaza-Urquijo, E. M., & Vemuri, P. (2018). Resistance vs resilience to Alzheimer disease: Clarifying terminology for preclinical studies. *Neurology*, *90*(15), 695–703. https://doi.org/10.1212/WNL.0000000000005303

Auriacombe, S, Fabrigoule, C., Lafont, S., Jacqmin-Gadda, H., & Dartigues, J.-F. (2001). Letter and Category Fluency in Normal Elderly Participants: A Population-Based Study. *Aging, Neuropsychology, and Cognition*, *8*(2), 98–108. https://doi.org/10.1076/anec.8.2.98.841

Azuma, T. (2004). Working memory and perseveration in verbal fluency. *Neuropsychology*, *18*(1), 69–77. https://doi.org/10.1037/0894-4105.18.1.69

Bäckman, L., & Nilsson, L.-G. (1996). Semantic Memory Functioning Across the Adult Life Span. *European Psychologist*, *1*(1), 27–33. https://doi.org/10.1027/1016-9040.1.1.27

Badre, D. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences*, *12*(5), 193–200. https://doi.org/10.1016/j.tics.2008.02.004

Bagarinao, E., Watanabe, H., Maesawa, S., Mori, D., Hara, K., Kawabata, K., Yoneyama, N., Ohdake, R., Imai, K., Masuda, M., Yokoi, T., Ogura, A., Taoka, T., Koyama, S., Tanabe, H. C., Katsuno, M., Wakabayashi, T., Kuzuya, M., Ozaki, N., … Sobue, G. (2019). Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. *Scientific Reports*, *9*(1), 11352. https://doi.org/10.1038/s41598-019-47922-x

Bak, T. H. (2013). The neuroscience of action semantics in neurodegenerative brain diseases. *Current Opinion in Neurology*, *26*(6), 671–677. https://doi.org/10.1097/WCO.0000000000000039

Balduino, E., de Melo, B. A. R., de Sousa Mota da Silva, L., Martinelli, J. E., & Cecato, J. F. (2019). The “SuperAgers” construct in clinical practice: Neuropsychological assessment of illiterate and educated elderly. *International Psychogeriatrics*, *32*(2), 191–198. https://doi.org/10.1017/S1041610219001364

Balinsky, B. (1941). An analysis of the mental factors of various age groups from nine to sixty. *Genetic Psychology Monographs*, *23*, 191–234.

Baltes, P B, & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: A new window to the study of cognitive aging? *Psychology and Aging*, *12*(1), 12–21.

Baltes, Paul B, Cornelius, S. W., Spiro, A., Nesselroade, J. R., & Willis, S. L. (1980). Integration versus differentiation of fluid/crytallized intelligence in old age. *Developmental Psychology*, *16*(6), 625–635. https://doi.org/10.1037/0012-1649.16.6.625

Banich, M. T. (1998). The Missing Link: The Role of Interhemispheric Interaction in Attentional Processing. *Brain and Cognition*, *36*(2), 128–157. https://doi.org/10.1006/brcg.1997.0950

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173.

Barrat, A., Barthélemy, M., Pastor-Satorras, R., & Vespignani, A. (2004). The architecture of complex weighted networks. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(11), 3747–3752. https://doi.org/10.1073/pnas.0400087101

Bartres-Faz, D., Sole-Padulles, C., Junque, C., Rami, L., Bosch, B., Bargallo, N., Falcon, C., Sanchez-Valle, R., & Molinuevo, J. L. (2009). Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. *Biological Psychology*, *80*(2), 256–259. https://doi.org/10.1016/j.biopsycho.2008.10.005

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, 17(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012

Benedet, M., & Alejandre, M. (1998). *TAVEC: Test de Aprendizaje Verbal España-Complutense. Manual*. TEA ediciones.

Benton, A., Hamsher, K., & Sivan, A. (1989). *Multilingual aphasia examination. Iowa City, IA: AJA Associates* (A. Associates, Ed.; 2nd Ed). University of Iowa.

Benton, A., Hamsher, S., Varney, O., & Spreen, N. (1983). *Contributions to neuropsychological assessment: A clinical manual.* (O. U. Press., Ed.).

Binder, J. R. (2015). The Wernicke area: Modern evidence and a reinterpretation. *Neurology*, *85*(24), 2170–2175.

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: A self-paced overt response fMRI study of verbal fluency. *NeuroImage*, *49*(1), 1099–1107. https://doi.org/10.1016/j.neuroimage.2009.07.036

Blessed, G., Tomlinso, B. E., & Roth, M. (1968). Association between quantitative measures of dementia and of senile change in cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, *114*(512), 797–811. https://doi.org/10.1192/bjp.114.512.797

Blondel, V. D., Guillaume, J.-L., Lambiotte, R., & Lefebvre, E. (2008). Fast unfolding of communities in large networks. *Journal of Statistical Mechanics: Theory and Experiment*, *2008*(10), P10008. https://doi.org/10.1088/1742-5468/2008/10/p10008

Bolla, K I, Lindgren, K. N., Bonaccorsy, C., & Bleecker, M. L. (1990). Predictors of verbal fluency (FAS) in the healthy elderly. *Journal of Clinical Psychology*, *46*(5), 623–628.

Bolla, Karen I, Gray, S., Resnick, S. M., Galante, R., & Kawas, C. (1998). Category and Letter Fluency in Highly Educated Older Adults. *The Clinical Neuropsychologist*, *12*(3), 330–338. https://doi.org/10.1076/clin.12.3.330.1986

Boyle, R., Jollans, L., Rueda-Delgado, L. M., Rizzo, R., Yener, G. G., McMorrow, J. P., Knight, S. P., Carey, D., Robertson, I. H., & Emek-Savaş, D. D. (2020). Brain-predicted age difference score is related to specific cognitive functions: A multi-site replication analysis. *Brain Imaging and Behavior*, 1–19.

Bryan, J, Luszcz, M. A., & Crawford, J. R. (1997). Verbal knowledge and speed of information processing as mediators of age differences in verbal fluency performance among older adults. *Psychology and Aging*, *12*(3), 473–478. https://doi.org/10.1037/0882-7974.12.3.473

Budisavljevic, S., Dell'Acqua, F., Zanatto, D., Begliomini, C., Miotto, D., Motta, R., & Castiello, U. (2017). Asymmetry and Structure of the Fronto-Parietal Networks Underlie Visuomotor Processing in Humans. *Cerebral Cortex*, *27*, 1532–1544. https://doi.org/10.1093/cercor/bhv348

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, *10*(3), 186–198. https://doi.org/10.1038/nrn2575

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, *13*(5), 336–349. https://doi.org/10.1038/nrn3214

Buuren, S. van, & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(1), 1–67. https://doi.org/10.18637/jss.v045.i03

Buzsáki, G., Geisler, C., Henze, D. A., & Wang, X.-J. (2004). Interneuron Diversity series: Circuit complexity and axon wiring economy of cortical interneurons. *Trends in Neurosciences*, *27*(4), 186–193. https://doi.org/10.1016/j.tins.2004.02.007

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. https://doi.org/10.1037//0882-7974.17.1.85

Cabeza, R, Albert, M., Belleville, S., Craik, F. I. M., Duarte, A., Grady, C. L., Lindenberger, U., Nyberg, L., Park, D. C., Reuter-Lorenz, P. A., Rugg, M. D., Steffener, J., & Rajah, M. N. (2018). Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing. *Nature Reviews. Neuroscience*, *19*(11), 701–710. https://doi.org/10.1038/s41583-018-0068-2

Cabeza, R, & Dennis, N. A. (2012). Frontal lobes and aging. *Principles of Frontal Lobe Function. 2d Ed. New York: Oxford University Press. p*, 628–652.

Carp, J., Park, J., Hebrank, A., Park, D. C., & Polk, T. A. (2011). Age-related neural dedifferentiation in the motor system. *PloS One*, *6*(12), e29411.

Christensen, A.-L. (1979). *Luria's neuropsychological investigation* (2nd Ed.).

Core, T. R. (2016). *R: A Language and Environment for Statistical Computing.*

Correia, R. (2010). *Cambios cognitivos en el envejecimiento normal: Influencia de la Edad y su relación con el Nivel Cultural y el Sexo*. PhD. Universidad de La Laguna.

Costafreda, S. G., Fu, C. H. Y., Lee, L., Everitt, B., Brammer, M. J., & David, A. S. (2006). A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Human Brain Mapping*, *27*(10), 799–810. https://doi.org/10.1002/hbm.20221

Crossley, M, D'Arcy, C., & Rawson, N. S. (1997). Letter and category fluency in community-dwelling Canadian seniors: A comparison of normal participants to those with dementia of the Alzheimer or vascular type. *Journal of Clinical and Experimental Neuropsychology*, *19*(1), 52–62. https://doi.org/10.1080/01688639708403836

Daigneault, S., Braun, C. M. J., & Whitaker, H. A. (1992). Early effects of normal aging on perseverative and non-perseverative prefrontal measures. *Developmental Neuropsychology*, *8*(1), 99–114. https://doi.org/10.1080/87565649209540518

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

Damoiseaux, J. S. (2017). Effects of aging on functional and structural brain connectivity. *Neuroimage*, *160*, 32–40.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Qué PASA? The posterior-anterior shift in aging. *Cerebral Cortex*, *18*(5), 1201–1209.

https://doi.org/10.1093/cercor/bhm155

D'Elia, L., & Saltz, P. (1989). *Color Trail 1 and 2*. Psychological Assessment Resources.

Dempster, F. N. (1992). The rise and fall of the inhibitory mechanism: Toward a unified theory of cognitive development and aging. *Developmental Review*, *12*(1), 45–75. https://doi.org/10.1016/0273-2297(92)90003-K

Dennis, E. L., & Thompson, P. M. (2014). Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychology Review*, *24*(1), 49–62. https://doi.org/10.1007/s11065-014-9249-6

Dennis, N. A., & Cabeza, R. (2008). Neuroimaging of healthy cognitive aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The Handbook of Aging and Cognition* (3rd Edn, pp. 1–54).

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Diaconescu, A., Schneebeli, M., Heinzle, J., Kasper, L., & Siemerkus, J. (2016). *Preprocessing of fMRI data (basic)- Practical session, SPM Course.*

Elgamal, S. A., Roy, E. A., & Sharratt, M. T. (2011). Age and Verbal Fluency: The Mediating Effect of Speed of Processing. *Canadian Geriatrics Journal: CGJ*, *14*(3), 66–72. https://doi.org/10.5770/cgj.v14i3.17

Erkinjuntti, T., Hokkanen, L., Sulkava, R., & Palo, J. (1988). The Blessed Dementia Scale as a screening test for dementia. *International Journal of Geriatric Psychiatry*, *3*(4), 267–273. https://doi.org/10.1002/gps.930030406

Farahani, F. V., Karwowski, W., & Lighthall, N. R. (2019). Application of Graph Theory for Identifying Connectivity Patterns in Human Brain Networks: A Systematic Review. *Frontiers in Neuroscience*, *13*, 585. https://doi.org/10.3389/fnins.2019.00585

Fedorenko, E., & Thompson-Schill, S. L. (2014). Reworking the language network. *Trends in Cognitive Sciences*, *18*(3), 120–126.

Fernández-Cabello, S., Valls-Pedret, C., Schurz, M., Vidal-Piñeiro, D., Sala-Llonch, R., Bargallo, N., Ros, E., & Bartrés-Faz, D. (2016). White matter hyperintensities and cognitive reserve during a working memory task: A functional magnetic resonance imaging study in cognitively normal older adults. *Neurobiology of Aging*, *48*, 23–33. https://doi.org/10.1016/j.neurobiolaging.2016.08.008

Ferreira, D. (2012). *Cambios cognitivos en la etapa adulta y sus correlatos neuroanatómicos: Un enfoque centrado en la mediana edad*. PhD. Universidad de La Laguna.

Ferreira, D., Correia, R., Nieto, A., Machado, A., Molina, Y., & Barroso, J. (2015). Cognitive decline before the age of 50 can be detected with sensitive cognitive measures. *Psicothema*, *27*(3), 216–222. https://doi.org/10.7334/psicothema2014.192

Ferreira, D., Molina, Y., Machado, A., Westman, E., Wahlund, L.-O., Nieto, A., Correia, R., Junqué, C., Díaz-Flores, L., & Barroso, J. (2014). Cognitive decline is mediated by gray matter changes during middle age. *Neurobiology of Aging*, *35*(5), 1086–1094.

Ferreira, D., Pereira, J. B., Volpe, G., & Westman, E. (2019). Subtypes of Alzheimer’s Disease Display Distinct Network Abnormalities Extending Beyond Their Pattern of Brain Atrophy. *Frontiers in Neurology*, *10*, 524. https://doi.org/10.3389/fneur.2019.00524

Ferreira, L. K., & Busatto, G. F. (2013). Resting-state functional connectivity in normal brain aging. *Neuroscience & Biobehavioral Reviews*, *37*(3), 384–400.

Festini, S. B., Zahodne, L., & Reuter-Lorenz, P. A. (2018). *Theoretical Perspectives on Age Differences in Brain Activation: HAROLD, PASA, CRUNCH—How Do They STAC Up?* Oxford Research Encyclopedia of Psychology. https://doi.org/10.1093/acrefore/9780190236557.013.400

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(20), 11050–11055. https://doi.org/10.1073/pnas.200033797

Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage*, *9*(2), 195–207. https://doi.org/10.1006/nimg.1998.0396

Fischl, Bruce, Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/s0896-6273(02)00569-x

Fitzhugh, M. C., Braden, B. B., Sabbagh, M. N., Rogalsky, C., & Baxter, L. C. (2019). Age-Related Atrophy and Compensatory Neural Networks in Reading Comprehension. *Journal of the International Neuropsychological Society*, *25*(6), 569–582. https://doi.org/10.1017/S1355617719000274

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, *21*(3), 187–221.

Foldi, N. S., Helm-Estabrooks, N., Redfield, J., & Nickel, D. G. (2003). Perseveration in normal aging: A comparison of perseveration rates on design fluency and verbal generative tasks. *Aging, Neuropsychology and Cognition (Neuropsychology, Development and Cognition: Section B)*, *10*(4), 268–280. https://doi.org/10.1076/anec.10.4.268.28970

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences*, *102*(27), 9673–9678.

Franzmeier, N., Hartmann, J., Taylor, A. N. W., Araque-Caballero, M. Á., Simon-Vermot, L., Kambeitz-Ilankovic, L., Bürger, K., Catak, C., Janowitz, D., Müller, C., Ertl-Wagner, B., Stahl, R., Dichgans, M., Duering, M., & Ewers, M. (2018). The left frontal cortex supports reserve in aging by enhancing functional network efficiency. *Alzheimer’s Research & Therapy*, *10*(1), 28. https://doi.org/10.1186/s13195-018-0358-y

Garcia-Ramos, C., Lin, J. J., Kellermann, T. S., Bonilha, L., Prabhakaran, V., & Hermann, B. P. (2016). Graph theory and cognition: A complementary avenue for examining neuropsychological status in epilepsy. *Epilepsy & Behavior: E&B*, *64*(Pt B), 329–335. https://doi.org/10.1016/j.yebeh.2016.02.032

Garcia-Ramos, C., Lin, J. J., Prabhakaran, V., & Hermann, B. P. (2015). Developmental Reorganization of the Cognitive Network in Pediatric Epilepsy. *PLOS ONE*, *10*(10), e0141186. https://doi.org/10.1371/journal.pone.0141186

Garrett, H. E. (1946). A developmental theory of intelligence. *The American Psychologist*, *1*(9), 372–378.

Geerligs, L., Maurits, N. M., Renken, R. J., & Lorist, M. M. (2014). Reduced specificity of functional connectivity in the aging brain during task performance. *Human Brain Mapping*, *35*(1), 319–330.

Gladsjo, J. A., Schuman, C. C., Evans, J. D., Peavy, G. M., Miller, S. W., & Heaton, R. K. (1999). Norms for Letter and Category Fluency: Demographic Corrections for Age, Education, and Ethnicity. *Assessment*, *6*(2), 147–178. https://doi.org/10.1177/107319119900600204

Golden, C. J. (1978). *Stroop Colour and Word Test: A manual for clinical and experimental uses.* Stoelting Company.

Gonzalez-Burgos, L., Barroso, J., & Ferreira, D. (2020). Cognitive reserve and network efficiency as compensatory mechanisms of the effect of aging on phonemic fluency. *Aging*, *12*(22), 23351–23378. https://doi.org/10.18632/aging.202177

Gonzalez-Burgos, L., Hernández-Cabrera, J. A., Westman, E., Barroso, J., & Ferreira, D. (2019). Cognitive compensatory mechanisms in normal aging: A study on verbal fluency and the contribution of other cognitive functions. *Aging*, *11*(12), 4090–4106. https://doi.org/10.18632/aging.102040

Grady, C. L. (2008). Cognitive Neuroscience of Aging. *Annals of the New York Academy of Sciences*, *1124*(1), 127–144. https://doi.org/10.1196/annals.1440.009

Grogan, A., Green, D. W., Ali, N., Crinion, J. T., & Price, C. J. (2009). Structural Correlates of Semantic and Phonemic Fluency Ability in First and Second Languages. *Cerebral Cortex (New York, NY)*, *19*(11), 2690–2698. https://doi.org/10.1093/cercor/bhp023

Gronwall, D. M. A. (1977). Paced Auditory Serial-Addition Task: A Measure of Recovery from Concussion. *Perceptual and Motor Skills*, *44*(2), 367–373. https://doi.org/10.2466/pms.1977.44.2.367

Halari, R., Sharma, T., Hines, M., Andrew, C., Simmons, A., & Kumari, V. (2006). Comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. *Experimental Brain Research*, *169*(1), 1–14. https://doi.org/10.1007/s00221-005-0118-7

Harada, C. N., Love, M. C. N., & Triebel, K. (2013). Normal Cognitive Aging. *Clin Geriatr Med.*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002.Normal

Henry, J. D., & Crawford, J. R. (2004). A Meta-Analytic Review of Verbal Fluency Performance Following Focal Cortical Lesions. *Neuropsychology*, *18*(2), 284–295. https://doi.org/10.1037/0894-4105.18.2.284

Herrera, E., Cuetos, F., & Ribacoba, R. (2012). Verbal fluency in Parkinson's disease patients on/off dopamine medication. *Neuropsychologia*, *50*(14), 3636–3640. https://doi.org/10.1016/j.neuropsychologia.2012.09.016

Horoufchin, H., Bzdok, D., Buccino, G., Borghi, A. M., & Binkofski, F. (2018). Action and object words are differentially anchored in the sensory motor system—A perspective on cognitive embodiment. *Scientific Reports*, *8*(1), 6583. https://doi.org/10.1038/s41598-018-24475-z

Hülür, G., Ram, N., Willis, S. L., Warner Schaie, K., & Gerstorf, D. (2015). Cognitive dedifferentiation with increasing age and proximity of death: Within-person evidence from the Seattle longitudinal study. *Psychology and Aging*, *30*(2), 311–323. https://doi.org/10.1037/a0039260

Jones, R. N., Manly, J., Glymour, M. M., Rentz, D. M., Jefferson, A. L., & Stern, Y. (2011). Conceptual and measurement challenges in research on cognitive reserve. *Journal of the International Neuropsychological Society: JINS*, *17*(4), 593–601. https://doi.org/10.1017/S1355617710001748

Jonker, F., Weeda, W., Rauwerda, K., & Scherder, E. (2019). The bridge between cognition and behavior in acquired brain injury: A graph theoretical approach. *Brain and Behavior*, *9*(3), e01208. https://doi.org/10.1002/brb3.1208

Kaplan, E. F., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test* (2nd Ed.). Lea & Febiger.

Katzman, R., Aronson, M., Fuld, P., Kawas, C., Brown, T., Morgenstern, H., Frishman, W., Gidez, L., Eder, H., & Ooi, W. L. (1989). Development of dementing illnesses in an 80-year-old volunteer cohort. *Annals of Neurology*, *25*(4), 317–324. https://doi.org/10.1002/ana.410250402

Katzman, Robert. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology*, *43*(1 Part 1), 13–13. https://doi.org/10.1212/WNL.43.1_Part_1.13

Kavé, G., & Knafo-Noam, A. (2015). Lifespan development of phonemic and semantic fluency: Universal increase, differential decrease. *Journal of Clinical and Experimental Neuropsychology*, *37*(7), 751–763. https://doi.org/10.1080/13803395.2015.1065958

Kavé, G., & Mashal, N. (2012). Age-related differences in word-retrieval but not in meaning generation. *Aging, Neuropsychology, and Cognition*, *19*(4), 515–529. https://doi.org/10.1080/13825585.2011.638975

Kellermann, T. S., Bonilha, L., Eskandari, R., Garcia-Ramos, C., Lin, J. J., & Hermann, B. P. (2016). Mapping the neuropsychological profile of temporal lobe epilepsy using cognitive network topology and graph theory. *Epilepsy & Behavior: E&B*, *63*, 9–16. https://doi.org/10.1016/j.yebeh.2016.07.030

Kellermann, T. S., Bonilha, L., Lin, J. J., & Hermann, B. P. (2015). Mapping the landscape of cognitive development in children with epilepsy. *Cortex: a Journal Devoted to the Study of the Nervous System and Behavior*, *66*, 1–8.

https://doi.org/10.1016/j.cortex.2015.02.001

Kemper, S., & Sumner, A. (2001). The Structure of Verbal Abilities in Young and Older Adults. *Psychology and Aging*, *16*(2), 312–322. https://doi.org/10.1037//0882-7974.16.2.312

Kempler, D., Teng, E. L., Dick, M., Taussig, I. M., & Davis, D. S. (1998). The effects of age, education, and ethnicity on verbal fluency. *Journal of the International Neuropsychological Society: JINS*, *4*(6), 531–538.

Kochhann, R., Holz, M. R., Beber, B. C., Chaves, M. L. F., & Fonseca, R. P. (2018). Reading and writing habits as a predictor of verbal fluency in elders. *Psychology & Neuroscience*, *11*(1), 39–49. https://doi.org/10.1037/pne0000125

Kraan, C., Stolwyk, R. J., & Testa, R. (2013). The abilities associated with verbal fluency performance in a young, healthy population are multifactorial and differ across fluency variants. *Applied Neuropsychology*, *20*(3), 159–168. https://doi.org/10.1080/09084282.2012.670157

La Fleur, C. G., Meyer, M. J., & Dodson, C. (2018). Exploring dedifferentiation across the adult lifespan. *Psychology and Aging*, *33*(5), 855–870. https://doi.org/10.1037/pag0000274

la Tourette, T. R., & Meeks, S. (2000). Perceptions of Patronizing Speech by Older Women in Nursing Homes and in the Community: Impact of Cognitive Ability and Place of Residence. *Journal of Language and Social Psychology*, *19*(4), 463–473. https://doi.org/10.1177/0261927X00019004004

Latora, V., & Marchiori, M. (2001). Efficient Behavior of Small-World Networks. *Physical Review Letters*, *87*(19), 198701. https://doi.org/10.1103/PhysRevLett.87.198701

Lee, D. H., Lee, P., Seo, S. W., Roh, J. H., Oh, M., Oh, J. S., Oh, S. J., Kim, J. S., & Jeong, Y. (2019). Neural substrates of cognitive reserve in Alzheimer's disease spectrum and normal aging. *NeuroImage*, *186*, 690–702. https://doi.org/10.1016/j.neuroimage.2018.11.053

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). Neuropsychological assessment, 5th ed. In *Neuropsychological assessment* (5th ed.). Oxford University Press.

Lezak, M., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (4th ed.). Oxford University Press.

Liaw, A., & Wiener, M. (2002). *Classification and Regression by random Forest*. *2*, 5.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-Recruitment and Nonselective Recruitment: Dissociable Neural Mechanisms Associated with Aging. *Neuron*, *33*(5), 827–840. https://doi.org/10.1016/S0896-6273(02)00612-8

Lowe, A. J., Paquola, C., Vos de Wael, R., Girn, M., Lariviere, S., Tavakol, S., Caldairou, B., Royer, J., Schrader, D. V, & Bernasconi, A. (2019). Targeting age-related differences in brain and cognition with multimodal imaging and connectome topography profiling. *Human Brain Mapping*, *40*(18), 5213–5230.

Machado, A., Barroso, J., Molina, Y., Nieto, A., Díaz-Flores, L., Westman, E., & Ferreira, D. (2018). Proposal for a hierarchical, multidimensional, and multivariate approach to investigate cognitive aging. *Neurobiology of Aging*, *71*, 179–188. https://doi.org/10.1016/j.neurobiolaging.2018.07.017

Marques, P., Moreira, P., Magalhães, R., Costa, P., Santos, N., Zihl, J., Soares, J., & Sousa, N. (2016). The functional connectome of cognitive reserve. *Human Brain Mapping*, *37*(9), 3310–3322. https://doi.org/10.1002/hbm.23242

Marsolais, Y., Methqal, I., & Joanette, Y. (2015). Marginal neurofunctional changes in high-performing older adults in a verbal fluency task. *Brain and Language*, *140*, 13–23. https://doi.org/10.1016/j.bandl.2014.10.010

Marsolais, Y., Perlbarg, V., Benali, H., & Joanette, Y. (2014). Age-related changes in functional network connectivity associated with high levels of verbal fluency performance. *Cortex*, *58*, 123–138. https://doi.org/10.1016/j.cortex.2014.05.007

Mathuranath, P. S., George, A., Cherian, P. J., Alexander, A., Sarma, S. G., & Sarma, P. S. (2003). Effects of Age, Education and Gender on Verbal Fluency. *Journal of Clinical and Experimental Neuropsychology*, *25*(8), 1057–1064. https://doi.org/10.1076/jcen.25.8.1057.16736

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., Gonzalez-Rothi, L., & Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. *Journal of Cognitive Neuroscience*, *21*(10), 2007–2018.

Methqal, I., Marsolais, Y., Wilson, M. A., Monchi, O., & Joanette, Y. (2019). More expertise for a better perspective: Task and strategy-driven adaptive neurofunctional reorganization for word production in high-performing older adults. *Aging, Neuropsychology, and Cognition*, *26*(2), 190–221.

Meunier, D., Achard, S., Morcom, A., & Bullmore, E. (2009). Age-related changes in modular organization of human brain functional networks. *NeuroImage*, *44*(3), 715–723. https://doi.org/10.1016/j.neuroimage.2008.09.062

Meunier, D., Stamatakis, E. A., & Tyler, L. K. (2014). Age-related functional reorganization, structural changes, and preserved cognition. *Neurobiology of Aging*, *35*(1), 42–54. https://doi.org/10.1016/j.neurobiolaging.2013.07.003

Mijalkov, M., Kakaei, E., Pereira, J. B., Westman, E., & Volpe, G. (2017). BRAPH: A graph theory software for the analysis of brain connectivity. *PLOS ONE*, *12*(8), e0178798.

https://doi.org/10.1371/journal.pone.0178798

Miller, E. K., Freedman, D. J., & Wallis, J. D. (2002). The prefrontal cortex: Categories, concepts and cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *357*(1424), 1123–1136. https://doi.org/10.1098/rstb.2002.1099

Molina, Y. (2015). *Cambios cognitivos y neuroanatómicos asociados a la mediana edad: Perfil neuropsicológico, temporalidad de los cambios y variables moduladoras*. PhD. Universidad de La Laguna.

Morcom, A. M., & Johnson, W. (2015). Neural reorganization and compensation in aging. *Journal of Cognitive Neuroscience*, *27*(7), 1275–1285. https://doi.org/10.1162/jocn_a_00783

Mortimer, J. A., Schuman, L., & French, L. (1981). Epidemiology of dementing illness. In *The epidemiology of dementia: Monographs in epidemiology and biostatistics* (Mortimer, J.A. & Schuman, L.M., pp. 323–333). Oxford University Press.

Muehlboeck, J.-S., Westman, E., & Simmons, A. (2014). TheHiveDB image data management and analysis framework. *Frontiers in Neuroinformatics*, *7*, 49. https://doi.org/10.3389/fninf.2013.00049

Nakajima, R., Kinoshita, M., Shinohara, H., & Nakada, M. (2019). The superior longitudinal fascicle: Reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging and Behavior*, *14*(6), 2817–2830. https://doi.org/10.1007/s11682-019-00187-4

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., & Bäckman, L. (2012). Memory aging and brain maintenance. *Trends in Cognitive Sciences*, *16*(5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005

Paek, E. J., Murray, L. L., & Newman, S. D. (2020). Neural Correlates of Verb Fluency Performance in Cognitively Healthy Older Adults and Individuals with Dementia: A Pilot fMRI Study. *Frontiers in Aging Neuroscience*, *12*, 73. https://doi.org/10.3389/fnagi.2020.00073

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004b). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences*, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Parkin, A. J., & Java, R. I. (1999). Deterioration of frontal lobe function in normal aging: Influences of fluid intelligence versus perceptual speed. *Neuropsychology*, *13*(4), 539–545. https://doi.org/10.1037//0894-4105.13.4.539

Perani, D., Cappa, S. F., Tettamanti, M., Rosa, M., Scifo, P., Miozzo, A., Basso, A., & Fazio, F. (2003). A fMRI study of word retrieval in aphasia. *Brain and Language*, *85*(3), 357–368.

Pereira, J. B., Aarsland, D., Ginestet, C. E., Lebedev, A. V., Wahlund, L.-O., Simmons, A., Volpe, G., & Westman, E. (2015). Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. *Human Brain Mapping*, *36*(8), 2980–2995. https://doi.org/10.1002/hbm.22822

Pereira, J. B., van Westen, D., Stomrud, E., Strandberg, T. O., Volpe, G., Westman, E., & Hansson, O. (2018). Abnormal Structural Brain Connectome in Individuals with Preclinical Alzheimer's Disease. *Cerebral Cortex*, *28*(10), 3638–3649. https://doi.org/10.1093/cercor/bhx236

Pfeffer, R. I., Kurosaki, T. T., Harrah, C. H., Chance, J. M., & Filos, S. (1982). Measurement of Functional Activities in Older Adults in the Community. *Journal of Gerontology*, *37*(3), 323–329. https://doi.org/10.1093/geronj/37.3.323

Piatt, A. L., Fields, J. A., Paolo, A. M., Koller, W. C., & Tröster, A. I. (1999a). Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology*, *21*(4), 435–443. https://doi.org/10.1076/jcen.21.4.435.885

Piatt, A. L., Fields, J. A., Paolo, A. M., & Tröster, A. I. (1999b). Action (verb naming) fluency as an executive function measure: Convergent and divergent evidence of validity. *Neuropsychologia*, *37*(13), 1499–1503. https://doi.org/10.1016/S0028-3932(99)00066-4

Piatt, A. L., Fields, J. A., Paolo, A. M., & Tröster, A. I. (2004). Action verbal fluency normative data for the elderly. *Brain and Language*, *89*(3), 580–583. https://doi.org/10.1016/j.bandl.2004.02.003

Ravdin, L. D., Katzen, H. L., Agrawal, P., & Relkin, N. R. (2003). *Letter and Semantic Fluency in Older Adults: Effects of Mild Depressive Symptoms and Age-Stratified Normative Data.* (Vol. 17). Taylor & Francis. https://doi.org/10.1076/clin.17.2.195.16500

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews*, *30*(6), 730–748.

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator. *Perceptual and Motor Skills*, *8*, 271–276.

Reuter, M., Rosas, H. D., & Fischl, B. (2010). Highly accurate inverse consistent registration: A robust approach. *NeuroImage*, *53*(4), 1181–1196. https://doi.org/10.1016/j.neuroimage.2010.07.020

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive Aging and the Compensation Hypothesis. *Current Directions in Psychological Science*, *17*(3), 177–182. https://doi.org/10.1111/j.1467-8721.2008.00570.x

Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: Reorganizing discoveries about the aging mind. *Current Opinion in Neurobiology*, *15*(2), 245–251. https://doi.org/10.1016/j.conb.2005.03.016

Reuter-lorenz, P. A., & Mikels, J. A. (2006). The Aging Mind and Brain: Implications of Enduring Plasticity for Behavioral and Cultural Change. In F. Rösler, P. A. Reuter-Lorenz, & P. B. Baltes (Eds.), *Lifespan Development and the Brain: The Perspective of Biocultural Co-Constructivism* (pp. 255–276). Cambridge University Press. https://doi.org/10.1017/CBO9780511499722.014

Reuter-Lorenz, P. A., & Park, D. C. (2014). How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. *Neuropsychology Review*, 24(3), 355–370. https://doi.org/10.1007/s11065-014-9270-9

Reuter-Lorenz, P. A., Stanczak, L., & Miller, A. C. (1999). Neural Recruitment and Cognitive Aging: Two Hemispheres Are Better Than One, Especially as You Age. *Psychological Science*, *10*(6), 494–500. https://doi.org/10.1111/1467-9280.00195

Rodríguez-Aranda, C., Castro-Chavira, S. A., Espenes, R., Barrios, F. A., & Vangberg, T. R. (2020). *The role of moderating variables on BOLD fMRI response during semantic verbal fluency and finger tapping in active and educated healthy seniors*.

Rodriguez-Aranda, C., & Martinussen, M. (2006). Age-related differences in performance of phonemic verbal fluency measured by Controlled Oral Word Association Task (COWAT): A meta-analytic study. *Developmental Neuropsychology*, *30*(2), 697–717. https://doi.org/10.1207/s15326942dn3002_3

Rodriguez-Aranda, C., & Sundet, K. (2006). The frontal hypothesis of cognitive aging: Factor structure and age effects on four frontal tests among healthy individuals. *Journal of Genetic Psychology*, *167*(3), 269–287. https://doi.org/10.3200/GNTP.167.3.269-287

Roldan-Tapia, L., Garcia, J., Canovas, R., & Leon, I. (2012). Cognitive reserve, age, and their relation to attentional and executive functions. *Applied Neuropsychology. Adult*, *19*(1), 2–8. https://doi.org/10.1080/09084282.2011.595458

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1997). The psychological construct of word fluency. *Brain and Language*, *57*(3), 394–405. https://doi.org/10.1006/brln.1997.1755

Sala-Llonch, R., Bartrés-Faz, D., & Junqué, C. (2015). Reorganization of brain networks in aging: A review of functional connectivity studies. *Frontiers in Psychology*, *6*, 663.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging*, *30*(4), 507–514. https://doi.org/10.1016/j.neurobiolaging.2008.09.023

Salthouse, T. A. (2010). Selective review of cognitive aging. *J Int Neuropsychol Soc*, *16*(5), 754–760. https://doi.org/10.1017/S1355617710000706.

Salthouse, T. A., Fristoe, N. M., Lineweaver, T. T., & Coon, V. E. (1995). Aging of attention: Does the ability to divide decline? *Memory & Cognition*, *23*(1), 59–71. https://doi.org/10.3758/BF03210557

Satz, P. (1993). Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology*, *7*(3), 273–295. https://doi.org/10.1037/0894-4105.7.3.273

Schuhfried, G. (1992). *Vienna Reaction Unit. Manual*. Schuhfried Ges.m.b.H.

Schwartz, S., Baldo, J., Graves, R. E., & Brugger, P. (2003). Pervasive influence of semantics in letter and category fluency: A multidimensional approach. *Brain and Language*, *87*(3), 400–411.

Ségonne, F., Dale, A. M., Busa, E., Glessner, M., Salat, D., Hahn, H. K., & Fischl, B. (2004). A hybrid approach to the skull stripping problem in MRI. *NeuroImage*, *22*(3), 1060–1075. https://doi.org/10.1016/j.neuroimage.2004.03.032

Ségonne, Florent, Pacheco, J., & Fischl, B. (2007). Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Transactions on Medical Imaging*, *26*(4), 518–529. https://doi.org/10.1109/TMI.2006.887364

Shafto, M. A., & Tyler, L. K. (2014). Language in the aging brain: The network dynamics of cognitive decline and preservation. *Science*, *346*(6209), 583–587.

Shao, Z., Janse, E., Visser, K., & Meyer, A. S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology*, *5*(772), 1–10. https://doi.org/10.3389/fpsyg.2014.00772

Signorini, M., & Volpato, C. (2006). Action fluency in Parkinson's disease: A follow-up study. *Movement Disorders: Official Journal of the Movement Disorder Society*, *21*(4), 467–472. https://doi.org/10.1002/mds.20718

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., Kloszewska, I., Wahlund, L.-O., Soininen, H., Lovestone, S., Evans, A., & Spenger, C. (2009). MRI measures of Alzheimer's disease and the AddNeuroMed study. *Annals of the New York Academy of Sciences*, *1180*, 47–55. https://doi.org/10.1111/j.1749-6632.2009.05063.x

Simmons, A., Westman, E., Muehlboeck, S., Mecocci, P., Vellas, B., Tsolaki, M., Kłoszewska, I., Wahlund, L.-O., Soininen, H., Lovestone, S., Evans, A., & Spenger,

C. (2011). The AddNeuroMed framework for multi-centre MRI assessment of Alzheimer's disease: Experience from the first 24 months. *International Journal of Geriatric Psychiatry*, *26*(1), 75–82. https://doi.org/10.1002/gps.2491

Singh-Manoux, A., Kivimaki, M., Glymour, M. M., Elbaz, A., Berr, C., Ebmeier, K. P., Ferrie, J. E., & Dugravot, A. (2012). Timing of onset of cognitive decline: Results from Whitehall II prospective cohort study. *British Medical Journal*, *344*. https://doi.org/10.1136/bmj.d7622

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging*, *17*(1), 87–97. https://doi.org/10.1109/42.668698

Sporns, O. (2012). *Discovering the Human Connectome*. MA: MIT Press.

Sporns, O. (2013). The human connectome: Origins and challenges. *NeuroImage*, *80*, 53–61. https://doi.org/10.1016/j.neuroimage.2013.03.023

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, *8*(3), 448–460. https://doi.org/10.1017/S1355617702813248

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., & Vuoksimaa, E. (2020). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, *16*(9), 1305–1311. https://doi.org/10.1016/j.jalz.2018.07.219

Stern, Y., Arenaza-Urquijo, E. M., Bartrés-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., Ewers, M., Franzmeier, N., Kempermann, G., Kremen, W. S., Okonkwo, O., Scarmeas, N., Soldan, A., Udeh-Momoh, C., Valenzuela, M., Vemuri, P., Vuoksimaa, E., Arenaza Urquiljo, E. M., Bartrés-Faz, D., … Vuoksimaa, E. (2018a). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*, 1–7.

Stern, Y., Gazes, Y., Razlighi, Q., Steffener, J., & Habeck, C. (2018). A task-invariant cognitive reserve network. *NeuroImage*, *178*, 36–45. https://doi.org/10.1016/j.neuroimage.2018.05.033

Stern, Y., Habeck, C., Moeller, J., Scarmeas, N., Anderson, K. E., Hilton, H. J., Flynn, J., Sackeim, H., & Van Heertum, R. (2005). Brain networks associated with cognitive reserve in healthy young and old adults. *Cerebral Cortex*, *15*(4), 394–402.

Stolwyk, R., Bannirchelvam, B., Kraan, C., & Simpson, K. (2015). The cognitive abilities associated with verbal fluency task performance differ across fluency variants and age groups in healthy young and old adults. *Journal of Clinical and Experimental Neuropsychology*, *37*(1), 70–83. https://doi.org/10.1080/13803395.2014.988125

Sungura, R., Onyambu, C., Mpolya, E., Sauli, E., & Vianney, J.-M. (2020). The extended scope of neuroimaging and prospects in brain atrophy mitigation: A systematic review. *Interdisciplinary Neurosurgery*, 100875.

Tessaro, B., Hermes-Pereira, A., Schilling, L. P., Fonseca, R. P., Kochhann, R., & Hübner, L. C. (2020). Verbal fluency in Alzheimer's disease and mild cognitive impairment in individuals with low educational level and its relationship with reading and writing habits. *Dementia & Neuropsychologia*, *14*(3), 300–307. https://doi.org/10.1590/1980-57642020dn14-030011

Tomasi, D, & Volkow, N. D. (2012). Resting functional connectivity of language networks: Characterization and reproducibility. *Molecular Psychiatry*, *17*(8), 841–854. https://doi.org/10.1038/mp.2011.177

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology*, *14*(2), 167–177. https://doi.org/10.1016/S0887-6177(97)00095-4

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. *Neuropsychology*, *11*(1), 138–146. https://doi.org/10.1037//0894-4105.11.1.138

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*, *17*(12), 683–696. https://doi.org/10.1016/j.tics.2013.09.012

van den Heuvel, M. P., & Sporns, O. (2019). A cross-disorder connectome landscape of brain dysconnectivity. *Nature Reviews Neuroscience*, *20*(7), 435–446. https://doi.org/10.1038/s41583-019-0177-6

Vaqué-Alcázar, L., Sala-Llonch, R., Abellaneda-Pérez, K., Coll-Padrós, N., Valls-Pedret, C., Bargalló, N., Ros, E., & Bartrés-Faz, D. (2020). Functional and structural correlates of working memory performance and stability in healthy older adults. *Brain Structure and Function*, *225*(1), 375–386. https://doi.org/10.1007/s00429-019-02009-1

Voevodskaya, O., Simmons, A., Nordenskjöld, R., Kullberg, J., Ahlström, H., Lind, L., Wahlund, L.-O., Larsson, E.-M., & Westman, E. (2014). The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. *Frontiers in Aging Neuroscience*, *6*, 264. https://doi.org/10.3389/fnagi.2014.00264

Wagner, S., Sebastian, A., Lieb, K., Tüscher, O., & Tadić, A. (2014). A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. *BMC Neuroscience*, *15*. https://doi.org/10.1186/1471-2202-15-19

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale—Administration and Scoring Manual* (3rd ed.). The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale – Third Edition Technical Manual* (3rd ed.). The Psychological Corporation.

Wilson, R. S., Segawa, E., Hizel, L. P., Boyle, P. A., & Bennett, D. A. (2012). Terminal dedifferentiation of cognitive abilities. *Neurology*, *78*(15), 1116–1122. https://doi.org/10.1212/WNL.0b013e31824f7ff2

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., … Petersen, R. C. (2004). Mild cognitive impairment—Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. https://doi.org/10.1111/j.1365-2796.2004.01380.x

Zhang, H., Sachdev, P. S., Wen, W., Kochan, N. A., Crawford, J. D., Brodaty, H., Slavin, M. J., Reppermund, S., Kang, K., & Trollor, J. N. (2013). Grey Matter Correlates of Three Language Tests in Non-demented Older Adults. *PLoS ONE*, *8*(11), e80215. https://doi.org/10.1371/journal.pone.0080215

9. ANNEXES

STUDY I

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Research Paper

Cognitive compensatory mechanisms in normal aging: a study on verbal fluency and the contribution of other cognitive functions

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ABSTRACT

Verbal fluency has been widely studied in cognitive aging. However, compensatory mechanisms that maintain its optimal performance with increasing age are not completely understood. Using cross-sectional data, we investigated differentiation and dedifferentiation processes in verbal fluency across the lifespan by analyzing the association between verbal fluency and numerous cognitive measures within four age groups (N=446): early middle-age (32-45 years), late middle-age (46-58 years), early elderly (59-71 years), and late elderly (72-84 years). ANCOVA was used to investigate the interaction between age and fluency modality. Random forest models were conducted to study the contribution of cognition to semantic, phonemic, and action fluency. All modalities declined with increasing age, but semantic fluency was the most vulnerable to aging. The most prominent reduction in performance was observed during the transition from middle-age to early elderly, when cognitive variables stopped contributing (differentiation), and new cognitive variables started contributing (dedifferentiation). Lexical access, processing speed, and executive functions were among the most contributing functions. We conclude that the association between age and verbal fluency is masked by age-specific influences of other cognitive functions. Differentiation and dedifferentiation processes can coexist. This study provides important data for better understanding of cognitive aging and compensatory processes.

INTRODUCTION

Cognitive decline is inherent to the normal aging process. Abilities such as executive functions, processing speed, memory, attention, and visuoconstructive and visuospatial functions decline with age [1–5]. Other functions such as crystallized abilities remain stable or even improve with age [1, 6, 7].

The effect of aging on language abilities has always attracted a great interest. Language is one of the most complex functions in humans, it is essential for the communication between people, and its impairment has traditionally been a subject of intense study [8]. Interestingly, perhaps due to its strong biological role, studies on normal aging have shown that some language abilities are quite resilient to the onslaught of aging.

Comprehension, semantic abilities, and vocabulary remain rather stable or even improve with age [9, 10]. Contrarily, other abilities such as verbal fluency and naming are among the most vulnerable cognitive functions to aging [11].

Cognitive tests of verbal fluency measure the ability to produce as many words as possible according to specific rules and a time limit. Phonemic fluency refers to the production of words beginning with a given letter (e.g. “F”). Semantic fluency refers to the production of words belonging to a semantic category (e.g. “animals”). Action fluency refers to the production of words belonging to the grammatical category of verbs (e.g. “to reflect”) [12]. Despite extensive research on the effect of age on verbal fluency, findings are not completely consistent. Numerous studies have shown that semantic fluency declines with age and phonemic fluency seems to be more stable [13–18]. However, contrary results are also common [19, 20]. Research on action fluency in normal aging is scarce. Some studies showed lower word production with increasing age [20–22], while other studies showed similar levels of word production with increasing age [12, 22, 23]. The reason for these contradictory findings is partly related to methodological differences across studies such as the use of different study designs (longitudinal *vs.* cross-sectional), the sample (size, selection criteria, age groups, age span, etc.), and the statistical approach (correlation *vs.* means comparison *vs.* covariance analysis, etc.), among others. In addition, variation on the age span studied has implications beyond mere methodological differences because different compensatory mechanisms may be active and influence fluency performance differently at different ages.

However, compensatory mechanisms have not been investigated in detail. Understanding how diverse cognitive functions contribute to maintain an optimal performance in verbal fluency is of relevance. Previous studies have reported an association of semantic fluency with processing speed [17, 24, 25], lexical access [25–27], executive functions [26, 28], and working memory [25]. Phonemic fluency has been reported to be associated with processing speed [17, 24, 25], attention [13, 29], lexical access [27], executive functions [26,28–31], and memory [29, 32]. Studies on action fluency did not find an association with episodic memory or picture naming [12, 23]. Whether these associations contribute to compensatory effects across age is unknown. In addition, these associations may change with age. According to the “age differentiation hypothesis” [33], the organizational structure of cognitive abilities changes with age [34]. In particular, cognitive abilities shift from a differentiated condition at younger ages (abilities are separate systems: differentiation), into a dedifferentiated condition at older ages (abilities are more interrelated with each other: dedifferentiation) [35]. This higher intercorrelation proposed by the “age dedifferentiation hypothesis” is associated with reduced neural specificity to cognitive processes as a consequence of biological brain aging and increased interhemispheric activations [35–37]. However, studies addressing the dedifferentiation hypothesis of cognitive aging have generated inconsistent findings, probably due to differences in cognitive abilities assessed, age ranges of the included samples, and analytical techniques used across studies [38]. Further, very few studies have investigated differentiation and dedifferentiation processes on verbal fluency across the whole lifespan [1, 17, 29, 31]. Advancing in our understanding of compensatory mechanisms, differentiation, and dedifferentiation processes is expected to have important implications. In clinical practice, this knowledge could contribute to reach a more accurate diagnosis of cognitive disorders, and could facilitate early and personalized therapeutic interventions. Scientifically, this knowledge may help to better understand age-related processes of the human brain, and its dynamic responses to both negative and positive influences.

The overall purpose of this cross-sectional study was to investigate how differentiation and dedifferentiation processes in verbal fluency are organized across the lifespan. Therefore, we investigated the association between performance in three components of verbal fluency (semantic, phonemic, and action) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly.

RESULTS

In order to study the association between age and verbal fluency, the sample was divided into four equidistant age groups based on the own sample age distribution: early middle-age (32 to 45.9 years), late middle-age (46 to 58.9 years), early elderly (59 to 71.9 years), and late elderly (72 to 84.9 years). Table 1 shows the demographic characteristics of these age groups.

Age-related differences on verbal fluency

A mixed ANCOVA model was conducted to examine the interaction between age and verbal fluency. The age groups (4 levels: early middle-age, late middle-age, early elderly, and late elderly) served as the between-subject factor, and the verbal fluency task (3 levels: animals, phonemic, and action fluency) served as the within-subject factor. WAIS-III Information was included as a covariate. This model showed a significant interaction ($F_{(6, 882)}=7.8$; $p<0.001$) (Figure 1). There is a clear association between age and verbal fluency, but this association is modulated by the fluency modality. The two middle-age groups do not differ with each other in performance on phonemic and action fluency ($p>0.05$), and perform rather similar on semantic fluency ($p=0.048$). However, the two middle-age groups always outperform the two elderly groups ($p<0.01$). In addition, the early-elderly group outperformed the late-elderly group, but only on semantic fluency ($p<0.05$) (Table 1). Due to this finding, the two middle-age groups were combined together and only three age groups were used for subsequent analyses (i.e. middle-age, early elderly, and late elderly) (Table 2).

Contribution of cognitive variables to verbal fluency by age groups

To assess whether the contribution of numerous cognitive variables to verbal fluency differs across age, a random forest regression model was performed separately for each of the three age groups (i.e. middle-age, early elderly, and late elderly). For a description of the cognitive variables (predictors) included in the

Table 1. Demographic characteristics and verbal fluency performance.

	Early middle-age (n=79)	Late middle-age (n=143)	Early elderly (n=162)	Late elderly (n=62)	
	M(SD)/count(%)	M(SD)/count	M(SD)/count	M(SD)/count	p-value
Age, years	41.4 (2.8) ^{a,b,c}	51.0 (3.9) ^{b,c}	65.6 (3.4) ^{c}	74.9 (2.3)	<0.001
(min-max)	(32-45.9)	(46-58.9)	(59-71.9)	(72-84.9)	
Sex (female, count (%))	43 (54.4)	79 (55.2)	91 (56.2)	32 (51.6)	0.943
Education level					
Illiteracy	0	0	6	1	<0.001
Unfinished primary studies	0	3	32	18	
Completed primary studies	34	52	52	24	
Completed secondary studies	25	39	24	13	
University studies	20	49	48	5	
WAIS-III Information	15.1 (5.9) ^{a,c}	17.3 (5.8) ^{b,c}	14.5 (6.3) ^{c}	12.4 (5.9)	<0.001
Semantic fluency	22.6 (5.6) ^{a,b,c}	22.2 (5.5) ^{b,c}	18.2 (5.2) ^{c}	15.7 (3.8)	<0.001
Phonemic fluency	34.8 (10.1) ^{b,c}	37.2 (11.8) ^{b,c}	28.1 (13.8)	25.8 (10.4)	<0.001
Action fluency	18.1 (6.8) ^{b,c}	19.3 (7.6) ^{b,c}	12.9 (7.4)	10.1 (4.9)	<0.001

WAIS-III: Wechsler Adult Intelligence Scale, Third edition.
[a] Significantly different from Late middle-age.
[b] Significantly different from Early elderly.
[c] Significantly different from Late elderly.

Table 2. Demographic characteristics and verbal fluency performance in the three age groups.

	Middle-age (n=222)	Early elderly (n=162)	Late elderly (n=62)	
	M(SD)	M(SD)	M(SD)	p-value
Age, years	47.6 (5.8) ^{a,b}	65.6 (3.4) ^{b}	74.9 (2.3)	<0.001
(min-max)	(32-58)	(59-71)	(72-84)	
Sex (female, n (%))	122 (55.0)	91 (56.2)	32 (51.6)	0.829
WAIS-III Information	16.5 (5.9) ^{a,b}	14.5 (6.3) ^{b}	12.4 (5.9)	<0.001
Semantic fluency	22.3 (5.5) ^{a,b}	18.2 (5.2)	15.7 (3.8)	<0.001
Phonemic fluency	36.4 (11.2) ^{a,b}	28.1 (13.8)	25.8 (10.4)	<0.001
Action fluency	18.9 (7.4) ^{a,b}	12.9 (7.3)	10.1 (4.9)	<0.001

WAIS-III: Wechsler Adult Intelligence Scale, Third edition. Middle-age = Early middle-age + Late middle-age.
[a] Significantly different from Early elderly.
[b] Significantly different from Late elderly.

random forests and their abbreviation please see "Neuropsychological assessment" in the Methods section as well as the Supplementary Table S1.

Table 3 shows that while similar cognitive abilities contributed to verbal fluency across age, some interesting differences can be observed.

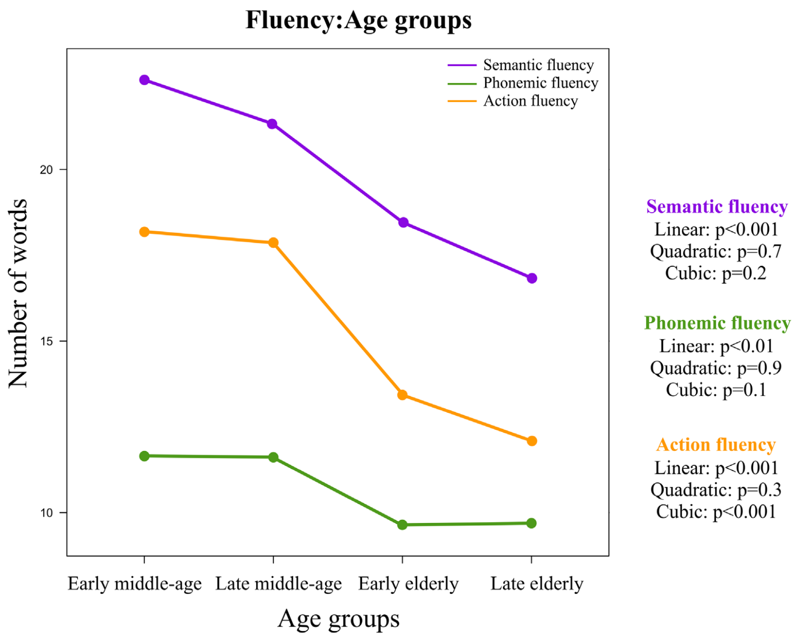

Figure 1. The mixed ANCOVA model for age-related differences on verbal fluency. The x-axis represents the age groups. The y-axis represents the number of words produced. The total number of words produced on phonemic fluency (F+A+S) was divided by three in order to allow comparability among the three fluency modalities (1 minute). P-values are reported for the estimation of linear, quadratic, and cubic effects from the trend analysis tested through the ANCOVA model. The lines represent the outcome from the mixed ANCOVA for age (between-subjects factor) and fluency modality (within-subjects factor) using cross-sectional data.

Table 3. Contribution of cognitive variables to verbal fluency by age groups (random forest regression models).

	Semantic fluency				**Phonemic fluency**				**Action fluency**			
	ME	**EE**	**LE**		**ME**	**EE**	**LE**		**ME**	**EE**	**LE**	
Sample size, n	222	162	62	Pattern	222	162	62	Pattern	222	162	62	Pattern
Explained variance	27%	33%	20%		35%	56%	39%		43%	47%	23%	
Predictors												
BNT	22	20	8	S/Dif.	35	48	17	S.	26	24	8	S/Dif.
PCV - Decision time	7		4	S.	5			Dif.				S.
PCV - Motor time	19			Dif.	3	8	2	S.				S.
PASAT	2	6	2	S.	5		1	S.				S.
STROOP Words	9	16	7	S.	30	28	19	S.	29	15	24	S.
STROOP Colors	11	14	18	S.	19	33	19	S.	21	9	10	S.
STROOP Inhibition	3	15	4	S.	2	20	3	S.	9	6	3	S.
TMT A	22	21	16	S.	19	22	14	S.	25	20	8	S/Dif.

CTT - Part 1	5	25	19	S/Ded.	5	32	24	S/Ded.	17	37	24	S.
CTT - Part 2	25	9	17	S.		31	13	Ded.	10	35	14	S.
FRT	2	3		Dif.			3	Ded.	4			Dif.
JLOT - First half	5	6		Dif.	2	8	5	S.		9	6	Ded.
JLOT - Second half	5	6		Dif.	2		16	S/Ded.	8	8		Dif.
Digit Span forward	5	12		Dif.	8	20	6	S.	24	10	2	S/Dif.
Digit Span backward	4	13		Dif.	35	14	3	S/Dif.	27	2		Dif.
Spatial Span forward	1			S/Dif.			6	Ded.	8	5		Dif.
Spatial Span backward		6		S.	5		9	S.	2	10	12	S.
LM A - Immediate	2	20	3	S.	5	9	4	S.	8	9	10	S.
LM B1 - Immediate	13	13		Dif.	12	19		Dif.	25	11	17	S.
LM B2 - Immediate	8	10		Dif.	7	14	15	S.	19	19	15	S.
LM A - Delay	3	14	4	S.	5	9		Dif.	14	10	3	S/Dif.
LM B - Delay	11	10		Dif.	7	16	3	S.	18	18	19	S.
LM A - Recognition	3			Dif.	3	2	6	S.	3	3		Dif.
LM B - Recognition	7	9		Dif.	16	13		Dif.	5	10	7	S.
TAVEC 1st trial	5		7	S.		4		S.			1	S/Ded.
TAVEC Learning	15	12	22	S.		7		S.		6		S.
TAVEC Short delay	6	11	4	S.		8		S.		1	3	Ded.
TAVEC Short delay-Clues		10	3	Ded.				S.				S.
TAVEC Long delay		1	6	Ded.		4		S.		5		S.
TAVEC Long delay-Clues	4	8	2	S.		3		S.	2	9		Dif.
TAVEC Intrusions	2	8		Dif.	1	4		Dif.	1			S/Dif.
TAVEC Intrusions-Clues	2			Dif.	3	7		Dif.	1		14	S/Ded.
TAVEC Perseverations	1		3	S.	5			Dif.	8			Dif.
TAVEC Recog. Correct		1		S.				S.				S.
TAVEC Recog. False Positive			5	Ded.		5	2	Ded.	4			Dif.
VR I – Total score	3	9		Dif.	3	9	6	S.	4	17	7	S.
VR II – Total score	5		7	S.		9	10	Ded.	3	14	12	S.
VR-Copying				S.	4	3		Dif.	6	4	5	S.
VR Total Recog.	7	9	8	S.		10	10	Ded.		16	8	Ded.
VR False Positive	6		7	S.	1		5	S.		1	8	Ded.
VR Visual discrimination				S.	4	2		Dif.	7		4	S.
Luria’s HAM Right	3	7	5	S.	11	10		Dif.	7	16	1	S.
Luria’s HAM Left	8		7	S.	3			Dif.	6	9		Dif.
Luria’s – Motor coordination			12	Ded.	5	3	18	S/Ded.	3	7	14	S.
Block Design	6		1	S.	21	9	8	S/Dif.	34	5		Dif.
Empty cells	8	15	19		13	11	18		12	12	18	
Associations	37	30	26		32	34	27		33	33	27	
Stable		53%				51%				53%		
Differentiation		36%				29%				33%		
Dedifferentiation		11%				20%				14%		

Importance NC <10 10 - 19 20 - 29 >30

ME = Middle-age, EE = Early elderly, LE = Late elderly. The explained variance is the total cumulative variance explained by all the predictors in the model. BNT = Boston Naming Test (spontaneous responses). PCV = PC-Vienna System. PASAT = Paced Auditory Serial Addition Test. TMT A = Trial Making Test A. CTT = Color Trails Test. FRT = Facial Recognition Test. JLOT = Judgment of Line Orientation Test. LM = Logical Memory. VR = Visual Reproduction Test. Luria’s HAM = Luria’s Premotor Functions, Hand Alternative Movements. The numbers inside the cells in the “Predictors” area show the importance of each variable in predicting the outcome variable, where the higher the value the higher the importance. The importance is calculated as the relative error in the prediction when a given predictor is excluded from the model. Gray-shaded cells denote that these variables were not important in the model. S.= Stable; Dif. = Differentiation; Ded. = Dedifferentiation; S/Dif. = Stable/Differentiation; S/Ded. = Stable/Dedifferentiation. NC = no contribution. Empty cells = the total number of variables without any contribution. Associations = the total number of variables that are important to predicting verbal fluency.

Regarding semantic fluency, the most important variables in predicting performance in the middle-age group were CCT, TMT, BNT, PC-Vienna, Logical Memory (Immediate and Delayed), and TAVEC (Learning). In the early elderly group, the most important variables in predicting performance were CCT, TMT, BNT, Logical Memory (Immediate and Delayed), and Stroop. In the late elderly group, the most important variables in predicting performance were CTT, TMT, TAVEC (Learning), Stroop, and Luria's motor coordination.

Regarding phonemic fluency, the most important variables in predicting performance in the middle-age group were BNT, Stroop, TMT, Digit Span backward, Logical Memory (Immediate), and Block Design. In the early elderly group, the most important variables in predicting performance were BNT, Stroop, TMT, Digit Span forward, and CTT. In the late elderly group, the most important variables in predicting performance were BNT, Stroop, Logical Memory (Immediate), CTT, Luria's motor coordination, and JLOT.

Regarding action fluency, the most important variables in predicting performance in the middle-age group were TMT, BNT, Logical Memory, Stroop, Block Design, and Digit Span. In the early elderly group, the most important variables in predicting performance were TMT, BNT, Logical Memory, CTT, Visual Reproduction, and Luria's hand alternative movements. In the late elderly group, the most important variables in predicting performance were Logical Memory, Stroop, CTT, Visual Reproduction, Luria's motor coordination, TAVEC (Intrusions), and Spatial Span.

Virtually the same results were obtained when including WAIS-III Information and sex as extra predictors in order to investigate their potential confounding effect (data not shown).

Differentiation, dedifferentiation, and stability patterns across age

Three different patterns can be observed in regard to the contribution of cognitive abilities to verbal fluency with increasing age. A differentiation pattern can be observed when cognitive variables stop contributing with increasing age. The dedifferentiation pattern is observed when variables start contributing with increasing age. A stability pattern is seen when the contribution of the variables remains stable across age. In some cases, a combination of these patterns can also be observed in the same variable. We classified as stable/differentiation and stable/dedifferentiation those variables that, despite showing mostly a stability pattern, stop or start contributing with increasing age, respectively. More detail on the procedure to ascertain these patterns is provided in Supplementary Table S2.

Overall, semantic fluency was associated with less cognitive variables with increasing age, indicating a differentiation pattern with aging (Table 3). This is explained because although stability in the associations was observed in 53% of the variables, the percentage of variables showing a differentiation pattern (36%) exceeded the percentage of variables showing a dedifferentiation pattern (11%). In particular, several recall variables of Logical Memory stop contributing to semantic fluency after the early elderly, together with JLOT, PC-Vienna, Digits, Visual Reproduction, and FRT (differentiation). On the other hand, several delayed recall variables of TAVEC as well as Luria's motor coordination start contributing to semantic fluency in the late elderly (dedifferentiation). Variables with stable contribution are shown in Table 3.

Phonemic fluency showed more stability in the number of cognitive associations with increasing age. The reason for this is that stability in the associations was observed in 51% of the variables, and the percentage of variables showing a differentiation pattern (29%) was rather comparable to the percentage of variables showing a dedifferentiation pattern (20%) with aging, thus cancelling each other. We observed that several recall variables of Logical Memory stop contributing to phonemic fluency after the early elderly, together with TAVEC errors, Visual Reproduction copy and visual discrimination, and Luria's hand alternative movements (differentiation). In contrast, several delayed recall variables of Visual Reproduction, TAVEC, FRT and CTT start contributing to phonemic fluency in the late elderly (dedifferentiation). Variables with stable contribution are shown in Table 3.

The results in action fluency are a combination of the patterns described above for semantic fluency and phonemic fluency. Stability in the number of cognitive associations prevailed from middle-age to early elderly, while a reduction in the contributing cognitive variables was observed when reaching the late elderly group. This is explained because stability in the associations was observed in a slightly superior proportion of variables as compared with the other two fluency modalities (53%), but the proportion of variables showing a differentiation pattern (33%) exceeded the number of variables showing a dedifferentiation pattern (14%). In particular, several variables of TAVEC stop contributing to action fluency after the early elderly, together with Luria's motor coordination, JLOT, Block design, Spatial span forward, Digit span backward and FRT (differentiation). The Delayed recall variables of Visual Reproduction and TAVEC start contributing to action fluency in the late elderly, together with JLOT (dedifferentiation).

DISCUSSION

The overall purpose of this study was to investigate how differentiation and dedifferentiation processes in verbal fluency are organized across the lifespan (32 to 84 years). Using cross-sectional data, we investigated the association between performance in three components of verbal fluency (semantic, phonemic, and action) and performance in numerous non-fluency cognitive measures within different age groups from the early middle-age to the late elderly.

Although we found a lower word production with increasing age in the three fluency modalities, age showed a stronger association with semantic fluency than with the other two modalities. The most prominent reduction in performance was observed between the middle-age and the early elderly in the three modalities. At that point in time, a high number of cognitive variables stopped contributing specially to semantic and action fluency. Despite potentially compensatory dedifferentiation patterns in the three modalities, a stronger differentiation process was observed in the three modalities.

The association between age and verbal fluency

Semantic fluency showed a lineal and progressive reduction throughout the whole age range investigated in this study. Other studies including cohorts with a wide range of age have also observed a linear association between age and semantic fluency [39–42]. Some authors have also reported relative stability until the age of 60 [2, 16, 17, 43, 44], followed by a decline in performance [1, 16, 20, 44–49]. Therefore, the association between age and semantic fluency is a quite well established finding, although negative reports also exist [30]. Phonemic fluency was rather stable during the middle-age, followed by a drop during the early elderly that seems to get stabilised in the late elderly. Despite these dynamics, our models showed that the linear trend was the best fit (as compared with quadratic and cubic trends). A linear association between age and phonemic fluency has also been observed in previous studies [41, 42, 50]. Similar to our results, several studies have shown certain stability until the ages of 60-65 years [2, 20, 43, 44], followed by decline [20, 39, 41, 47, 49]. However, no association between age and phonemic fluency has also been reported [13, 16, 26, 31, 48]. Regarding action fluency, a cubic trend was the best fit in our data. We observed a plateau of high performance during the middle-age, with a drop during the early elderly, and a trend for stability in performance during the late elderly. Previous studies only included elderly individuals and did not found an association between age and action fluency [12, 23]. Such finding is in line with the trend for stability in our older age strata.

Fewer studies have simultaneously compared the association between age and the different fluency modalities in the same cohort and statistical model. Indeed, these studies have only compared semantic and phonemic fluency, whereas no data existed on action fluency to the present date. Although we found a significant interaction between age and fluency modality, this result mainly reflects the relationship between action and phonemic fluency. We thus interpret that, in our cohort, semantic and phonemic fluency have a similar association with age. Other groups have also found that semantic and phonemic fluency have a similar association with age [1, 39]. However, some studies have shown different results, as for example, an association between semantic fluency and age but not between phonemic fluency and age [13–17, 48]. The age range investigated is a major confounder, accounting for part of these contradicting results. Importantly, by covering a wide range of age, from 32 to 84 years, our data help to further understand these discrepancies as well as to delineate the age dynamics in fluency performance.

Differentiation, dedifferentiation, and stability patterns

The contribution of various cognitive functions to verbal fluency performance was different depending on the fluency modality and the age group. Regarding semantic fluency, in the middle-age group, the main contribution was seen for lexical access, processing speed, and verbal memory. In the early elderly group, we observed a greater contribution of executive functions, including working memory, in addition to verbal memory. Lexical access also contributed somehow but the contribution of processing speed was lesser than in the middle-age. Previous studies have found an association of semantic fluency with lexical access [24–26,28], processing speed [32], executive functions [28], and working memory [25]. The novelty of our study is that we reveal age-specific contributions of different cognitive functions to semantic fluency. It is very interesting that the contribution of executive functions was observed in the range of age with greater reduction in word production. This happened in a context of differentiation. This means that when several relevant cognitive functions stop contributing to semantic fluency (differentiation), performance in semantic fluency drops, but new executive components emerge (dedifferentiation), likely being recruited as a compensatory mechanism. This interpretation implies that both differentiation and dedifferentiation patterns can co-occur simultaneously from young ages and not only at the oldest ages, as previously suggested [37, 38, 51]. New brain networks or new parts of the same networks may be involved in this process, thus extending from the original differentiated function or network. According to the "Compensation-Related Utilization of Neural Circuits Hypothesis" (CRUNCH), the aged brain has to deal with processing inefficiencies and recruits more neuronal resources in order to achieve the same level of performance than a younger brain [52]. This hypothesis is further supported by our results obtained in the late elderly. Executive functions and memory functions remained to contribute to semantic fluency, and premotor functions emerged as a new contributor, also supporting the greater participation of the frontal lobe. The "scaffolding theory of aging and cognition" (STAC) [7] suggests a generalized increased frontal activation with age as a compensatory response. However, we found that the differentiation process is more prominent than the dedifferentiation process. This may be explained by the fact that executive functions can not completely compensate for the onslaught of aging; or this compensation coexists with the overall executive dysfunction observed in normal aging [53]; or both explanations at the same time.

Regarding phonemic fluency, lexical access, working memory, processing speed, and visuoconstructive abilities were the most important contributors in the middle-age. Verbal memory also contributed to a lesser extent. The contribution of visuoconstructive abilities may be explained by the strong executive component of the test used to measure this ability in our cohort. It is possible that shared processes such as planning and processing speed underlie both this test of visuoconstructive abilities [54] and phonetic fluency. The contribution of executive functions on phonemic fluency has been shown in previous studies [28, 29, 31]. In addition, premotor and visuospatial abilities emerged at the late elderly. Thus, new brain regions seem to be recruited as for semantic fluency (dedifferentiation), but possibly extending more to the posterior cortex in phonetic fluency. The visuoconstructive and visuospatial component of the tasks suggest a greater participation of the right hemisphere with increasing age, in line with the hemispheric asymmetry reduction postulated by the "hemispheric asymmetry reduction in older adults" (HAROLD) model [55]. The HAROLD effect observed by Cabeza (2002) [55] was interpreted as a compensatory function in which the brain additionally recruits homologous contralateral brain areas [56, 57]. Our results suggest that this potential reorganization of the brain is rather effective, minimising the negative onslaught of aging on phonemic fluency, despite how challenging this task can be. This effectiveness contrasts with semantic and action fluency, where we observed a stronger association with age, perhaps due to less effective compensatory mechanisms and a more limited brain reorganisation. Potential explanations for this finding may be that phonemic fluency might be more relevant for the daily life, is more intensively trained during the lifespan, or category strategies are easier [24]. Alternatively, grammatical storages (semantic and actions) may be more vulnerable to aging, while phonemic fluency may allow more flexibility for the activation of different storages through switching strategies [13]. Other researchers have found an association of phonemic fluency with lexical access [29], memory function [31, 32], and processing speed [25, 26]. Again, the novelty of our study is that we reveal age-specific contributions of different cognitive functions to phonemic fluency.

The functions contributing the most to action fluency in the middle-age were executive functions, processing speed, and verbal memory. In addition to these, visual functions (visual memory and visuospatial functions) started contributing in the older age strata (dedifferentiation). This suggests that new brain networks or parts of the same networks are recruited, including more posterior and right hemispheric regions [55]. The same as for semantic fluency, this finding emerged in the age range with greater reduction in word production, possibly as a compensatory response. We are not aware of studies investigating the association of action fluency with cognitive functions other than episodic memory or picture naming [12, 23].

Our interpretations in these last paragraphs regarding cognitive functions underlying different neuropsychological tests are based on the widely used classification of Lezak (2012) [21]. However, neuropsychological tests are known to tap on several cognitive functions, which may reflect that different cognitive functions partially share the same neuronal networks, a finding that would delineate the optimal organization of the human brain (the balance between differentiated and dedifferentiated cognitive components). This organization is adaptive to age-related brain changes and the share of neuronal networks will increase with aging as part of compensatory mechanisms (dedifferentiation).

The present study has some limitations. We analyzed cross-sectional data. Therefore, our age-related differences may partially be explained by cohort effects. We controlled for performance on WAIS-III Information as a means to control for generational effects often overlapped with crystallized intelligence [11, 54]. Also, multivariate analysis methods such as random forest have been proven to maximize the covariance between the predictors and the outcome variable, being less vulnerable to confounders such as cohort effects [11]. Nonetheless, we are currently collecting follow-up data so that our present cross-sectional findings can be substantiated in a longitudinal design. In addition, future studies should further disentangle the mechanisms behind co-occurring differentiation and dedifferentiation processes. For example, how executive functioning substitutes the contribution of other cognitive functions, in a context of overall executive dysfunction as individuals age, needs to be further investigated. Fluency performance varies according to the type of stimulus (either letter or a category) [58]. Therefore, it is warranted to replicate our current findings using other stimulus for semantic (e.g. vegetables) and phonemic fluency (e.g. C-F-L). In this study we focused on high order cognitive functions. However, previous studies have shown that dedifferentiation findings extend to peripheral sensori-motor abilities such as visual and auditory acuity [59], which deserves further attention in the future. Also, we focused on the contribution of non-language functions (other than lexical access: BNT) towards the prediction of verbal fluency. Therefore, investigating the contribution of non-fluency language components towards the prediction of verbal fluency is warranted in future studies. The association between age and cognition is largely determined by biological changes taking place in the brain during aging. Therefore, extending our analyses to neuroimaging measures in the future is warranted and might help to better understand the neural correlates of our current findings.

Conclusions

Verbal fluency declines with increasing age. Semantic fluency seems to be more vulnerable to aging than phonemic and action fluency. However, these dynamics are masked by the influence of other cognitive functions, which may themselves be declining with age as well. Lexical access, processing speed, and executive functions are among the most contributing functions. The most striking contribution of new cognitive functions takes place during the transition from the middle-age to the early elderly. Differentiation processes (functions stop contributing with increasing age) coexist with dedifferentiation processes (new functions start contributing with increasing age). Compensatory mechanisms are postulated to underlie these patterns. All in all, we present important data towards advancing to a better understanding of cognitive aging and compensatory processes. These findings may be relevant for personalizing age-specific cognitive interventions by guiding the development of materials for cognitive stimulation and/or rehabilitation in the close future. This knowledge may also be relevant for the clinical practice, improving interpretation of cognitive performance, and eventually improving diagnosis of cognitive disorders. Furthermore, our research could easily be extended to the study of other cognitive functions.

METHODS

Participants

A total of 446 participants were selected from the GENIC-database (Group of Neuropsychological Studies of the Canary Islands) [11], with ages between 32 and 84 years, and a balanced distribution of sex across age. All participants were evaluated with a comprehensive neuropsychological protocol, which assesses language, processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, and visuoconstructive, visuoperceptive and visuospatial functions (see Supplementary Table S1 and [60,61] for detailed information about the protocol). Inclusion criteria were: (1) normal cognitive performance in comprehensive neuropsychological assessment using pertinent clinical normative data (i.e. individuals with mild cognitive impairment or dementia were excluded); (2) preserved global cognitive and functional status operationalized as a Mini-Mental State Examination (MMSE) score ≥24, a Blessed Dementia Scale (BDRS) score <4 and/or a Functional Activity Questionnaire (FAQ) score <6); (3) no neurologic, psychiatric or systemic diseases; and (4) no history of substance abuse. An exception was done for BDRS. Although the BDRS scale cut-off for abnormality is frequently established at ≥4 points [62,63], the 'changes in personality, interests and drive' subscale may influence the BDRS total score and does not necessary reflect functional impairment. With the objective of excluding only individuals with functional impairment, we included those participants with total BDRS scores ≥4 (n=24) if: a) 70% or higher percentage of the BDRS total score resulted from the 'changes in personality, interests and drive' subscale; and b) if a score ≤1.5 was obtained in the other two subscales ('changes in performance of everyday activities' and 'changes in habits'). The same procedure has been used in previous studies [11,64]. The study was approved by the ethics committee of the University of La Laguna (Spain) and all participants gave their written informed consent.

Neuropsychological assessment

Among all the tests included in our neuropsychological protocol, three tests of verbal fluency are of special relevance for the current study:

Phonemic verbal fluency

The Controlled Oral Word Association Test (COWAT; [65]) was administrated. Participants had to recall words that begin with the letters F, A, and S, taking one minute on each of the letters. Proper nouns, numbers, and derived words were considered intrusion errors. A total score (F+A+S) was calculated as the number of correct words produced, excluding intrusions and perseverations (repetitions of correct words).

Semantic verbal fluency

Instructions were given following the administration procedures described in the Multilingual Aphasia Examination [65]. Participants had to recall names of animals during one minute. The total number of words, perseverations, and intrusions were registered.

Action verbal fluency

Participants had to recall verbs in infinitive form (e.g. "to reflect"). Verbs included as part of a sentence (e.g. "to dance the tango") and repetitions of the same verb were considered errors [12]. The total number of correct verbs, intrusions, and perseverations were counted.

Other neuropsychological tests selected for this study are explained in Supplementary Table S1, including Information Subtest (from the WAIS-III), Boston Naming Test (BNT), PC-Vienna System, Paced Auditory Serial Addition Test (PASAT), Stroop Test, Trail Making Test (TMT), Colour Trial Test (CTT), Facial Recognition Test (FRT), Judgment of Line Orientation Test (JLOT), Digit Span (from the WMS-III), Visuospatial Span (from the WMS-III), Logical Memory (LM, from the WMS-III), "Test de Aprendizaje Verbal España-Complutense" (TAVEC, the Spanish adaptation and validation of the California Verbal Learning Test), Visual Reproduction (VR, from the WMS-III), Luria's Premotor Functions ("hand alternative movements" and "motor coordination"), and Block Design (from the WAIS-III).

Statistical analysis

Statistical analyses were performed using the R programming environment [66]. The association between age (between-subject factor, 3 or 4 age groups) and verbal fluency (within-subject factor, 3 fluency modalities) was tested using mixed ANCOVA, including WAIS-III Information as a covariable in order to control for between-subjects variability in the level of crystallized intelligence [11]. With the aim of investigating potential non-linear associations between age and performance in verbal fluency, we tested for quadratic and cubic associations in addition to linear associations in the mixed ANCOVA. To do this, we used the technique "trend analysis", which is a way of decomposing the variance explained by the factor that accompanies an ANOVA using specially chosen linear weights called "orthogonal polynomials". The polynomial contrast will test for trends in the data depending on the number of levels of the numeric factor. Since we have more than two levels in our independent variable, the polynomial contrast will examine other trends that can exist in the data such as quadratic and cubic trends. Random forest regression analyses were used to investigate the multivariate association between the measures of verbal fluency and a total of 45 cognitive variables. In random forest models, the contribution of the predictors in the models is reported as Imp (from Importance), which reflects the relative error in the prediction when a predictor is excluded from the model. Imp values higher than zero denote that a given variable contributes to the prediction of the outcome. The larger the Imp value, the greater the contribution. Imp values do not have an upper limit and they can rather be interpreted by considering the obtained values in relation to the variable yielding the highest Imp value in the model. Two per cent of the values were missing across the 48 cognitive variables and were thus imputed. Only the random forest analyses were performed on this imputed dataset. For the demographic variables, ANOVA was used for both continuous and dichotomous (dummy) variables. Simple regression analysis was performed to investigate the association between pairs of continuous variables. Significant differences were considered when $p<0.05$.

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CONFLICTS OF INTEREST

All the authors declared no conflicts of interest relevant to the current study.

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REFERENCES

1. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, Ferrie JE, Dugravot A. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ. 2012; 344:d7622–7622. https://doi.org/10.1136/bmj.d7622 PMID:22223828
2. Ferreira D, Correia R, Nieto A, Machado A, Molina Y, Barroso J. Cognitive decline before the age of 50 can be detected with sensitive cognitive measures. Psicothema. 2015; 27:216–22. https://doi.org/10.7334/psicothema2014.192 PMID:26260927
3. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med. 2013; 29:737–52. https://doi.org/10.1016/j.cger.2013.07.002 PMID:24094294
4. Salthouse TA. When does age-related cognitive decline begin? Neurobiol Aging. 2009; 30:507–14. https://doi.org/10.1016/j.neurobiolaging.2008.09.023 PMID:19231028
5. Salthouse TA, Fristoe NM, Lineweaver TT, Coon VE. Aging of attention: does the ability to divide decline? Mem Cognit. 1995; 23:59–71. https://doi.org/10.3758/BF03210557 PMID:7885266
6. Salthouse TA. Selective review of cognitive aging. J Int Neuropsychol Soc. 2010; 16:754–60. https://doi.org/10.1017/S1355617710000706 PMID:20673381
7. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009; 60:173–96. https://doi.org/10.1146/annurev.psych.59.103006.093656 PMID:19035823
8. La Tourette TR, Meeks S. Perceptions of patronizing speech by older women in nursing homes and in the community: impact of cognitive ability and place of residence. J Lang Soc Psychol. 2000; 19:463–73. https://doi.org/10.1177/0261927X00019004004
9. Shafto MA, Tyler LK. Language in the aging brain: the network dynamics of cognitive decline and preservation. Science. 2014; 346:583–87. https://doi.org/10.1126/science.1254404 PMID:25359966
10. Ansado J, Marsolais Y, Methqal I, Alary F, Joanette Y. The adaptive aging brain: evidence from the preservation of communication abilities with age. Eur J Neurosci. 2013; 37:1887–95. https://doi.org/10.1111/ejn.12252 PMID:23773057
11. Machado A, Barroso J, Molina Y, Nieto A, Díaz-Flores L, Westman E, Ferreira D. Proposal for a hierarchical, multidimensional, and multivariate approach to investigate cognitive aging. Neurobiol Aging. 2018; 71:179–88. https://doi.org/10.1016/j.neurobiolaging.2018.07.017 PMID:30149289
12. Piatt AL, Fields JA, Paolo AM, Tröster AI. Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity. Neuropsychologia. 1999; 37:1499–503. https://doi.org/10.1016/S0028-3932(99)00066-4 PMID:10617270
13. Troyer AK, Moscovitch M, Winocur G. Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. Neuropsychology. 1997; 11:138–46. https://doi.org/10.1037/0894-4105.11.1.138 PMID:9055277
14. Parkin AJ, Java RI. Deterioration of frontal lobe function in normal aging: influences of fluid intelligence versus perceptual speed. Neuropsychology. 1999; 13:539–45. https://doi.org/10.1037/0894-4105.13.4.539 PMID:10527062
15. Kemper S, Sumner A. The structure of verbal abilities in young and older adults. Psychol Aging. 2001; 16:312–22. https://doi.org/10.1037/0882-7974.16.2.312 PMID:11405318
16. Foldi NS, Helm-Estabrooks N, Redfield J, Nickel DG. Perseveration in normal aging: A comparison of perseveration rates on design fluency and verbal generative tasks. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2003; 10:268–80. https://doi.org/10.1076/anec.10.4.268.28970
17. Elgamal SA, Roy EA, Sharratt MT. Age and verbal fluency: the mediating effect of speed of processing. Can Geriatr J. 2011; 14:66–72.

https://doi.org/10.5770/cgj.v14i3.17 PMID:23251316

18. Troyer AK. Normative data for clustering and switching on verbal fluency tasks. J Clin Exp Neuropsychol. 2000; 22:370–78. https://doi.org/10.1076/1380-3395(200006)22:3;1-V;FT370 PMID:10855044
19. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. Appl Neuropsychol. 2001; 8:161–66. https://doi.org/10.1207/S15324826AN0803_5 PMID:11686651
20. Rodriguez-Aranda C, Martinussen M. Age-related differences in performance of phonemic verbal fluency measured by Controlled Oral Word Association Task (COWAT): a meta-analytic study. Dev Neuropsychol. 2006; 30:697–717. https://doi.org/10.1207/s15326942dn3002_3 PMID:16995832
21. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York, NY, US: Oxford University Press; 2012.
22. Bryan J, Luszcz MA. Measurement of executive function: considerations for detecting adult age differences. J Clin Exp Neuropsychol. 2000; 22:40–55. https://doi.org/10.1076/1380-3395(200002)22:1;1-8;FT040 PMID:10649544
23. Piatt AL, Fields JA, Paolo AM, Tröster AI. Action verbal fluency normative data for the elderly. Brain Lang. 2004; 89:580–83. https://doi.org/10.1016/j.bandl.2004.02.003 PMID:15120548
24. Kavé G, Mashal N. Age-related differences in word-retrieval but not in meaning generation. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012; 19:515–29. https://doi.org/10.1080/13825585.2011.638975 PMID:22221146
25. Kraan C, Stolwyk RJ, Testa R. The abilities associated with verbal fluency performance in a young, healthy population are multifactorial and differ across fluency variants. Appl Neuropsychol Adult. 2013; 20:159–68. https://doi.org/10.1080/09084282.2012.670157 PMID:23383872
26. Stolwyk R, Bannirchelvam B, Kraan C, Simpson K. The cognitive abilities associated with verbal fluency task performance differ across fluency variants and age groups in healthy young and old adults. J Clin Exp Neuropsychol. 2015; 37:70–83. https://doi.org/10.1080/13803395.2014.988125 PMID:25658578
27. Lezak M, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York, NY: Oxford University Press; 2004.
28. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front Psychol. 2014; 5:772. https://doi.org/10.3389/fpsyg.2014.00772 PMID:25101034
29. Ruff RM, Light RH, Parker SB, Levin HS. The psychological construct of word fluency. Brain Lang. 1997; 57:394–405. https://doi.org/10.1006/brln.1997.1755 PMID:9126423
30. Rodríguez-Aranda C, Sundet K. The frontal hypothesis of cognitive aging: factor structure and age effects on four frontal tests among healthy individuals. J Genet Psychol. 2006; 167:269–87. https://doi.org/10.3200/GNTP.167.3.269-287 PMID:17278416
31. Bolla KI, Lindgren KN, Bonaccorsy C, Bleecker ML. Predictors of verbal fluency (FAS) in the healthy elderly. J Clin Psychol. 1990; 46:623–28. https://doi.org/10.1002/1097-4679(199009)46:5<623::AID-JCLP2270460513>3.0.CO;2-C PMID:2246370
32. Ardila A, Galeano LM, Rosselli M. Toward a model of neuropsychological activity. Neuropsychol Rev. 1998; 8:171–90. https://doi.org/10.1023/A:1021618218943 PMID:9951709
33. Garrett HE. A developmental theory of intelligence. Am Psychol. 1946; 1:372–78. https://doi.org/10.1037/h0056380 PMID:20280373
34. Balinsky B. An analysis of the mental factors of various age groups from nine to sixty. Genet Psychol Monogr. 1941; 23:191–234.
35. Baltes PB, Cornelius SW, Spiro A, Nesselroade JR, Willis SL. Integration versus differentiation of fluid/crytallized intelligence in old age. Dev Psychol. 1980; 16:625–35. https://doi.org/10.1037/0012-4
36. Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol Aging. 1997; 12:12–21. https://doi.org/10.1037/0882-7974.12.1.12 PMID:9100264
37. Hülür G, Ram N, Willis SL, Schaie KW, Gerstorf D. Cognitive dedifferentiation with increasing age and proximity of death: Within-person evidence from the Seattle Longitudinal Study. Psychol Aging. 2015; 30:311–23.

https://doi.org/10.1037/a0039260 PMID:25961879

38. La Fleur CG, Meyer MJ, Dodson C. Exploring dedifferentiation across the adult lifespan. Psychol Aging. 2018; 33:855–70. https://doi.org/10.1037/pag0000274 PMID:30091632

39. Bolla KI, Gray S, Resnick SM, Galante R, Kawas C. Category and Letter Fluency in Highly Educated Older Adults. Clin Neuropsychol. 1998; 12:330–38. https://doi.org/10.1076/clin.12.3.330.1986

40. Brickman AM, Paul RH, Cohen RA, Williams LM, MacGregor KL, Jefferson AL, Tate DF, Gunstad J, Gordon E. Category and letter verbal fluency across the adult lifespan: relationship to EEG theta power. Arch Clin Neuropsychol. 2005; 20:561–73. https://doi.org/10.1016/j.acn.2004.12.006 PMID:15939182

41. Kavé G, Knafo-Noam A. Lifespan development of phonemic and semantic fluency: universal increase, differential decrease. J Clin Exp Neuropsychol. 2015; 37:751–63. https://doi.org/10.1080/13803395.2015.1065958 PMID:26299188

42. Olabarrieta-Landa L, Rivera D, Galarza-Del-Angel J, Garza MT, Saracho CP, Rodríguez W, Chávez-Oliveros M, Rábago B, Leibach G, Schebela S, Martínez C, Luna M, Longoni M, et al. Verbal fluency tests: normative data for the Latin American Spanish speaking adult population. NeuroRehabilitation. 2015; 37:515–61. https://doi.org/10.3233/NRE-151279 PMID:26639930

43. Daigneault S, Braun CM, Whitaker HA. Early effects of normal aging on perseverative and non-perseverative prefrontal measures. Dev Neuropsychol. 1992; 8:99–114. https://doi.org/10.1080/87565649209540518

44. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999; 14:167–77. PMID:14590600

45. Kempler D, Teng EL, Dick M, Taussig IM, Davis DS. The effects of age, education, and ethnicity on verbal fluency. J Int Neuropsychol Soc. 1998; 4:531–38. https://doi.org/10.1017/S1355617798466013 PMID:10050357

46. Ravdin LD, Katzen HL, Agrawal P, Relkin NR. Letter and semantic fluency in older adults: effects of mild depressive symptoms and age-stratified normative data. Clin Neuropsychol. 2003; 17:195–202. https://doi.org/10.1076/clin.17.2.195.16500 PMID:13680426

47. Auriacombe S, Fabrigoule C, Lafont S, Jacqmin-Gadda H, Dartigues JF. Letter and Category Fluency in Normal Elderly Participants: a Population-Based Study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2001; 8:98–108. https://doi.org/10.1076/anec.8.2.98.841

48. Crossley M, D'Arcy C, Rawson NS. Letter and category fluency in community-dwelling Canadian seniors: a comparison of normal participants to those with dementia of the Alzheimer or vascular type. J Clin Exp Neuropsychol. 1997; 19:52–62. https://doi.org/10.1080/01688639708403836 PMID:9071641

49. Bryan J, Luszcz MA, Crawford JR. Verbal knowledge and speed of information processing as mediators of age differences in verbal fluency performance among older adults. Psychol Aging. 1997; 12:473–78. https://doi.org/10.1037/0882-7974.12.3.473 PMID:9308094

50. Bäckman L, Nilsson LG. Semantic Memory Functioning Across the Adult Life Span. Eur Psychol. 1996; 1:27–33. https://doi.org/10.1027/1016-9040.1.1.27

51. Wilson RS, Segawa E, Hizel LP, Boyle PA, Bennett DA. Terminal dedifferentiation of cognitive abilities. Neurology. 2012; 78:1116–22. https://doi.org/10.1212/WNL.0b013e31824f7ff2 PMID:22491858

52. Reuter-Lorenz PA, Cappell KA. Neurocognitive Aging and the Compensation Hypothesis. Curr Dir Psychol Sci. 2008; 17:177–82. https://doi.org/10.1111/j.1467-8721.2008.00570.x

53. Dempster FN. The rise and fall of the inhibitory mechanism: toward a unified theory of cognitive development and aging. Dev Rev. 1992; 12:45–75. https://doi.org/10.1016/0273-2297(92)90003-K

54. Ferreira D, Bartrés-Faz D, Nygren L, Rundkvist LJ, Molina Y, Machado A, Junqué C, Barroso J, Westman E. Different reserve proxies confer overlapping and unique endurance to cortical thinning in healthy middle-aged adults. Behav Brain Res. 2016; 311:375–83. https://doi.org/10.1016/j.bbr.2016.05.061 PMID:27263072

55. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 2002; 17:85–100. https://doi.org/10.1037/0882-7974.17.1.85 PMID:11931290

56. Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol. 2005; 15:245–51.

https://doi.org/10.1016/j.conb.2005.03.016 PMID:15831410

57. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. J Gerontol B Psychol Sci Soc Sci. 2010; 65:405–15. https://doi.org/10.1093/geronb/gbq035 PMID:20478901

58. Diaz M, Sailor K, Cheung D, Kuslansky G. Category size effects in semantic and letter fluency in Alzheimer's patients. Brain Lang. 2004; 89:108–14. https://doi.org/10.1016/S0093-934X(03)00307-9 PMID:15010242

59. Lindenberger U, Ghisletta P. Cognitive and sensory declines in old age: gauging the evidence for a common cause. Psychol Aging. 2009; 24:1–16. https://doi.org/10.1037/a0014986 PMID:19290733

60. Ferreira D, Molina Y, Machado A, Westman E, Wahlund LO, Nieto A, Correia R, Junqué C, Díaz-Flores L, Barroso J. Cognitive decline is mediated by gray matter changes during middle age. Neurobiol Aging. 2014; 35:1086–94. https://doi.org/10.1016/j.neurobiolaging.2013.10.095 PMID:24239436

61. Correia R, Nieto A, Ferreira D, Sabucedo M, Barroso J. Fund of Information is More Strongly Associated with Neuropsychological Functioning Than Education in Older Spanish Adults. Arch Clin Neuropsychol. 2015; 30:310–21. https://doi.org/10.1093/arclin/acv011 PMID:25762800

62. Blessed G. Tomlinson Be, Roth M. The Association Between Quantitative Measures of Dementia and of Senile Change in the Cerebral Grey Matter of Elderly Subjects. Br J Psychiatry. 1968; 114:797–811. https://doi.org/10.1192/bjp.114.512.797 PMID:5662937

63. Erkinjuntti T, Hokkanen L, Sulkava R, Palo J. The Blessed Dementia Scale as a screening test for dementia. Int J Geriatr Psychiatry. 1988; 3:267–73. https://doi.org/10.1002/gps.930030406

64. Cedres N, Machado A, Molina Y, Diaz-Galvan P, Hernández-Cabrera JA, Barroso J, Westman E, Ferreira D. Subjective Cognitive Decline Below and Above the Age of 60: A Multivariate Study on Neuroimaging, Cognitive, Clinical, and Demographic Measures. J Alzheimers Dis. 2019; 68:295–309. https://doi.org/10.3233/JAD-180720 PMID:30741680

65. Benton A, Hamsher K, Sivan A. Multilingual aphasia examination. Iowa City, IA: AJA Associates. 2nd Ed. Associates A, editor. Iowa City, IA: University of Iowa; 1989.

66. Core TR. A Language and Environment for Statistical Computing. Vienna, Austria; 2016.

SUPPLEMENTARY MATERIAL

Supplementary Tables

Table S1. List of neuropsychological tests grouped by cognitive functions.

Cognitive functions - Neuropsychological test (according to Lezak's (2012) classification)	Most prominent cognitive component
Global cognition and clinical variables	
Mini-Mental State Examination (MMSE) [1]	
Blessed Dementia Rating Scale (BDRS) [2]	
Functional Activity Questionnaire (FAQ) [3]	
Geriatric Depression Scale, Spanish version (GDS-VE) [4]	
Beck's Depression Inventory (BDI) [5]	
WAIS-III Information subtest (WAIS-III) [6]	
Processing Speed and Attention	
Choice Reaction Time – Motor and Reaction times (PC-Vienna System) [7]	cognitive and motor reaction times
Paced Auditory Serial Addition Test (PASAT) [8]	maintenance of attention
Trail Making Test-A (TMT-A) [9]	focusing/visual tracking
Color Trails Test - Part 1 (CTT-1) [10]	focusing/visual tracking
Visuospatial, visuoconstructive, and visuoperceptive functions	
Judgment of Line Orientation Test (JLOT, H form) [11]	visuospatial abilities
Facial Recognition Test (FRT-brief version) [11]	visuoperceptive abilities
Block Design – standard and extended version (WAIS-III) [6]	3-D visuoconstructive abilities
Visual Reproduction Test, Copy subtest (VRT, WMS- III) [12]	2-D visuoconstructive abilities
Visual Reproduction Test, Visual Discrimination subtest (VRT, WMS- III) [12]	visuoperceptive abilities
Working Memory, Executive Functions, and Premotor Functions	
Color Trail Test - Part 2 (CTT-2) [10]	mental flexibility/ executive control
Digit Span – forward and backwards (WMS-III) [12]	working memory: amplitude (forward) and manipulation (backward)
Visuospatial Span – forward and backwards (WMS-III) [12]	working memory: amplitude (forward) and manipulation (backward)
Stroop Test [13]	Sheet 1 Words and Sheet 2 Colors: processing speed Sheet 3 Inhibition: executive function
Phonemic fluency – FAS (COWAT) [14]	
Semantic fluency – animals [14]	
Action fluency – verbs [15]	
Luria's Premotor Functions (Luria's) [16]	hand alternative movements and motor coordination
Learning and Memory	
Logical Memory (LM, WMS-III) [12]	Immediate recall, delayed recall, and recognition subtests (verbal)
Test de Aprendizaje Verbal España-Complutense (TAVEC, Spanish version of the California Verbal Learning Test (CVLT)) [17]	Immediate recall, delayed recall, and recognition subtests (verbal)
Visual Reproduction Test, (VRT, WMS-III) [12]	Immediate recall, delayed recall, and recognition subtests (visual)
Language	
Boston Naming Test (BNT) [18]	lexical access by visual confrontation

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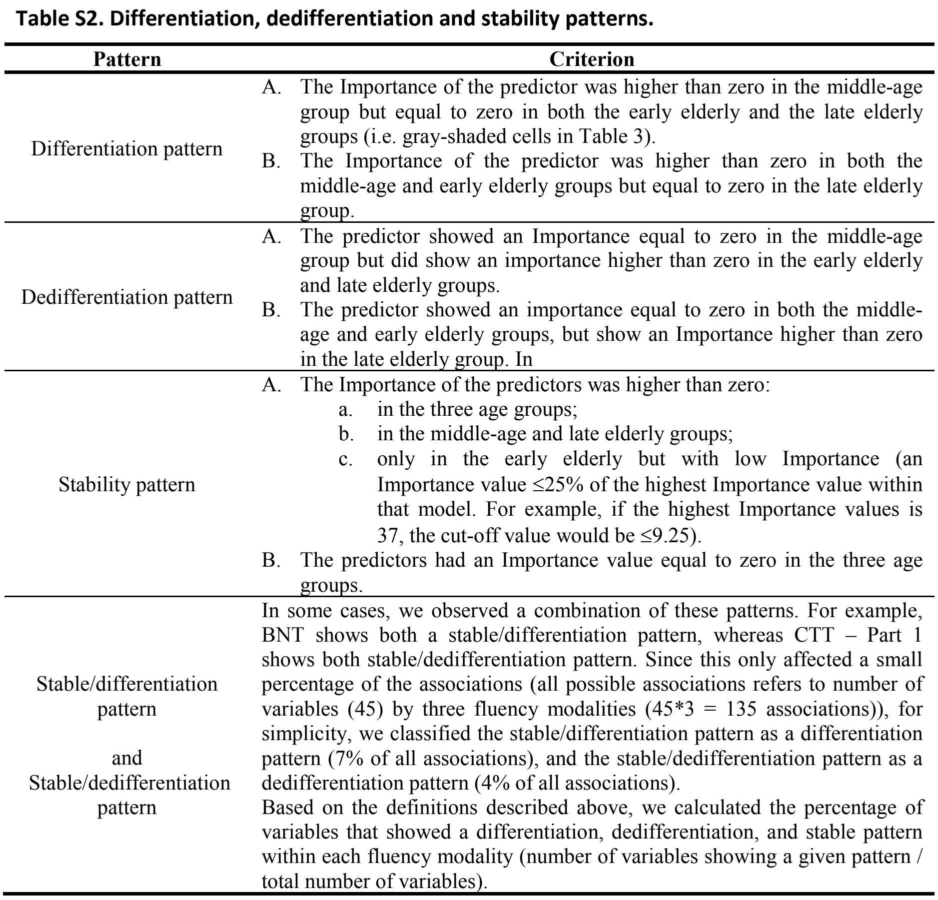

Table S2. Differentiation, dedifferentiation and stability patterns.

Pattern	Criterion
Differentiation pattern	A. The Importance of the predictor was higher than zero in the middle-age group but equal to zero in both the early elderly and the late elderly groups (i.e. gray-shaded cells in Table 3). B. The Importance of the predictor was higher than zero in both the middle-age and early elderly groups but equal to zero in the late elderly group.
Dedifferentiation pattern	A. The predictor showed an Importance equal to zero in the middle-age group but did show an importance higher than zero in the early elderly and late elderly groups. B. The predictor showed an importance equal to zero in both the middle-age and early elderly groups, but show an Importance higher than zero in the late elderly group. In
Stability pattern	A. The Importance of the predictors was higher than zero: a. in the three age groups; b. in the middle-age and late elderly groups; c. only in the early elderly but with low Importance (an Importance value ≤25% of the highest Importance value within that model. For example, if the highest Importance values is 37, the cut-off value would be ≤9.25). B. The predictors had an Importance value equal to zero in the three age groups.
Stable/differentiation pattern and Stable/dedifferentiation pattern	In some cases, we observed a combination of these patterns. For example, BNT shows both a stable/differentiation pattern, whereas CTT – Part 1 shows both stable/dedifferentiation pattern. Since this only affected a small percentage of the associations (all possible associations refers to number of variables (45) by three fluency modalities (45*3 = 135 associations)), for simplicity, we classified the stable/differentiation pattern as a differentiation pattern (7% of all associations), and the stable/dedifferentiation pattern as a dedifferentiation pattern (4% of all associations). Based on the definitions described above, we calculated the percentage of variables that showed a differentiation, dedifferentiation, and stable pattern within each fluency modality (number of variables showing a given pattern / total number of variables).

Supplementary References

1. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12: 189–98.
2. Blessed G, Tomlinso BE, Roth M. Association between quantitative measures of dementia and of senile change in cerebral grey matter of elderly subjects. Br J Psychiatry. 1968; 114: 797–811.
3. Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37: 323–9.
4. Martínez de la Iglesia J, Onís Vilches MC, Dueñas depresión en mayores de 65 años: adaptación y validación. Medifam. 2002; 12: 620–30.
5. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4: 561–71.
6. Wechsler D. Wechsler Adult Intelligence Scale - Administration and Scoring Manual. 3rd ed. San Antonio, Texas: The Psychological Corporation; 1997.
7. Schuhfried G. Vienna Reaction Unit. Manual. Vienna: Schuhfried Ges.m.b.H.; 1992.
8. Gronwall DMA. Paced Auditory Serial-Addition Task: A Measure of Recovery from Concussion. Percept Mot Skills. 1977; 44: 367-73

9. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958; 8: 271–6.

10. D'Elia L, Saltz P. Color Trail 1 and 2. Odessa, FL: Psychological Assessment Resources; 1989.

11. Benton A, Hamsher S, Varney O, Spreen N. Contributions to neuropsychological assessment: A clinical manual. Press. OU, editor. New York; 1983.

12. Wechsler D. Wechsler Memory Scale – Third Edition Technical Manual. 3rd ed. San Antonio, Texas: The Psychological Corporation; 1997.

13. Golden CJ. Stroop Colour and Word Test: A manual for clinical and experimental uses. Chicago, Illinois: Stoelting Company; 1978.

14. Benton A, Hamsher K, Sivan A. Multilingual aphasia examination. Iowa City, IA: AJA Associates. 2nd Ed. Associates A, editor. Iowa City, IA: University of Iowa; 1989.

15. Piatt AL, Fields JA, Paolo AM, Koller WC, Tröster AI. Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. J Clin Exp Neuropsychol. 1999; 21: 435–43.

16. Christensen A. Luria's neuropsychological investigation. 2nd ed. Copenhagen: Munksgaard; 1979.

17. Benedet M, Alejandre M. TAVEC: Test de Aprendizaje Verbal España-Complutense. Manual. Madrid: TEA ediciones; 1998.

18. Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. 2nd Ed. Philadelphia: Lea & Febiger; 1983.

STUDY II

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Research Paper

Cognitive reserve and network efficiency as compensatory mechanisms of the effect of aging on phonemic fluency

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ABSTRACT

Compensation in cognitive aging is a topic of recent interest. However, factors contributing to cognitive compensation in functions such as phonemic fluency (PF) are not completely understood. Using cross-sectional data, we investigated cognitive reserve (CR) and network efficiency in young (32-58 years) versus old (59-84 years) individuals with high versus low performance in PF. ANCOVA was used to investigate the interaction between CR, age, and performance in PF. Random forest and graph theory analyses were conducted to study the contribution of cognition to PF and efficiency measures, respectively. Higher CR increased performance in PF and reduced age-related differences in PF. A slightly higher number of cognitive functions contributed to performance in high CR groups. The networks were more integrated in high CR individuals, both in the older age and high-performance groups. The strength and segregation of the networks were decreased in high-performance groups with high CR. We conclude that PF decreases less with age in individuals with higher CR, possibly due to a greater capacity to recruit non-linguistic cognitive networks, and efficient use of language networks, thereby integrating information in a rapid way across less fragmented networks. High CR and network efficiency seem to be important factors for cognitive compensation.

INTRODUCTION

Language is essential for human communication. Although many cognitive functions decline with age, language is one of the few functions that can resist the onslaught of aging [1, 2]. An explanation for this is that language abilities are broadly distributed through different neural networks across the brain [3]. Comprehension, semantic abilities, and vocabulary remain rather stable or even improve with age [2, 4]. In contrast, verbal fluency and naming decline with age [5].

It has been suggested that brain functional reorganization is the mechanism through which cognitive performance is maintained with increasing age [6]. Compensation refers to the maintenance or enhancement of performance by recruiting brain areas or networks not normally used for a specific task, as a response to brain deterioration [7] or high cognitive demands [8]. From a cognitive perspective, compensation can be approached by investigating how different cognitive functions are associated with or contribute to language abilities [9]. In particular, performance in phonemic fluency has been associated with processing speed [10–12], attention [13, 14], lexical access [15], executive functions [14, 16–19], and memory [14, 20]. Due to the complexity of human cognition, an interesting approach is to investigate the contribution of different cognitive functions to verbal fluency by using multivariate methods for data analysis. We previously used the random forest multivariate method to investigate the contribution of 45 cognitive variables to phonemic fluency [9]. In younger individuals, lexical access, working memory, processing speed, and visuoconstructive abilities were the most contributing functions to performance in phonemic fluency. In older individuals, the same functions contributed to phonemic fluency but, interestingly, cognitive functions such as premotor and visuospatial abilities contributed to phonemic fluency as well. In that previous study, compensation was suggested as the mechanism possibly underlying the findings. However, further research is needed to elucidate the factors involved in these compensatory mechanisms.

Previous studies have linked compensatory mechanisms to the concepts of cognitive reserve (CR) and neural efficiency. CR is “the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult” [7]. People with higher CR produce more words in phonemic fluency [21–25]. Furthermore, people with higher CR have greater neural efficiency [26, 27]. Graph theory is a popular approach to compute and analyze different measures of efficiency. For instance, the measures of average strength, average global efficiency, and transitivity are commonly used to investigate the magnitude of the associations, network integration, and network segregation, respectively. Integration is the capacity of the brain to rapidly combine information from distributed brain regions [28]. Segregation is the biologically meaningful feature of the brain to enable highly specialized processing through densely interconnected communities of regions [29]. There are numerous studies investigating efficiency on neuroimaging data, both in normal aging [30] and neurodegenerative disorders [31, 32]. However, to our knowledge, only two studies investigated efficiency on cognitive data, and these investigated individuals with epilepsy and did not focus on compensatory mechanisms [33, 34]. Applying graph theory analysis on cognitive data may be useful to characterize compensatory mechanisms associated with cognitive reserve, which is indeed a cognitive construct.

In the current study, we sought to advance our understanding of factors contributing to cognitive compensation. The overall goal was to investigate how CR and efficiency levels contribute to phonemic fluency differently in people with high versus low fluency performance and in younger versus older individuals. Firstly, we investigated the effects of CR, performance level, and age on phonemic fluency. Secondly, we studied the contribution of other linguistic and non-linguistic cognitive functions to phonemic fluency. Thirdly, we compared efficiency measures of average strength, global efficiency, and transitivity in individuals with high and low performance in phonemic fluency. We hypothesized that older adults would perform worse than younger adults in verbal fluency, but this difference would be minimized by high CR levels and high efficiency of cognitive networks. In other words, high CR levels and network efficiency would help to maintain high performance in older adults, thus contributing to compensate for the negative effect of age.

RESULTS

To address the three aims of this study, we stratified the cohort into groups of CR, performance in phonemic fluency, and age as detailed in Figure 1. Table 1 shows the demographic characteristics and Supplementary Table 1 shows cognitive performance across the CR, performance, and age groups.

Regarding our first aim, the ANCOVA did not show any significant triple interaction among CR, performance, and age groups (p=0.084). However, the ANCOVA showed a significant interaction between CR and age groups ($F_{(3, 442)}=38.68$; $p<0.001$) (Figure 2A), and between CR and performance groups ($F_{(3, 442)}=10.34$; $p<0.01$) (Figure 2B). We elaborate on these two interactions in the next two sections, respectively.

High cognitive reserve reduces age-related differences in phonemic fluency

The significant interaction between CR and age revealed that the younger age (YA) group outperformed the older age (OA) group ($p<0.001$), but this difference was smaller in the high CR (highCR) group than in the low CR (lowCR) group (Figure 2A). Hence, higher CR reduces age-related differences.

To answer our second aim, four random forest regression models were performed separately within each group (YA+lowCR, OA+lowCR, YA+highCR, and OA+highCR) (Table 2A). For a description of the cognitive variables (predictors) included in the random forests and their abbreviation please see Table 3. In the OA+highCR group, the model explained 38% of the variance and 24 variables contributed to performance in phonemic fluency. The most important variables in predicting performance were Stroop (Colors and Inhibition) and BNT (Table 2A). In the YA+highCR group, the model explained 19% of the variance and 23 variables contributed to performance. The most important variables in predicting performance were Stroop (Colors) and Digit span backward. In the OA+lowCR, the model explained 19% of the variance and 18 variables contributed to performance. The most important variables in predicting performance were CTT-Part 1 and Stroop (Colors). In the YA+lowCR group, the model explained

24% of the variance and 22 variables contributed to performance. The most important variables in predicting performance were Stroop (Words) and Digit span backward. Hence, a slightly higher number of variables contribute to performance in the highCR groups, and the strength of this contribution is the greatest in OA+highCR individuals (as reflected by the % of variance). When entering sex as an extra predictor, these results were virtually the same (data not shown), demonstrating that sex does not have any confounding effect in these models.

In order to reduce the number of comparisons as part of our third aim, following the finding from the random forest models above, the OA+highCR group was compared against the OA+lowCR and YA+lowCR groups, across the graph measures. Because our interest was to understand why individuals achieve higher performance, all these comparisons were restricted to high performance groups. All these analyses were controlled for the effect of sex. There were no significant differences in the average strength of the OA+highCR group as compared to the OA+lowCR and YA+lowCR groups (p>0.05) (Figure 3). Global efficiency was increased in the OA+highCR group as compared to both OA+lowCR and YA+lowCR groups. There were no significant differences in transitivity (p>0.05).

The effect of high cognitive reserve is amplified in high-performance individuals, independently of their age

The significant interaction between CR and performance group revealed that the difference between low phonemic fluency (lowPF) and high phonemic fluency (highPF) performance groups was greater in the highCR group than in the lowCR group (Figure 1B). Hence, higher CR increases performance on phonemic fluency, irrespectively of the age (the partial effect of age was controlled for in the ANCOVA).

To achieve our second aim, four random forest regression models were performed separately within each group (lowPF+lowCR, highPF+lowCR, lowPF+highCR, and highPF+highCR) (Table 2B). In the highPF+highCR group, the model explained 13% of the variance and 13 variables contributed to performance in phonemic fluency (Table 2B). The most important variables in predicting performance were Stroop (Inhibition) and Visual reproduction (Immediate). In the lowPF+highCR group, the model explained 17% of the variance and 19 variables contributed to performance. The most important variables in predicting performance were Visual reproduction (False positives) and JLOT. In the highPF+lowCR group, the model explained 45% of the variance and 32 variables contributed to performance. The most important variables in predicting performance were Stroop (Words) and Luria's motor coordination. In the lowPF+lowCR group, the model explained 50% of the variance and 28 variables contributed to performance. The most important variables in predicting performance were Stroop (Colors) and CTT-Part 1. Hence, highCR groups need a lower number of contributing variables in order to achieve high performance, and the strength of this contribution is the lowest in highPF+highCR individuals (as reflected by

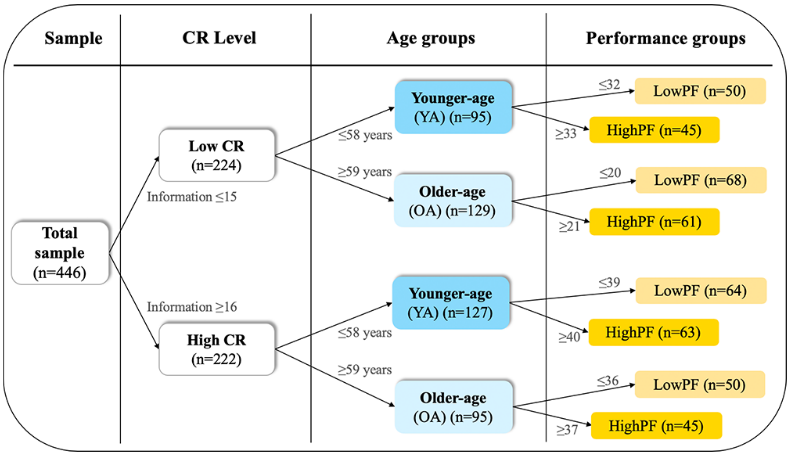


Figure 1. Cohort stratification. The cohort was stratified into groups of CR, performance in phonemic fluency, and age, using the median values for these variables as shown next to the arrows in the Figure. CR, cognitive reserve. PF, phonemic fluency performance.

Table 1. Demographic characteristics and performance in phonemic fluency by study group.

	Low Cognitive Reserve (lowCR)				High Cognitive Reserve (highCR)				
	Younger-age (YA, n=95)		Older-age (OA, n=129)		Younger-age (YA, n=127)		Older-age (OA, n=95)		
	Low performance (lowPF)	High performance (highPF)	Low performance (lowPF)	High performance (highPF)	Low performance (lowPF)	High performance (highPF)	Low performance (lowPF)	High performance (highPF)	
	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	M(SD)/ count(%)	*p*-value
n	50	45	68	61	64	63	50	45	
Age, years (min-max)	46.9 (5.7) (37-58) ^{b,c,f,g}	46.6 (5.7) (34-58) ^{b,c,f,g}	68.8 (4.8) (59-79) ^{d,e}	69.3 (4.6) (60-80) ^{d,e,g}	48.0 (5.7) (38-58) ^{f,g}	48.5 (6.0) (32-58) ^{f,g}	67.8 (5.3) (59-79)	66.1 (6.0) (59-84)	p<0.001
Sex (female, count (%))	39 (78%) $^{d-g}$	31 (69%) ^{d,f}	42 (62%) ^{d}	41 (67%) ^{d,f}	22 (34%)	30 (48%)	19 (38%)	21 (47%)	p<0.001
Education level									p<0.001
Illiteracy	0	0	5	2	0	0	0	0	
Unfinished primary studies	1	2	27	20	0	0	3	0	
Completed primary studies	38	26	28	29	14	8	12	7	
Completed secondary studies	8	12	7	8	26	18	15	7	
University studies	3	5	1	2	24	37	20	30	
WAIS-III Information	10.1 (3.1) $^{d-g}$	11.3 (2.8) $^{b,d-g}$	8.8 (2.8) $^{d-g}$	9.7 (3.2) $^{d-g}$	20.4 (2.8)	21.4 (3.1)	19.8 (2.8)	20.9 (3.0)	p<0.001
MMSE	28,7 (1,2) ^{b}	28,9 (1,4) ^{b,c}	27,1 (1,6) $^{c-e}$	27,9 (1,4)	29,2 (0,9)	29,3 (0,9)	28,5 (1,5)	28,7 (1,1)	p<0.001
(min-max)	25 - 30	25 - 30	24 - 30	25 - 30	27 - 30	27 - 30	25 - 30	25 - 30	
Phonemic fluency	23.9 (4.9) $^{a-g}$	38.9 (6.2) $^{b-g}$	14.2 (4.2) $^{c-g}$	27.6 (5.2) ^{d,e,g}	32.0 (5.3) $^{e-g}$	48.8 (8.3) ^{f}	27.8 (6.7) ^{g}	47.1 (8.4)	p<0.001
(min-max)	(14-32)	(33-67)	(5-20)	(21-43)	(16-39)	(40-71)	(12-36)	(37-74)	

MMSE: Mini-Mental State Examination; WAIS-III: Wechsler Adult Intelligence Scale; Third edition. ^{a} Significantly different from YA+highPF+lowCR, ^{b} Significantly different from OA+lowPF+lowCR, ^{c} Significantly different from OA+highPF+lowCR, ^{d} Significantly different from YA+lowPF+highCR, ^{e} Significantly different from YA+highPF+highCR, ^{f} Significantly different from OA+lowPF+highCR, ^{g} Significantly different from OA+highPF+highCR.

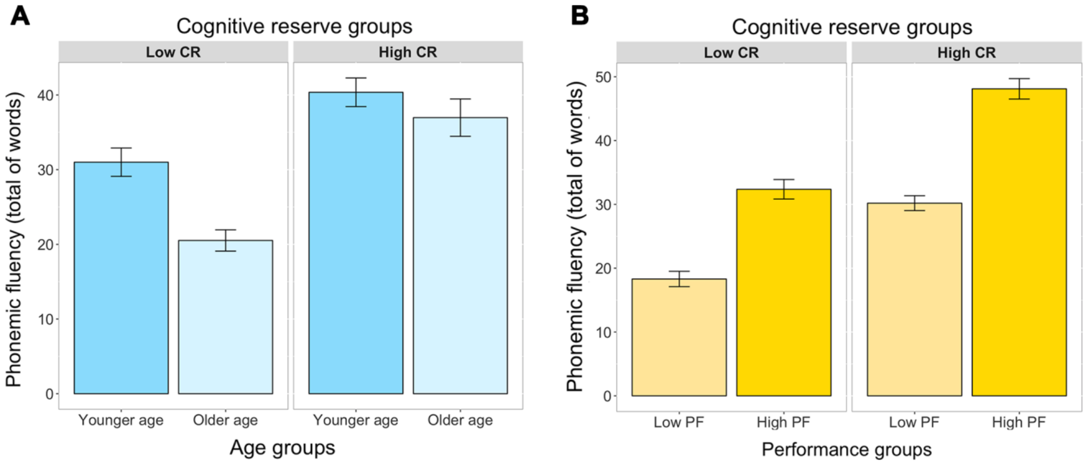


Figure 2. Interaction between CR levels and age (**A**), and between CR levels and performance groups (**B**), in the prediction of phonemic fluency (ANCOVA). Bars represent the mean of words produced and the jack-knifes represent the 95% confidence intervals. Panel **A** represents the interaction between CR and age. Panel **B** represents the interaction between CR and performance groups. CR, cognitive reserve; YA, younger age; OA, older age; Low PF, low phonemic fluency performance; High PF, high phonemic fluency performance.

Table 2. Contribution of cognitive variables to phonemic fluency (random forest regression models).

	A) CR by age groups.				B) CR by performance groups.			
	Low CR (n=224)		High CR (n=222)		Low CR (n=224)		High CR (n=222)	
	YA	OA	YA	OA	LowPF	HighPF	LowPF	HighPF
Group size	95	129	127	95	118	106	114	108
Explained variance	24%	19%	19%	38%	50%	45%	17%	13%
Predictors								
BNT	8	15	5	25	20	14	13	
PCV - Decision time				7		6		
PCV - Motor time	6				1	16	17	
PASAT			4					4
STROOP Words	26	9	13	25	13	31	17	14
STROOP Colors	7	27	26	37	29	19	10	
STROOP Inhibition	10	9	13	31	13	15	4	31
TMT A	11	10	6	12	12	23	17	17
CTT - Part 1		31	4	9	35	24		
CTT - Part 2	6	20			28	23		
FRT				4	13		1	3
JLOT - First half		1			5		18	4
JLOT - Second half		6						
Digit Span forward	6	4	8	14		4		
Digit Span backward	20		22	4	1		4	1
Spatial Span forward	2		8			10		6
Spatial Span backward			5		4	4		
LM A - Immediate	2					4		
LM B1 - Immediate	2		7	11	16	4		
LM B2 - Immediate			7	9		10		
LM A - Delay						2		
LM B - Delay			5	12		7		2
LM A - Recognition	8	2				1		
LM B - Recognition			9	4		4	4	
TAVEC 1st trial			4	7				
TAVEC Learning				18	2			
TAVEC Short delay				5	6		4	
TAVEC Short delay-Clues							6	
TAVEC Long delay				4	5	13		
TAVEC Long delay-Clues				1	3	4	9	
TAVEC Intrusions Delay	3							
TAVEC Intrusions Delay-Clues	1	7	2		2	4	4	
TAVEC Perseverations	9		8			2		
TAVEC Recog. Correct	2							
TAVEC Recog. False Positive		9		6	2			
VR I – Total score		5	6		14	6		22
VR II – Total score		12		4	22	11		11
VR-Copying	2			4	3	13	3	
VR Total Recog.		7	1	5	7	4	8	
VR False Positive		3			7		22	
VR Visual discrimination	6	2	3			2		
Luria's HAM Right	2		13		11	12		4
Luria's HAM Left	2		2	3	21	19	9	4
Luria's - Coordination					25	29		
Block Design WAIS	4				10	24	8	
Total of variables contributing to the prediction of PF	**22**	**18**	**23**	**24**	**28**	**32**	**19**	**13**
Importance	Not important	<10		10 - 19		20 - 29	>30	

Panel A) Cognitive reserve by age groups. Panel B) Cognitive reserve by performance groups. The explained variance is the total cumulative variance explained by all the predictors in the model. The numbers inside the cells in the "Predictors" area show the importance of each variable in predicting the outcome variable, where the higher the value the higher the importance. The importance is calculated as the relative error in the prediction when a given predictor is excluded from the model. Blank cells denote that these variables were not important in the model. Total variables: the total number of variables that are important to predicting phonemic fluency. CR: cognitive reserve; YA: younger age; OA: older age; LowPF: low phonemic fluency performance; HighPF: high phonemic fluency performance; BNT: Boston Naming Test (spontaneous responses); PCV: PC-Vienna System; PASAT: Paced Auditory Serial Addition Test; TMT A: Trial Making Test A; CTT: Color Trails Test; FRT: Facial Recognition Test; JLOT: Judgment of Line Orientation Test; LM: Logical Memory; VR: Visual Reproduction Test; Luria's HAM: Luria's Premotor Functions; Hand Alternative Movements; PF: phonemic fluency.

Table 3. List of predictors (random forest) / nodes (graph analysis), neuropsychological tests, and cognitive components.

Predictors/Nodes	Neuropsychological test	Cognitive component
BNT	Boston Naming Test (BNT) [65]	Lexical access by visual confrontation
PCV - Decision time*		
PCV - Motor time*		
PASAT*	Paced Auditory Serial Addition Test (PASAT) [67]	Maintenance of attention
STROOP Words		Sheet 1 Words: processing speed
STROOP Colors		Sheet 2 Colors: processing speed
STROOP Inhibition		Sheet 3 Inhibition: executive function
TMT A	Trail Making Test-A (TMT-A) [69]	Focusing/visual tracking
CTT - Part 1	Color Trails Test - Part 1 (CTT-1) [70]	Focusing/visual tracking
CTT - Part 2	Color Trail Test - Part 2 (CTT-2) [70]	Mental flexibility/executive control
FRT	Facial Recognition Test (FRT-brief version) [71]	Visuoperceptive abilities
JLOT - First half		
JLOT - Second half		
Digit Span forward		Working memory: amplitude
Digit Span backward		Working memory: manipulation
Spatial Span forward		Working memory: amplitude
Spatial Span backward		Working memory: manipulation
LM A – Immediate		Immediate recall (verbal)
LM B1 - Immediate		Immediate recall (verbal)
LM B2 - Immediate		Immediate recall (verbal)
LM A - Delay		Delayed recall (verbal)
LM B - Delay		Delayed recall (verbal)
LM A - Recognition		Recognition subtests (verbal)
LM B - Recognition		Recognition subtests (verbal)
TAVEC 1st trial		Immediate recall (verbal)
TAVEC Learning		Immediate recall (verbal)
TAVEC Short delay		delayed recall (verbal)
TAVEC Short delay-Clues		delayed recall (verbal)
TAVEC Long delay		delayed recall (verbal)
TAVEC Long delay-Clues		delayed recall (verbal)
TAVEC Intrusions Delay		
TAVEC Intrusions Delay-Clues		
TAVEC Perseverations*		
TAVEC Recog. Correct		recognition subtests (verbal)
TAVEC Recog. False Positive		
VR I – Total score		Immediate recall (visual)
VR II – Total score		Delayed recall (visual)
VR-Copying		2-D visuoconstructive abilities
VR Total Recog.		Recognition subtests (visual)
VR False Positive		
VR Visual discrimination*		Visuoperceptive abilities
Luria's HAM Right		hand alternative movements
Luria's HAM Left		hand alternative movements
Luria's - Coordination		motor coordination
Block Design WAIS	Block Design – standard and extended version (WAIS-III) [60]	3-D visuoconstructive abilities

* Nodes excluded from graph analysis. PCV - Decision time and PCV - Motor time were combined as PCV – Total time and included as a single node for graph analysis.

the % of variance). When entering sex as an extra predictor, these results were virtually the same, demonstrating that sex does not have any confounding effect in these models.

As in the previous section, we reduced the number of comparisons as part of our third aim by performing follow-up analyses guided by the findings from the random forest models above. We were interested in comparing the highPF+highCR group against the lowPF+highCR and highPF+lowCR groups, as well as in comparing the highPF+lowCR group against the lowPF+lowCR group, across graph measures (Figure 4). All these analyses were controlled for the effect of sex. The highPF+highCR group showed lower average strength than the highPF+lowCR (*p*<0.001), but comparable average strength than the lowPF+highCR group (*p*=0.246). Global efficiency was increased in highPF+highCR as compared with the highPF+lowCR group, and tended to be increased when compared to the lowPF+highCR group. Transitivity was decreased in the highPF+highCR group as compared with both highPF+lowCR and lowPF+highCR groups. When comparing the highPF+lowCR and lowPF+lowCR groups, we did not observe any significant difference in the average strength, global efficiency, or transitivity.

DISCUSSION

The overall goal of this study was to investigate how CR and efficiency levels contribute to phonemic fluency differently in people with high versus low performance and in younger versus older individuals. We found that older adults performed worse than younger adults in verbal fluency, but this difference was minimized by high CR levels and high efficiency of cognitive networks.

High cognitive reserve reduces age-related differences in phonemic fluency

Older participants produced fewer words than younger participants, a finding that has repeatedly been reported in previous studies [35, 36]. This reduction in words with increasing age was buffered by high CR levels. High CR levels have been associated with higher performance in phonemic fluency [21–25]. In the current study, we demonstrate that high CR levels minimize the differences in phonemic fluency between younger and older individuals. Indeed, CR is commonly considered as a factor that contributes to maintaining cognitive performance in the presence of increasing age or pathology [7]. We conducted several random forest and graph theory analyses to further understand some of the mechanisms underlying this finding.

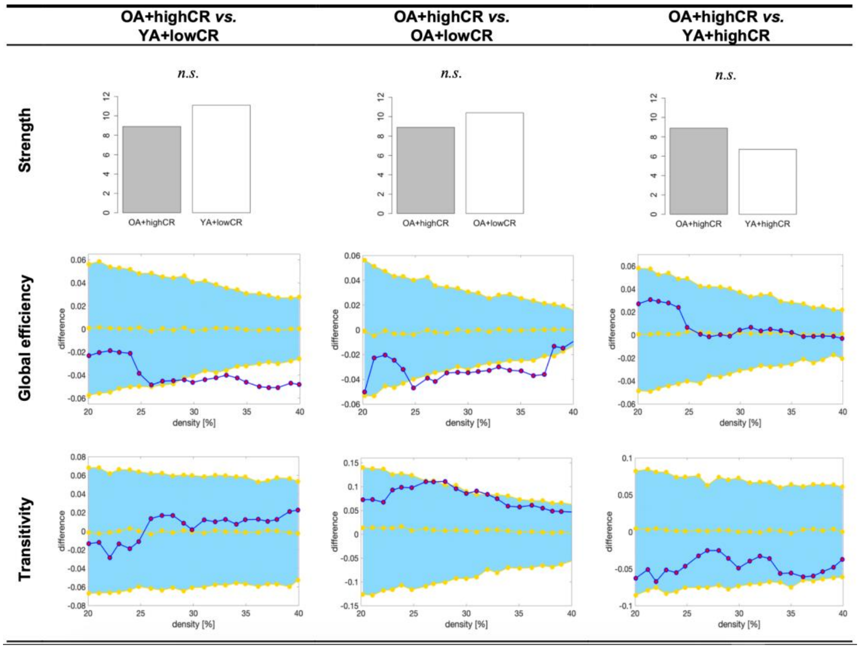


Figure 3. Graph results for CR by age groups. For global efficiency and transitivity measures, network densities are displayed on the x-axis from min = 20% to max = 40%, in steps of 1%. Between-group differences in the efficiency measures are displayed on the y-axis. Between-group differences are significant when the red circles fall out of the blue-shaded area. CR, cognitive reserve. HP, high performance. OA+highCR, older age participants with high CR. YA+lowCR, younger age participants with low CR. OA+lowCR, older age participants with low CR. YA+highCR, younger age participants with high CR. *n.s.*, non significant results (p>0.05).

The random forest analyses showed that the contribution of various cognitive functions to performance in phonemic fluency differed depending on CR levels and the age. Despite the number of variables contributing to performance was largely the same in high and low CR groups, the strength of this contribution was clearly the greatest in older individuals with high CR levels. Processing speed contributed to better performance in all the four groups. Executive functions substantially increased performance and it was an important contributor to performance in all groups except for older adults with low CR. Interestingly, lexical access contributed to performance only in older adults with high CR levels. The contribution of processing speed, executive functions, and lexical access to phonemic fluency, and better executive functions in individuals with higher CR has been shown in previous studies [12, 14, 16, 18, 19]. The novelty of our study is the signature contribution to verbal fluency associated with CR and age, i.e. lexical access and a strong contribution of executive functions allow for older individuals with high CR to maintain their high performance on verbal fluency.

The graph theory analyses showed that the average global efficiency was increased in older participants with high CR levels. Previous studies have reported higher average global efficiency in individuals with high CR, using graph analysis on neuroimaging data [37, 38]. The novelty in our study is that we report data on the effect of CR on global efficiency stratifying by age, using graph analysis on cognitive data. When calculated on cognitive data, the global efficiency reflects whether cognitive variables correlate with each other in short paths, with higher average global efficiency values reflecting the capacity to quickly distribute information via short paths [39]. In the context of our study, high average global efficiency reflects how the performance in non-fluency tasks contributes to performance in phonemic fluency. Since high CR levels allowed for older individuals to perform better, it is possible that high CR enabled them to rapidly access the lexical storage to retrieve more words (BNT had a high contribution in these individuals), perhaps supported by better executive capacities such as using better strategies, inhibiting distractions, etc. (executive functions also had a high

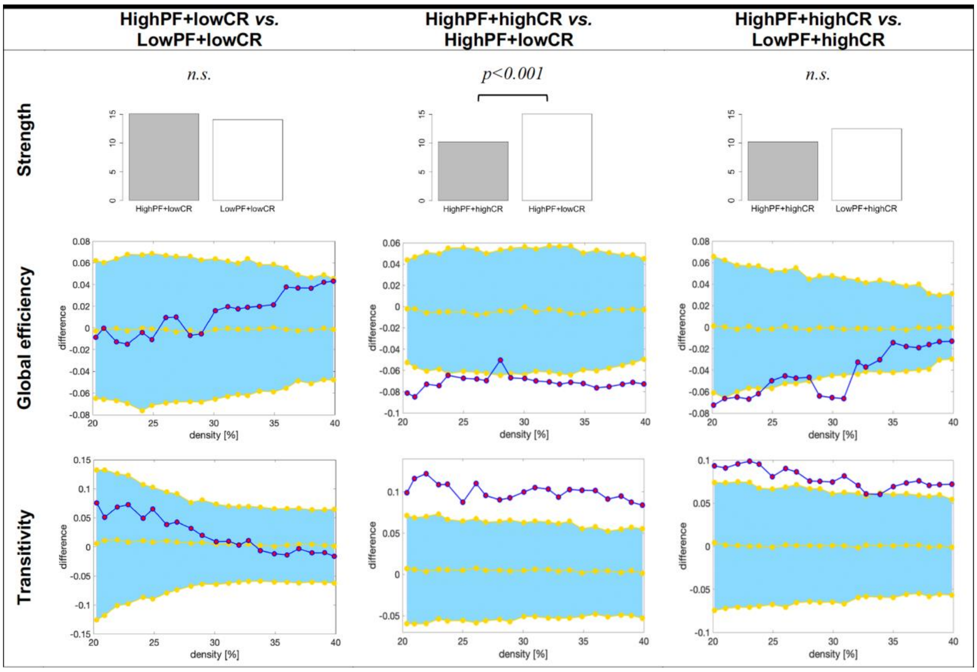


Figure 4. Graph results for CR by performance groups. For global efficiency and transitivity measures, network densities are displayed on the x-axis from min = 20% to max = 40%, in steps of 1%. Between-group differences in the efficiency measures are displayed on the y-axis. Between-group differences are significant when the red circles fall out of the blue-shaded area. CR, cognitive reserve. HighPF+lowCR, high performance participants with low CR. LowPF+lowCR, low performance participants with low CR. HighPF+highCR, high performance participants with high CR. LowPF+highCR, low performance participants with high CR. *n.s.*, non significant results (p>0.05).

contribution in these individuals). On the contrary, our graph analyses did not show any differences in the average strength or transitivity measures when analyzing CR by age groups. In cognitive networks, the average strength represents the overall magnitude of the correlations among the cognitive measures included in the network. The transitivity reflects how well the nodes are connected to nearby nodes forming cliques, that is, whether our cognitive data tend to be organized into communities of cognitive measures that are strongly correlated to nearby cognitive measures, but weakly correlated to cognitive measures belonging to other communities. Hence, our findings suggest that CR and age groups differ in integration features (global efficiency), rather than in segregation features (transitivity) or the magnitude of the associations among cognitive functions (average strength). Altogether, our findings show that despite largely the same number of cognitive functions contributing to fluency performance in older individuals with high CR levels, they predict a much higher variance of verbal fluency as compared to the other groups. This finding emerges in the absence of significant differences in the average strength or segregation of cognitive networks. It is possible that the healthy nature of our cohort highlights the role of integration features in cognitive compensation, rather than segregation features, which are likely to be related to the reorganization of brain networks seen in neurodegenerative diseases as a consequence of more overt brain pathology [31, 32].

The effect of high cognitive reserve is amplified in high-performance individuals, independently of their age

An interesting finding of our study is that although individuals with high CR levels performed better, we observed variability with some individuals achieving very high performance and some achieving lower performance. Again, we conducted several random forest and graph theory analyses to further understand the mechanisms underlying this finding.

The random forest analyses showed that individuals with high CR levels need a lower number of contributing variables in order to achieve high performance. Among these, individuals with high CR who achieved lower performance needed a greater number of contributing variables, which contributed to predicting a higher variance of verbal fluency. This finding may suggest that fluency performance partly relies on the number of contributing variables but, also, on the efficiency of the cognitive networks (a lower number of contributing variables and lower predicted variance would suggest more efficient cognitive networks). This is supported by the graph analysis showing that individuals with high CR but low performance had less efficient networks as reflected by higher transitivity values, i.e., a more fragmented cognitive network. Individuals with low CR levels also relied more on processing speed, independently of their age, which we saw in the previous section that it is not the most efficient contribution to verbal fluency. Interestingly, individuals with high CR levels recruited networks involved in visual abilities (immediate visual memory and JLOT). The difference between high CR individuals who achieved very high performance and those who achieved lower performance is that the former recruited executive functions, as already discussed in the previous section, and is also supported by the analyses discussed in this section. These findings may suggest the recruitment of right fronto-parietal networks, which are contralateral to the language networks of the left hemisphere.

Again, these results highlight the lower efficiency of cognitive networks of individuals performing worse, amplified by lower CR levels. The graph theory analyses showed that the signature feature of high CR levels is the lower average strength, and the signature feature of individuals performing better is the less segregated (or fragmented) cognitive networks (lower transitivity). We interpret the finding on lower average strength as a highly efficient network in high CR individuals who are able to achieve high performance by involving the right fronto-parietal network and integrating information in a very efficient manner. In contrast, low CR individuals are much less efficient and their verbal fluency strongly relies on processing speed.

In our previous study, we showed that the contribution of cognitive functions to verbal fluency differed across age groups, and we suggested that this could be due to compensatory processes [9]. In the current study, we confirm that hypothesis and show that high CR and efficiency levels could be at the base of compensatory mechanisms to maintain performance in phonemic fluency with increasing age. Compensation refers to the maintenance or enhancement of performance by recruiting brain areas or networks not normally used for a specific task, as a response to brain deterioration [7] or high cognitive demands [8]. Our findings suggest that older individuals with higher CR levels may have been able to compensate for the negative effect of aging by recruiting brain networks underlying lexical access and using executive networks in a more efficient way. The greater contribution of executive functions in older individuals with high CR levels is supported by the "scaffolding theory of aging and cognition" (STAC) [40]. The STAC theory suggests increased frontal activation with age as a compensatory response. The possible involvement of the right fronto-parietal network discussed above suggests a greater participation of the right hemisphere with increasing age, as postulated by the "hemispheric asymmetry reduction in older adults" (HAROLD) model [41]. The HAROLD model suggests the recruitment of contralateral brain areas as a compensatory mechanism [42, 43]. Recruitment of right fronto-parietal and lexical access networks are also supported by the "Compensation-Related Utilization of Neural Circuits Hypothesis" (CRUNCH), which postulates that new brain regions are recruited, leading to the functional reorganization of the brain.

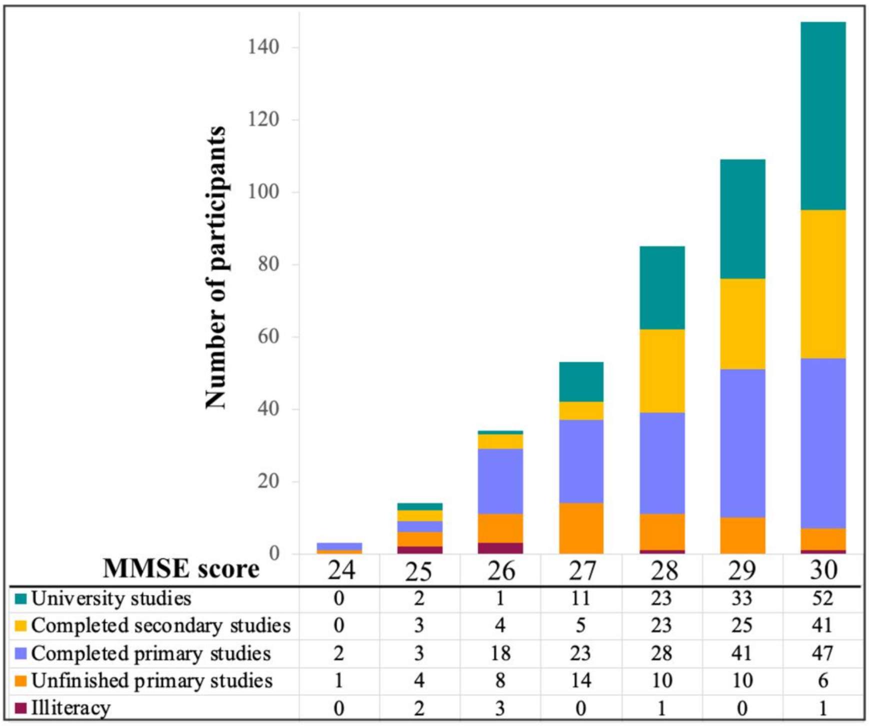
This study has some limitations. We analyzed cross-sectional data. Therefore, our age-related differences may partially be explained by cohort effects. Nonetheless, multivariate analysis methods such as random forest maximize the covariance between the predictors and the outcome variable, being less vulnerable to confounders such as cohort effects [5]. Also, we are currently collecting follow-up data so that our cross-sectional findings can be substantiated in a longitudinal design in our future studies. The literature on graph theory analysis on cognitive data is very limited, and our current study is one of the few published so far. We demonstrate that graph theory shows great potential to deepen the previous cognitive findings obtained using univariate and other multivariate methods. Another consideration is that performance in verbal fluency varies according to the type of stimulus [44]. We used the F-A-S version of phonemic fluency, and our current findings should be replicated using other stimulus such as the P-M-R version, which is also common and validated in the Spanish language [45]. Further, there is currently an ongoing discussion on whether cognitive reserve and compensation occur through a universal brain network or their effects are task-dependent [46]. Our studies are approaching this question by investigating the language function, because language is one of the few functions that can resist the onslaught of aging [1, 2], hence, possibly reflecting the result of successful compensatory mechanisms. While comprehension, semantic abilities, and vocabulary remain rather stable or even improve with age [2, 4], verbal fluency and naming decline with age [5]. We have repeatedly seen in our cohort that naming is the language component most vulnerable to age [5, 47–49]. Therefore, we focused on verbal fluency, which also provides the opportunity to compare different fluency modalities. In our previous study, we demonstrated that phonemic fluency, semantic fluency, and action fluency have different age-dependent trajectories [9]. In particular, performance in semantic fluency and action fluency showed a prominent decline with age, while phonemic fluency showed some decline with age but also showed signs of stability [9]. These characteristics make phonemic fluency an ideal cognitive function to investigate compensatory processes. However, future studies should extend our current analyses to other language components such as naming, as well as to other non-language cognitive functions. Applying random forest and graph theory analyses to different cognitive functions in the future will help to substantiate our current findings, contributing to answer the question on a universal network *vs.* task-dependent networks underpinning cognitive reserve and compensation. Also, extending our cognitive network analyses to neuroimaging measures is warranted in the future in order to better understand the neural correlates of our current findings. We used group-level analysis in graph measures (low *vs.* high fluency performance). This is the most common form of studying network topology. However, future work should explore methods that can generate individual networks [50], enabling correlations between network measures and performance in verbal fluency, age, and CR as a continuous variable. We used the WAIS-III Information subtest and our findings should be tested using other proxies of cognitive reserve. A final consideration is that we excluded individuals with mild cognitive impairment (MCI) using a comprehensive neuropsychological protocol and appropriate normative data. However, we showed that some individuals had MMSE scores in the range 24-26, mostly related to low education. These data can be seen in Figure 5. Including these individuals increases the generalization of our findings to the whole range of education, also including the strata with lowest education. Nonetheless, we acknowledge that other studies using samples with higher education have excluded individuals with an MMSE score below 27 [51].

In conclusion, the current study provides the data to unveil some of the cognitive mechanisms underlying cognitive compensation of verbal fluency during aging. Phonemic fluency decreases less with age in those individuals who have higher CR levels. Our data suggest that the factors determining this finding may include greater capacity to recruit contralateral fronto-parietal networks, and efficiently use ipsilateral language networks, integrating information in a rapid way across less fragmented networks. In terms of functions, these networks are represented by executive/visual abilities and access to the lexicon, respectively. All these abilities can be trained, and CR levels (performance in WAIS-III Information) can also be increased through reading, writing, and learning new materials throughout the lifespan [52]. Hence, this study shows some possibilities for cognitive stimulation of healthy individuals and possibly, also individuals with cognitive impairment. Further, our current results may help to improve clinical interpretation of performance in verbal fluency, as well as serve as an example for future studies on other cognitive functions.

MATERIALS AND METHODS

Participants

A total of 446 participants were selected from the GENIC-database (Group of Neuropsychological Studies of the Canary Islands) [5], with ages between 32 and 84 years, and a balanced distribution of sex across age (54.9% females). All participants were assessed with a comprehensive neuropsychological protocol, applied by an experienced neuropsychologist. Afterwards, for each participant, cognitive profile and diagnosis were established at consensus by at least two qualified clinical neuropsychologists, using pertinent age-, sex-, and education-adjusted normative data. The diagnostic procedure consisted on a two-step process: Firstly, we excluded individuals with dementia based on the Blessed Dementia Scale (BDRS [53]) cut point of ≥4, the Functional Activity Questionnaire (FAQ, [54]) cut point of >5, and the Mini-Mental State Examination (MMSE, [55]) score cut point of <24. Secondly, for the specific purposes of this study, we further excluded individuals with MCI based on Winblad's et al. criteria [56], as applied on our comprehensive neuropsychological protocol. Inclusion criteria for the current study were: (1) normal cognitive performance in comprehensive neuropsychological assessment (2) no neurologic, psychiatric or systemic diseases; and (3) no history of substance abuse. An exception was made for the BDRS. Although the BDRS scale cut-off for abnormality is frequently established at ≥4 points [53, 57], the 'changes in personality, interests and drive' subscale may influence the BDRS total score and does not necessarily reflect functional impairment. With the aim of excluding only individuals with functional impairment, we included those participants with total BDRS scores ≥4 (n=24) if: a) 70% or higher percentage of the BDRS total score resulted from the 'changes in personality, interests and drive' subscale; and b) if a score ≤1.5 was obtained in the other two subscales ('changes in performance of everyday activities' and 'changes in habits'). The same procedure has been used in previous studies [5, 9, 58]. Hence, all the individuals in this study are cognitively normal. The current study was approved by the ethics committee of the University of La Laguna (Spain), and all participants gave their written informed consent.



MMSE score	24	25	26	27	28	29	30
■ University studies	0	2	1	11	23	33	52
■ Completed secondary studies	0	3	4	5	23	25	41
■ Completed primary studies	2	3	18	23	28	41	47
■ Unfinished primary studies	1	4	8	14	10	10	6
■ Illiteracy	0	2	3	0	1	0	1

Figure 5. MMSE scores by education level. MMSE: Mini-Mental State Examination.

Neuropsychological assessment and cognitive reserve

The neuropsychological protocol includes tests of language, processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, and visuoconstructive, visuoperceptive and visuospatial functions (Table 3). Among all these tests, the test of phonemic verbal fluency is of special relevance to the current study. Phonemic verbal fluency was assessed with the Controlled Oral Word Association Test (COWAT) [59]. Participants had to recall words that begin with the letters F, A, and S, taking one minute on each of the letters. Proper nouns, numbers, and derived words were scored as intrusion errors. A total score (F+A+S) was calculated as the number of correct words produced, excluding intrusions and perseverations (repetitions of correct words). The other neuropsychological tests and cognitive variables used in this study are listed in Table 3.

Following previous studies [49, 52], the WAIS-III Information subtest [60], a measure of premorbid IQ, was used as an indicator of cognitive reserve. Among several reserve proxies, WAIS-III Information showed the greatest compensation capacity of the effect of cortical thinning on cognition [52]. Scores in WAIS-III information range from 0 to 28, with higher values reflecting greater capacity.

Network construction and graph analysis

The cognitive variables detailed in Table 3 were selected as nodes for network construction. Performance in these cognitive measures was corrected for the effect of sex using multiple linear regression, and the resulting residual values were used to substitute the raw values for network analysis [61]. As detailed in Table 1, the variables PCV - Decision time and PCV - Motor time were replaced with PCV - Total time as a single node for network analyses. The edges between the nodes were calculated through group-specific association matrices of Pearson correlation coefficients from each pair of nodes (Figure 6, please see Supplementary Figures 1–8 for

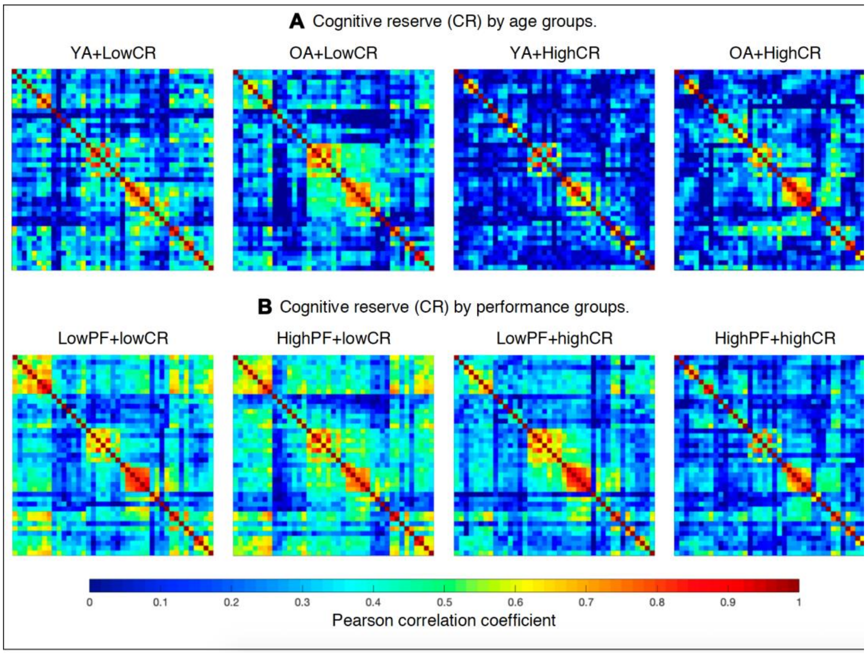


Figure 6. Weighted correlation matrices (See Supplementary Figures 1–8 for matrices with larger size and labeled regions). (**A**) Cognitive reserve by age groups: YA+LowCR, younger age group with low CR; OA+LowCR, older age group with low CR; YA+HighCR, younger age group with high CR; OA+HighCR, older age group with high CR. (**B**) Cognitive reserve by performance groups: LowPF+lowCR, low performance group with low CR; HighPF+lowCR, high performance group with low CR; LowPF+highCR, low performance group with high CR; HighPF+highCR, high performance group with high CR. Rows and columns correspond to the correlations between cognitive measures. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.

matrices with larger size and labeled regions). The matrices were binarized by thresholding the correlation coefficients at a range of network densities (min = 20% to max = 40%, in steps of 1%). Both self-connections and negative correlations were excluded. Network topologies were compared across this range, making sure that random topologies and disconnected networks were excluded from the analysis. For this reason, the PASAT, TAVEC Perseverations, and VR Visual discrimination variables listed in Table 3 were excluded, because they were not correlated with the other cognitive variables. Once the networks were constructed, different global measures were calculated: the *average global efficiency* (a measure of integration) and *the transitivity* (a measure of segregation) measures were calculated from the binary networks across the different densities, and the *average strength* was calculated from the weighted network (before binarization). The *average strength* is given by the sum of the weights of all edges connected to a node. In a cognitive network, the average strength represents the overall magnitude of correlations among cognitive measures in the network [28]. The *average global efficiency* is the average inverse shortest path length between a node and the rest of the network, which in contrast to the characteristic path length, can be meaningfully computed on disconnected networks [28]. The average global efficiency measures how efficiently information is exchanged throughout the network [62]. In a cognitive network, the average global efficiency represents whether the performance in non-fluency tasks contributes to performance in phonemic fluency through short paths of correlations. The *transitivity* refers to the fraction of a node's neighbors that are also neighbors of each other in the whole network, normalized by the whole network. It reflects how well the nodes are connected to nearby nodes forming cliques. In a cognitive network, the transitivity reflects whether our cognitive data tend to be organized into communities of cognitive measures that are strongly correlated to nearby cognitive measures, but weakly correlated to cognitive measures belonging to other communities.

Statistical analysis

Statistical analyses were performed using the R programming environment [63] and BRAPH (http://braph.org, [64]). We stratified the cohort into groups of CR, performance in phonemic fluency, and age, using the median values of these variables as detailed in Figure 1. We addressed our first aim by testing for the effects of CR level, performance level, and age over phonemic fluency using a factorial analysis of covariance (ANCOVA), including sex as a covariate. We addressed our second aim by using random forest regression analyses to investigate the multivariate association between the measure of phonemic fluency and the 45 cognitive variables detailed in Table 3. In random forest models, the contribution of the predictors in the models is reported as *Imp* (for *Importance*), which reflects the relative error in the prediction when a predictor is excluded from the model. *Imp* values higher than zero denote that a given variable contributes to the prediction of the outcome. The larger the *Imp* value, the greater the contribution. *Imp* values do not have an upper limit and they can rather be interpreted by considering the obtained values in relation to the variable yielding the highest *Imp* value in the model. Our third aim was addressed by comparing the graph measures of average strength, global efficiency, and transitivity across the CR, performance, and age groups.

Two percent of the values was missing across the 45 cognitive variables and were thus imputed. ANCOVA, random forest, and graph analyses were performed on the imputed dataset. For the demographic variables, ANOVA was used for both continuous and dichotomous (dummy) variables and the Chi-square test for categorical variables. P-values in all *post-hoc* analyses were adjusted with the Hochberg's correction for multiple comparisons. Significant differences were considered when $p \leq 0.05$ (two-tailed). Between-group comparisons of graph measures were conducted through 1000 nonparametric permutations over a range of network densities (min = 20% to max = 40%, in steps of 1%). The 95% confidence intervals of each distribution were used as critical values for testing the null hypothesis at $p \leq 0.05$ (two-tailed).

AUTHOR CONTRIBUTIONS

LGB contributed to the design of the study, organized the database, performed statistical analyses, contributed to the interpretation of the results, and wrote the first draft of the manuscript. JB contributed to the interpretation of the results, obtained funding, and co-supervised the study. DF contributed to the design of the study, wrote sections of the manuscript, contributed to the interpretation of the results, obtained funding, and supervised the study. All authors contributed to manuscript revision, and read and approved the submitted version.

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CONFLICTS OF INTEREST

All the authors declared no conflicts of interest relevant to the current study.

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REFERENCES

1. Schaie KW, Willis SL. Age difference patterns of psychometric intelligence in adulthood: generalizability within and across ability domains. Psychol Aging. 1993; 8:44–55. https://doi.org/10.1037//0882-7974.8.1.44 PMID:8461114
2. Ansado J, Marsolais Y, Methqal I, Alary F, Joanette Y. The adaptive aging brain: evidence from the preservation of communication abilities with age. Eur J Neurosci. 2013; 37:1887–95. https://doi.org/10.1111/ejn.12252 PMID:23773057
3. Gernsbacher MA, Kaschak MP. Neuroimaging studies of language production and comprehension. Annu Rev Psychol. 2003; 54:91–114. https://doi.org/10.1146/annurev.psych.54.101601.145128 PMID:12359916
4. Shafto MA, Tyler LK. Language in the aging brain: the network dynamics of cognitive decline and preservation. Science. 2014; 346:583–87. https://doi.org/10.1126/science.1254404 PMID:25359966
5. Machado A, Barroso J, Molina Y, Nieto A, Díaz-Flores L, Westman E, Ferreira D. Proposal for a hierarchical, multidimensional, and multivariate approach to investigate cognitive aging. Neurobiol Aging. 2018; 71:179–88. https://doi.org/10.1016/j.neurobiolaging.2018.07.017 PMID:30149289
6. Wingfield A, Grossman M. Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. J Neurophysiol. 2006; 96:2830–39. https://doi.org/10.1152/jn.00628.2006 PMID:17110737
7. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, Ewers M, Franzmeier N, Kempermann G, Kremen WS, Okonkwo O, Scarmeas N, Soldan A, et al, and the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimers Dement. 2020; 16:1305–11. https://doi.org/10.1016/j.jalz.2018.07.219 PMID:30222945
8. Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, Grady CL, Lindenberger U, Nyberg L, Park DC, Reuter-Lorenz PA, Rugg MD, Steffener J, Rajah MN. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. Nat Rev Neurosci. 2018; 19:701–710. https://doi.org/10.1038/s41583-018-0068-2 PMID:30305711
9. Gonzalez-Burgos L, Hernández-Cabrera JA, Westman E, Barroso J, Ferreira D. Cognitive compensatory mechanisms in normal aging: a study on verbal fluency and the contribution of other cognitive functions. Aging (Albany NY). 2019; 11:4090–106. https://doi.org/10.18632/aging.102040 PMID:31232698
10. Elgamal SA, Roy EA, Sharratt MT. Age and verbal fluency: the mediating effect of speed of processing. Can Geriatr J. 2011; 14:66–72. https://doi.org/10.5770/cgj.v14i3.17 PMID:23251316
11. Kavé G, Mashal N. Age-related differences in word-retrieval but not in meaning generation. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2012; 19:515–29. https://doi.org/10.1080/13825585.2011.638975 PMID:22221146
12. Kraan C, Stolwyk RJ, Testa R. The abilities associated with verbal fluency performance in a young, healthy

population are multifactorial and differ across fluency variants. Appl Neuropsychol Adult. 2013; 20:159–68. https://doi.org/10.1080/09084282.2012.670157 PMID:23383872

13. Troyer AK, Moscovitch M, Winocur G. Clustering and switching as two components of verbal fluency: evidence from younger and older healthy adults. Neuropsychology. 1997; 11:138–46. https://doi.org/10.1037//0894-4105.11.1.138 PMID:9055277
14. Ruff RM, Light RH, Parker SB, Levin HS. The psychological construct of word fluency. Brain Lang. 1997; 57:394–405. https://doi.org/10.1006/brln.1997.1755 PMID:9126423
15. Lezak M, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York, NY: Oxford University Press; 2004.
16. Stolwyk R, Bannirchelvam B, Kraan C, Simpson K. The cognitive abilities associated with verbal fluency task performance differ across fluency variants and age groups in healthy young and old adults. J Clin Exp Neuropsychol. 2015; 37:70–83. https://doi.org/10.1080/13803395.2014.988125 PMID:25658578
17. Rodríguez-Aranda C, Sundet K. The frontal hypothesis of cognitive aging: factor structure and age effects on four frontal tests among healthy individuals. J Genet Psychol. 2006; 167:269–87. https://doi.org/10.3200/GNTP.167.3.269-287 PMID:17278416
18. Bolla KI, Lindgren KN, Bonaccorsy C, Bleecker ML. Predictors of verbal fluency (FAS) in the healthy elderly. J Clin Psychol. 1990; 46:623–28. https://doi.org/10.1002/1097-4679(199009)46:5<623::aid-jclp2270460513>3.0.co;2-c PMID:2246370
19. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? predictors of verbal fluency performance in older adults. Front Psychol. 2014; 5:772. https://doi.org/10.3389/fpsyg.2014.00772 PMID:25101034
20. Ardila A, Galeano LM, Rosselli M. Toward a model of neuropsychological activity. Neuropsychol Rev. 1998; 8:171–90. https://doi.org/10.1023/a:1021618218943 PMID:9951709
21. Crossley M, D'Arcy C, Rawson NS. Letter and category fluency in community-dwelling Canadian seniors: a comparison of normal participants to those with dementia of the Alzheimer or vascular type. J Clin Exp Neuropsychol. 1997; 19:52–62. https://doi.org/10.1080/01688639708403836 PMID:9071641
22. Balduino E, de Melo BA, de Sousa Mota da Silva L, Martinelli JE, Cecato JF. The "SuperAgers" construct in clinical practice: neuropsychological assessment of illiterate and educated elderly. Int Psychogeriatr. 2020; 32:191–98. https://doi.org/10.1017/S1041610219001364 PMID:31556369
23. Roldán-Tapia L, García J, Cánovas R, León I. Cognitive reserve, age, and their relation to attentional and executive functions. Appl Neuropsychol Adult. 2012; 19:2–8. https://doi.org/10.1080/09084282.2011.595458 PMID:22385373
24. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999; 14:167–77. PMID:14590600
25. Auriacombe S, Fabrigoule C, Lafont S, Jacqmin-Gadda H, Dartigues JF. Letter and Category Fluency in Normal Elderly Participants: a Population-Based Study. Aging Neuropsychol Cogn. 2001; 8:98–108. https://doi.org/10.1076/anec.8.2.98.841
26. Bartrés-Faz D, Solé-Padullés C, Junqué C, Rami L, Bosch B, Bargalló N, Falcón C, Sánchez-Valle R, Molinuevo JL. Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders. Biol Psychol. 2009; 80:256–59. https://doi.org/10.1016/j.biopsycho.2008.10.005 PMID:19022337
27. Fernández-Cabello S, Valls-Pedret C, Schurz M, Vidal-Piñeiro D, Sala-Llonch R, Bargallo N, Ros E, Bartrés-Faz D. White matter hyperintensities and cognitive reserve during a working memory task: a functional magnetic resonance imaging study in cognitively normal older adults. Neurobiol Aging. 2016; 48:23–33. https://doi.org/10.1016/j.neurobiolaging.2016.08.008 PMID:27636672
28. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage. 2010; 52:1059–69. https://doi.org/10.1016/j.neuroimage.2009.10.003 PMID:19819337
29. Newman ME. Fast algorithm for detecting community structure in networks. Phys Rev E Stat Nonlin Soft Matter Phys. 2004; 69:066133. https://doi.org/10.1103/PhysRevE.69.066133 PMID:15244693
30. Meunier D, Stamatakis EA, Tyler LK. Age-related functional reorganization, structural changes, and

preserved cognition. Neurobiol Aging. 2014; 35:42–54. https://doi.org/10.1016/j.neurobiolaging.2013.07.003 PMID:23942392

31. Pereira JB, Aarsland D, Ginestet CE, Lebedev AV, Wahlund LO, Simmons A, Volpe G, Westman E. Aberrant cerebral network topology and mild cognitive impairment in early Parkinson's disease. Hum Brain Mapp. 2015; 36:2980–95. https://doi.org/10.1002/hbm.22822 PMID:25950288

32. Ferreira D, Pereira JB, Volpe G, Westman E. Subtypes of Alzheimer's disease display distinct network abnormalities extending beyond their pattern of brain atrophy. Front Neurol. 2019; 10:524. https://doi.org/10.3389/fneur.2019.00524 PMID:31191430

33. Kellermann TS, Bonilha L, Lin JJ, Hermann BP. Mapping the landscape of cognitive development in children with epilepsy. Cortex. 2015; 66:1–8. https://doi.org/10.1016/j.cortex.2015.02.001 PMID:25776901

34. Kellermann TS, Bonilha L, Eskandari R, Garcia-Ramos C, Lin JJ, Hermann BP. Mapping the neuropsychological profile of temporal lobe epilepsy using cognitive network topology and graph theory. Epilepsy Behav. 2016; 63:9–16. https://doi.org/10.1016/j.yebeh.2016.07.030 PMID:27532489

35. Rodriguez-Aranda C, Martinussen M. Age-related differences in performance of phonemic verbal fluency measured by controlled oral word association task (COWAT): a meta-analytic study. Dev Neuropsychol. 2006; 30:697–717. https://doi.org/10.1207/s15326942dn3002_3 PMID:16995832

36. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, Ferrie JE, Dugravot A. Timing of onset of cognitive decline: results from whitehall II prospective cohort study. BMJ. 2012; 344:d7622. https://doi.org/10.1136/bmj.d7622 PMID:22223828

37. Li Y, Liu Y, Li J, Qin W, Li K, Yu C, Jiang T. Brain anatomical network and intelligence. PLoS Comput Biol. 2009; 5:e1000395. https://doi.org/10.1371/journal.pcbi.1000395 PMID:19492086

38. van den Heuvel MP, Stam CJ, Kahn RS, Hulshoff Pol HE. Efficiency of functional brain networks and intellectual performance. J Neurosci. 2009; 29:7619–24. https://doi.org/10.1523/JNEUROSCI.1443-09.2009 PMID:19515930

39. Sporns O. Graph theory methods: applications in brain networks. Dialogues Clin Neurosci. 2018; 20:111–21. PMID:30250388

40. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol. 2009; 60:173–96. https://doi.org/10.1146/annurev.psych.59.103006.093656 PMID:19035823

41. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging. 2002; 17:85–100. https://doi.org/10.1037//0882-7974.17.1.85 PMID:11931290

42. Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol. 2005; 15:245–51. https://doi.org/10.1016/j.conb.2005.03.016 PMID:15831410

43. Reuter-Lorenz PA, Park DC. Human neuroscience and the aging mind: a new look at old problems. J Gerontol B Psychol Sci Soc Sci. 2010; 65:405–15. https://doi.org/10.1093/geronb/gbq035 PMID:20478901

44. Diaz M, Sailor K, Cheung D, Kuslansky G. Category size effects in semantic and letter fluency in Alzheimer's patients. Brain Lang. 2004; 89:108–14. https://doi.org/10.1016/S0093-934X(03)00307-9 PMID:15010242

45. Peña-Casanova J, Quiñones-Ubeda S, Gramunt-Fombuena N, Quintana-Aparicio M, Aguilar M, Badenes D, Cerulla N, Molinuevo JL, Ruiz E, Robles A, Barquero MS, Antúnez C, Martínez-Parra C, et al, and NEURONORMA Study Team. Spanish multicenter normative studies (NEURONORMA project): norms for verbal fluency tests. Arch Clin Neuropsychol. 2009; 24:395–411. https://doi.org/10.1093/arclin/acp042 PMID:19648583

46. Stern Y, Gazes Y, Razlighi Q, Steffener J, Habeck C. A task-invariant cognitive reserve network. Neuroimage. 2018; 178:36–45. https://doi.org/10.1016/j.neuroimage.2018.05.033 PMID:29772378

47. Ferreira D, Molina Y, Machado A, Westman E, Wahlund LO, Nieto A, Correia R, Junqué C, Díaz-Flores L, Barroso J. Cognitive decline is mediated by gray matter changes during middle age. Neurobiol Aging. 2014; 35:1086–94. https://doi.org/10.1016/j.neurobiolaging.2013.10.095 PMID:24239436

48. Ferreira D, Correia R, Nieto A, Machado A, Molina Y, Barroso J. Cognitive decline before the age of 50 can be detected with sensitive cognitive measures. Psicothema. 2015; 27:216–22. https://doi.org/10.7334/psicothema2014.192 PMID:26260927

49. Ferreira D, Machado A, Molina Y, Nieto A, Correia R, Westman E, Barroso J. Cognitive variability during middle-age: possible association with neurodegeneration and cognitive reserve. Front Aging Neurosci. 2017; 9:188. https://doi.org/10.3389/fnagi.2017.00188 PMID:28649200

50. Tijms BM, Seriès P, Willshaw DJ, Lawrie SM. Similarity-based extraction of individual networks from gray matter MRI scans. Cereb Cortex. 2012; 22:1530–41. https://doi.org/10.1093/cercor/bhr221 PMID:21878484

51. O'Bryant SE, Humphreys JD, Smith GE, Ivnik RJ, Graff-Radford NR, Petersen RC, Lucas JA. Detecting dementia with the mini-mental state examination in highly educated individuals. Arch Neurol. 2008; 65:963–67. https://doi.org/10.1001/archneur.65.7.963 PMID:18625866

52. Ferreira D, Bartrés-Faz D, Nygren L, Rundkvist LJ, Molina Y, Machado A, Junqué C, Barroso J, Westman E. Different reserve proxies confer overlapping and unique endurance to cortical thinning in healthy middle-aged adults. Behav Brain Res. 2016; 311:375–83. https://doi.org/10.1016/j.bbr.2016.05.061 PMID:27263072

53. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry. 1968; 114:797–811. https://doi.org/10.1192/bjp.114.512.797 PMID:5662937

54. Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S. Measurement of functional activities in older adults in the community. J Gerontol. 1982; 37:323–29. https://doi.org/10.1093/geronj/37.3.323 PMID:7069156

55. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–98. https://doi.org/10.1016/0022-3956(75)90026-6 PMID:1202204

56. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment. J Intern Med. 2004; 256:240–46. https://doi.org/10.1111/j.1365-2796.2004.01380.x PMID:15324367

57. Erkinjuntti T, Hokkanen L, Sulkava R, Palo J. The Blessed Dementia Scale as a screening test for dementia. Int J Geriatr Psychiatry. 1988; 3:267–73. https://doi.org/10.1002/gps.930030406

58. Cedres N, Machado A, Molina Y, Diaz-Galvan P, Hernández-Cabrera JA, Barroso J, Westman E, Ferreira D. Subjective cognitive decline below and above the age of 60: a multivariate study on neuroimaging, cognitive, clinical, and demographic measures. J Alzheimers Dis. 2019; 68:295–309. https://doi.org/10.3233/JAD-180720 PMID:30741680

59. Benton A, Hamsher K, Sivan A. Multilingual aphasia examination. Iowa City, IA: AJA Associates. 2nd Ed. Associates A, editor. Iowa City, IA: University of Iowa; 1989.

60. Wechsler D. Wechsler Adult Intelligence Scale - Administration and Scoring Manual (3rd ed.). San Antonio: The Psychological Corporation; 1997.

61. Voevodskaya O, Simmons A, Nordenskjöld R, Kullberg J, Ahlström H, Lind L, Wahlund LO, Larsson EM, Westman E, and Alzheimer's Disease Neuroimaging Initiative. The effects of intracranial volume adjustment approaches on multiple regional MRI volumes in healthy aging and Alzheimer's disease. Front Aging Neurosci. 2014; 6:264. https://doi.org/10.3389/fnagi.2014.00264 PMID:25339897

62. Latora V, Marchiori M. Efficient behavior of small-world networks. Phys Rev Lett. 2001; 87:198701. https://doi.org/10.1103/PhysRevLett.87.198701 PMID:11690461

63. Core TR. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2016.

64. Mijalkov M, Kakaei E, Pereira JB, Westman E, Volpe G, and Alzheimer's Disease Neuroimaging Initiative. BRAPH: a graph theory software for the analysis of brain connectivity. PLoS One. 2017; 12:e0178798. https://doi.org/10.1371/journal.pone.0178798 PMID:28763447

65. Kaplan EF, Goodglass H, Weintraub S. The Boston Naming Test. 2nd Ed. Philadelphia: Lea & Febiger; 1983.

66. Schuhfried G. Vienna Reaction Unit. Manual. Vienna: Schuhfried Ges.m.b.H.; 1992.

67. Gronwall DM. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills. 1977; 44:367–73. https://doi.org/10.2466/pms.1977.44.2.367 PMID:866038

68. Golden CJ. Stroop Colour and Word Test: A manual for clinical and experimental uses. Chicago, Illinois: Stoelting Company; 1978.

69. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958; 8:271–6. https://doi.org/10.2466/PMS.8.7.271-276

70. D'Elia L, Saltz P. Color Trail 1 and 2. Odessa, FL: Psychological Assessment Resources; 1989.

71. Benton A, Hamsher S, Varney O, Spreen N. Contributions to neuropsychological assessment: A clinical manual. Press. OU, editor. New York; 1983.

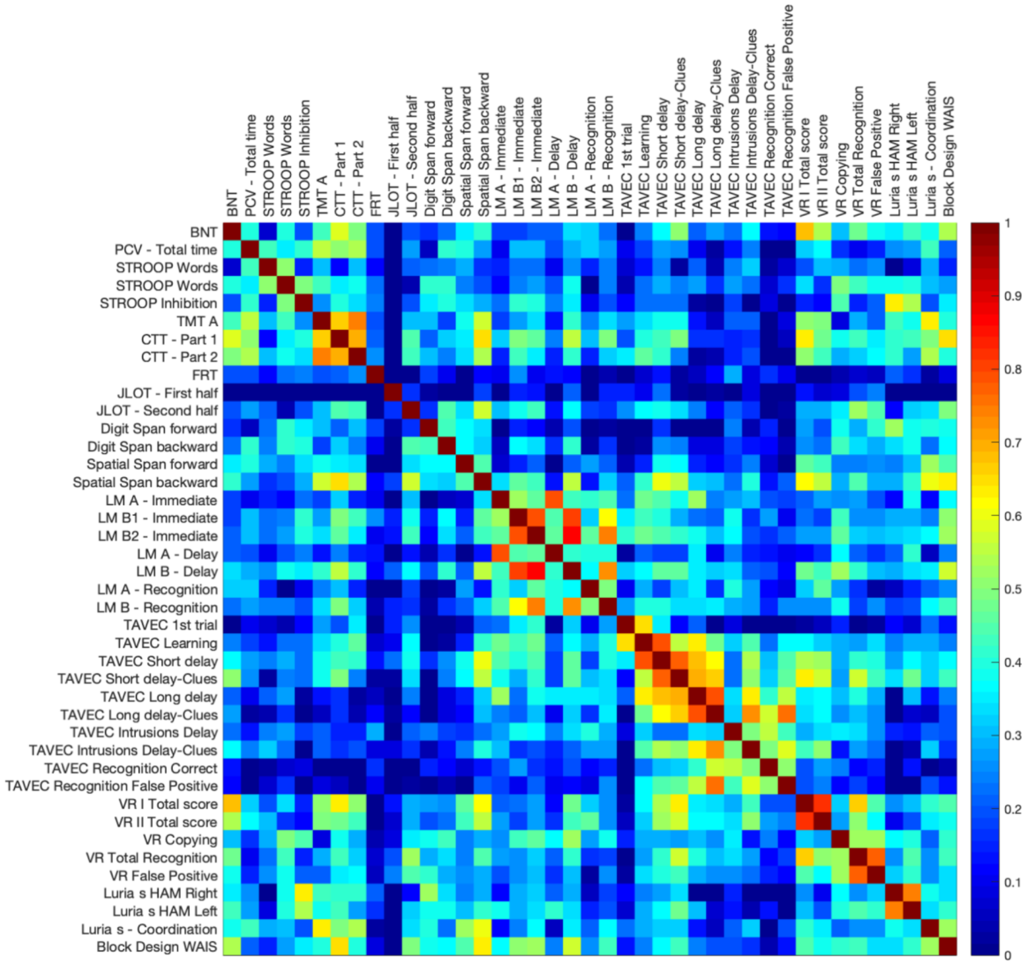
72. Wechsler D. Wechsler Memory Scale – Third Edition Technical Manual. 3rd ed. San Antonio, Texas: The Psychological Corporation; 1997. https://doi.org/10.1037/t49755-000

73. Benedet M, Alejandre M. TAVEC: Test de Aprendizaje Verbal España-Complutense. Manual. Madrid: TEA ediciones; 1998.

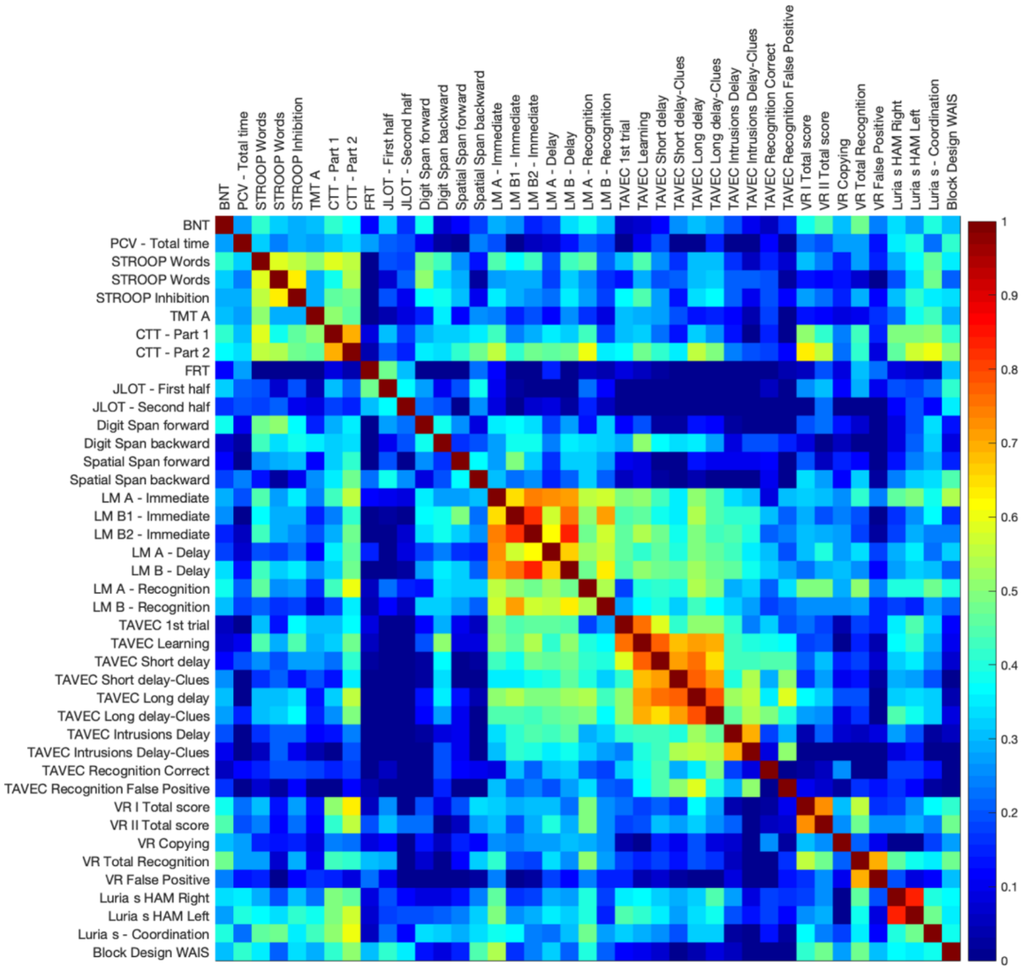
74. Christensen AL. Luria's neuropsychological investigation. 2nd Ed. Copenhagen: Munksgaard; 1979.

SUPPLEMENTARY MATERIALS

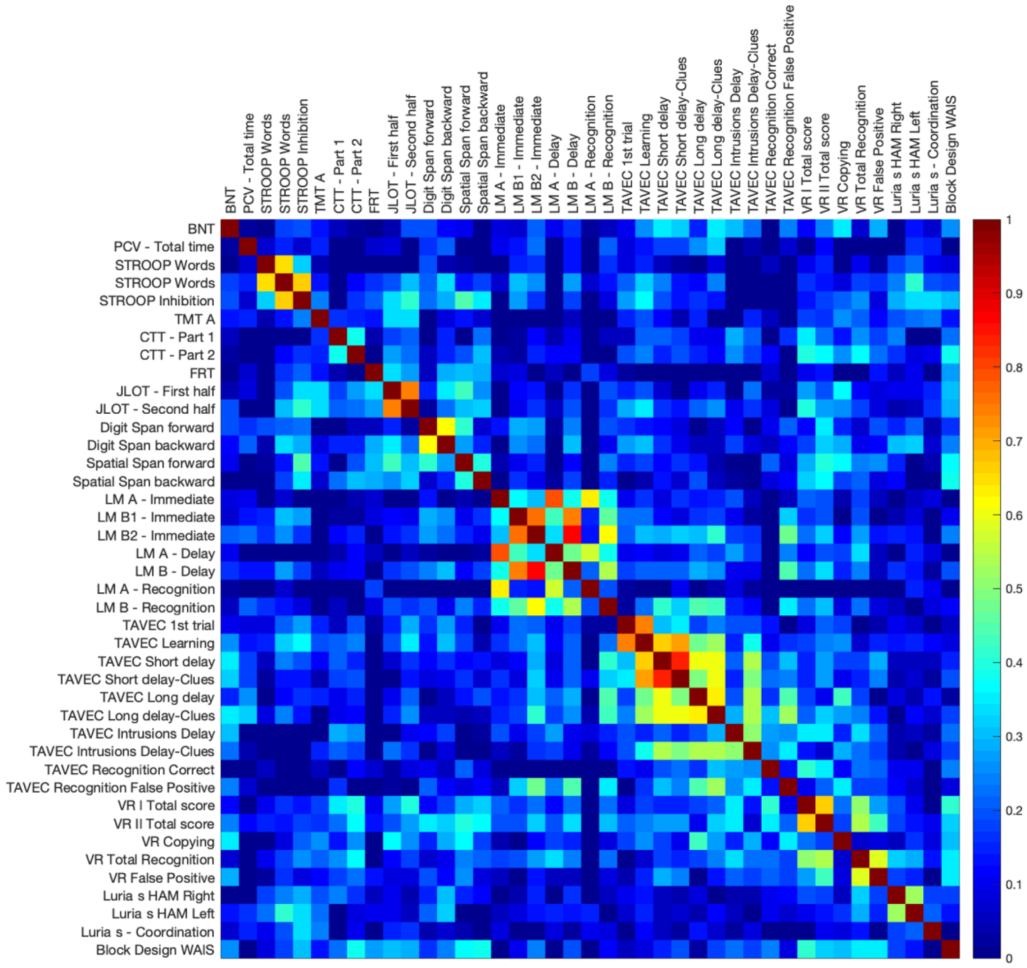
Supplementary Figures



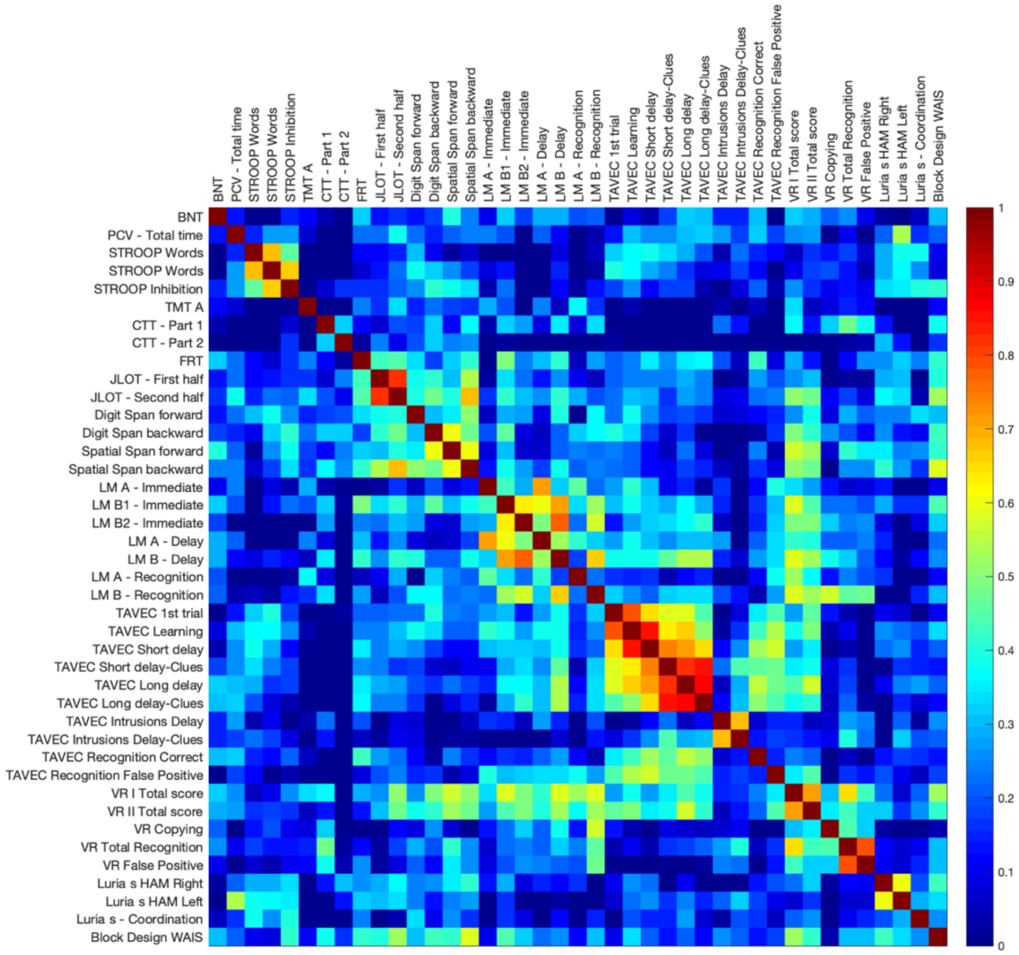
Supplementary Figure 1. Weighted correlation matrix (YA+lowCR). YA, younger age. lowCR, low cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



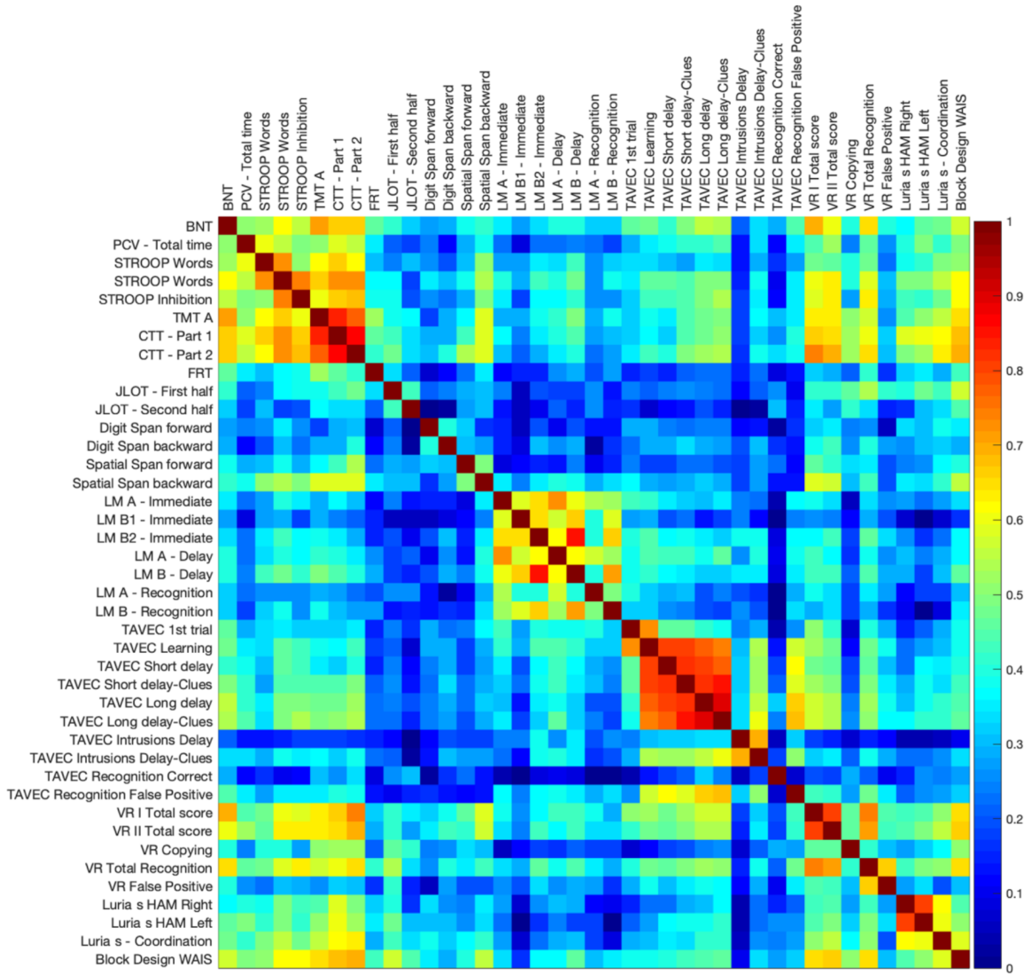
Supplementary Figure 2. Weighted correlation matrix (OA+lowCR). OA, older age. lowCR, low cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



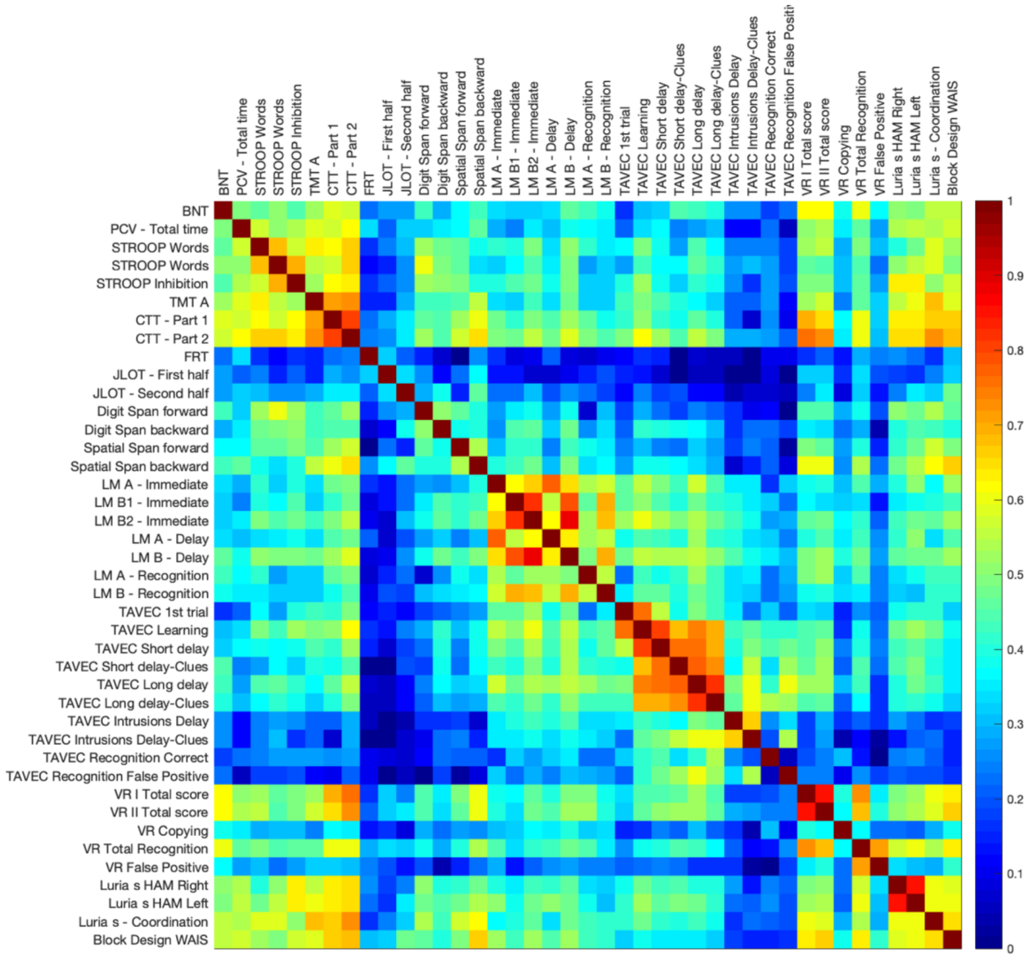
Supplementary Figure 3. Weighted correlation matrix (YA+highCR). YA, younger age. highCR, high cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



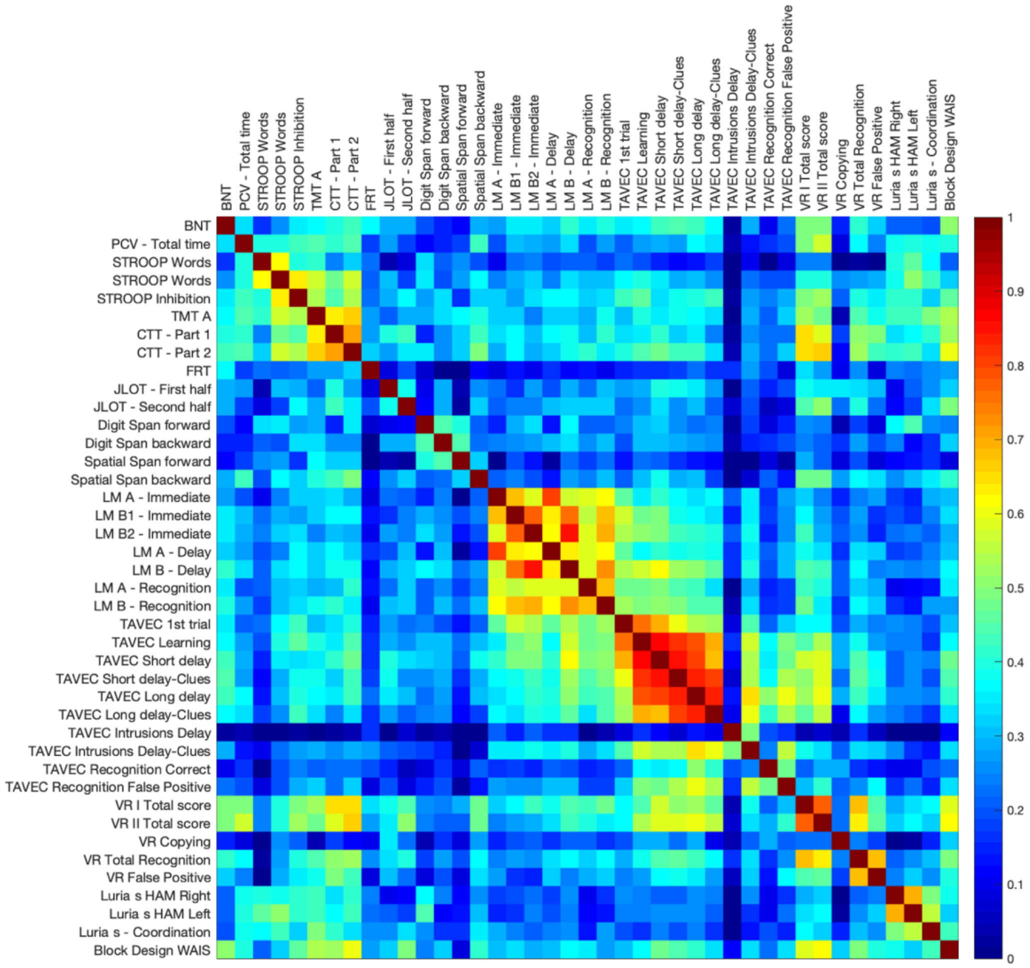
Supplementary Figure 4. Weighted correlation matrix (OA+highCR). OA, older age. highCR, high cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



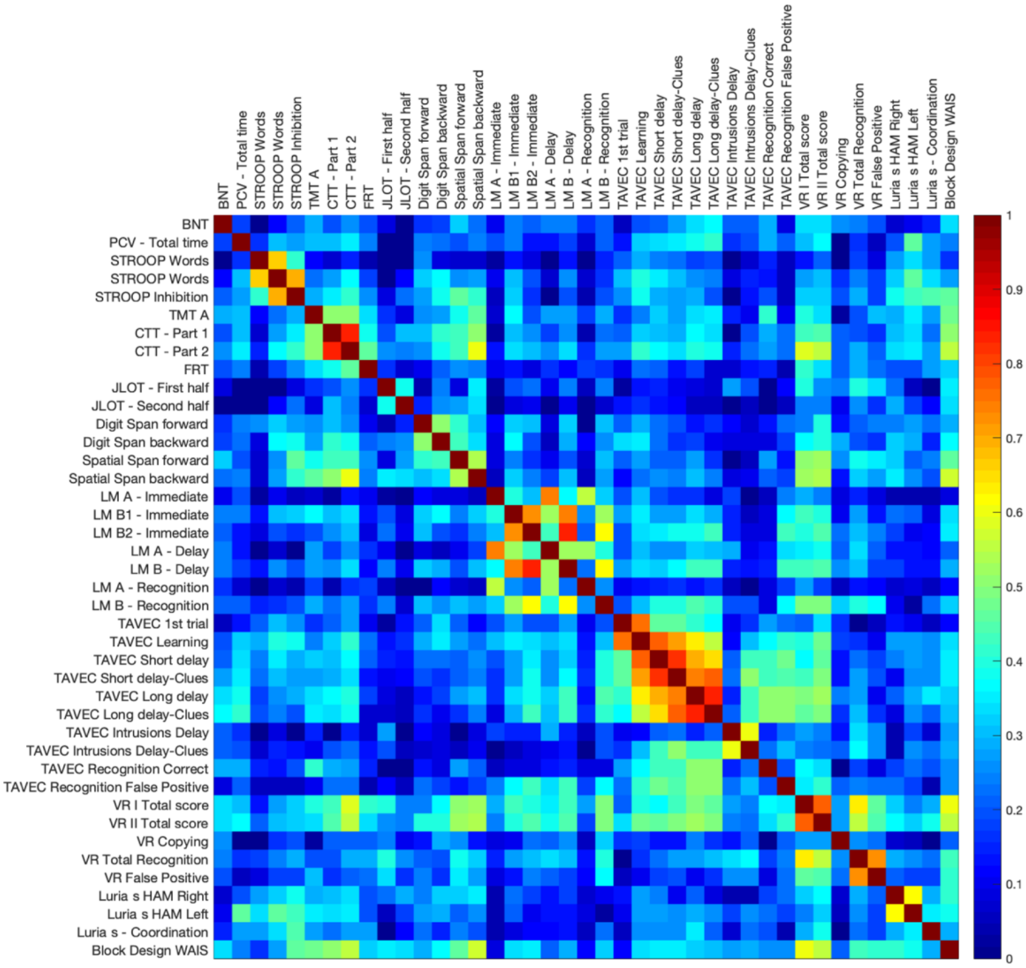
Supplementary Figure 5. Weighted correlation matrix (LowPF+lowCR). LowPF, low phonemic fluency performance. lowCR: low cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



Supplementary Figure 6. Weighted correlation matrix (HighPF+lowCR). HighPF, high phonemic fluency performance. lowCR: low cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



Supplementary Figure 7. Weighted correlation matrix (LowPF+highCR). LowPF, low phonemic fluency performance. highCR: high cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



Supplementary Figure 8. Weighted correlation matrix (HighPF+highCR), HighPF, high phonemic fluency performance. highCR: high cognitive reserve. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.

Supplementary Table

Supplementary Table 1. Performance in neuropsychological test by group.

		Low Cognitive Reserve (lowCR)				High Cognitive Reserve (highCR)			
		Younger-age (YA, n=95)		Older-age (OA, n=129)		Younger-age (YA, n=127)		Older-age (OA, n=95)	
		LowPF	**HighPF**	**LowPF**	**HighPF**	**LowPF**	**HighPF**	**LowPF**	**HighPF**
	n	**50**	**45**	**68**	**61**	**64**	**63**	**50**	**45**
Neuropsychological test									
	M	24.7	25.5	19.8	21.9	28.3	29.1	26.3	28.0
	SD	3.5	3.2	4.7	3.9	1.7	1.2	2.2	2.5
	M	462.4	463.3	576.9	563.1	459.8	456.3	554.5	491.6
	SD	64.3	67.7	121.7	109.9	61.7	61.6	85.9	82.2
	M	212.8	191.2	294.1	266.0	191.6	181.3	243.2	225.6
	SD	53.0	72.4	83.1	71.3	54.0	50.9	71.5	62.3
	M	58.7	58.8	58.1	58.4	59.0	59.6	58.6	59.5
	SD	1.5	2.6	3.6	2.1	1.6	1.0	2.2	1.9
	M	92.2	103.6	67.7	78.2	103.9	110.7	93.4	106.6
	SD	14.6	18.6	19.9	18.2	14.4	12.8	14.7	14.5
	M	64.7	70.9	45.8	53.5	69.1	76.3	57.6	68.7
	SD	10.6	12.7	10.8	14.2	10.5	11.1	11.3	10.6
	M	34.8	40.5	22.0	27.6	40.2	44.8	30.8	38.8
	SD	8.4	9.4	7.6	9.9	8.0	8.5	6.5	8.3
	M	42.3	36.8	83.9	62.9	33.4	30.0	48.7	41.3
	SD	13.5	12.6	34.6	18.1	8.9	8.3	15.8	16.5
	M	51.9	47.5	105.0	83.8	40.0	36.4	66.0	49.6
	SD	18.4	17.2	34.8	29.1	10.1	10.7	26.0	16.3
	M	117.5	96.0	210.5	172.7	91.3	85.4	135.9	115.7
	SD	46.2	37.2	57.4	50.9	24.7	22.5	42.8	33.4
	M	22.2	22.3	20.5	21.4	23.0	23.5	21.7	21.7
	SD	2.1	1.9	2.3	2.0	2.0	2.0	1.9	2.1
	M	12.6	12.9	10.6	11.6	13.9	13.9	13.2	13.4
	SD	2.0	2.3	3.0	2.8	1.2	1.2	1.7	1.4
	M	8.4	9.4	6.8	8.0	11.2	11.3	9.4	10.3
	SD	2.9	2.7	2.7	2.5	2.4	2.5	2.7	2.7
	M	6.9	8.1	5.8	6.3	8.2	9.5	7.3	8.8
	SD	1.7	1.9	1.3	1.5	1.9	2.2	2.0	2.0
	M	4.6	5.6	3.8	4.2	6.3	7.2	5.4	6.4
	SD	1.4	1.8	1.1	1.4	1.8	2.1	1.9	1.8
	M	7.3	8.3	6.2	6.6	8.1	8.6	7.5	7.5
	SD	1.6	1.5	1.5	1.7	2.0	1.9	1.7	2.0
	M	6.6	7.0	4.6	5.2	7.8	8.5	6.6	7.1
	SD	1.5	1.8	1.7	1.5	1.6	1.7	1.8	2.1
	M	11.0	11.7	8.8	9.7	14.1	14.3	12.1	13.7
	SD	3.0	3.1	3.4	3.8	3.6	3.1	3.9	3.4
	M	8.0	9.5	6.9	7.4	12.4	13.7	9.7	11.6
	SD	3.3	3.9	2.8	3.2	3.6	3.8	3.9	3.2
	M	12.4	14.7	9.9	10.8	16.9	18.4	13.9	16.8
	SD	4.2	4.3	3.3	4.0	3.8	3.6	3.7	3.6
	M	8.4	9.4	5.4	6.1	11.5	12.1	9.0	10.1
	SD	3.8	4.2	3.8	4.0	3.7	4.0	4.2	4.4
	M	11.1	13.2	7.8	9.1	15.7	17.2	12.2	15.8
	SD	4.2	4.3	3.9	4.3	4.0	3.8	3.9	3.6
	M	11.3	11.4	9.6	10.1	12.4	12.4	11.0	11.6
	SD	2.0	2.2	2.2	2.0	2.0	1.9	2.2	1.9
	M	12.0	12.7	10.9	11.5	13.9	14.2	12.5	13.4
	SD	2.0	1.6	2.2	1.9	1.3	1.2	2.0	1.4

TAVEC 1st trial, score	M	7.1	6.9	5.5	5.6	7.4	7.5	5.8	7.1
	SD	1.9	1.7	1.8	1.8	1.8	2.0	1.8	2.2
	M	54.9	56.5	44.8	48.1	58.0	60.2	49.0	54.3
	SD	8.0	7.9	11.2	9.7	8.3	7.8	9.9	10.5
	M	11.7	11.7	8.4	9.8	12.4	13.3	9.8	10.8
	SD	2.6	2.5	3.2	2.9	2.7	2.6	3.3	2.7
	M	13.0	12.9	9.8	11.0	13.6	14.2	11.4	11.9
	SD	2.2	2.6	3.4	2.6	2.4	2.1	3.1	2.6
	M	13.6	13.7	9.9	11.1	14.4	15.0	11.5	12.7
	SD	2.1	2.2	3.8	3.0	2.0	1.8	3.3	3.2
	M	14.6	14.4	11.1	12.4	15.0	15.2	12.5	13.4
	SD	1.6	1.9	3.7	2.7	1.5	1.3	3.1	3.1
	M	3.9	3.7	5.3	5.4	3.0	3.5	3.7	4.4
	SD	3.3	2.9	4.8	5.5	3.0	3.1	3.8	3.9
	M	1.8	1.8	4.4	3.2	0.9	1.1	2.4	1.9
	SD	1.9	2.1	3.7	3.4	1.2	1.2	2.5	1.9
	M	5.3	6.7	6.8	6.3	6.3	3.7	4.9	4.8
	SD	6.2	5.9	6.7	5.7	6.7	3.6	3.7	3.5
	M	15.5	15.7	14.8	15.0	15.7	15.8	15.2	15.4
	SD	0.7	0.5	2.0	1.6	0.6	0.4	1.1	1.2
	M	1.0	1.0	2.9	1.7	0.5	0.6	1.1	1.1
	SD	0.9	1.0	2.9	1.8	0.7	0.7	1.6	1.0
	M	78.3	82.0	52.2	55.9	88.4	89.6	70.9	76.7
	SD	12.7	14.1	16.0	18.5	8.6	8.7	15.6	13.9
	M	62.9	67.0	27.9	31.9	76.0	80.1	45.8	55.8
	SD	19.4	19.5	15.0	18.3	16.4	15.0	19.8	18.6
	M	99.2	99.2	93.4	95.8	100.0	100.3	99.0	99.6
	SD	3.6	2.6	8.4	7.0	2.5	3.0	3.4	3.0
	M	43.7	44.4	38.6	40.1	44.8	45.5	42.7	43.8
	SD	3.1	3.0	3.1	3.3	2.3	2.4	3.1	2.8
	M	2.4	2.0	4.3	3.7	1.8	1.3	2.7	2.2
	SD	2.1	1.7	2.7	3.2	1.4	1.1	2.3	1.9
	M	6.5	6.4	6.3	6.7	6.7	6.6	6.7	6.7
	SD	0.6	0.7	0.9	0.6	0.5	0.5	0.5	0.6
	M	15.2	17.9	9.9	10.8	17.1	19.4	13.3	15.9
	SD	5.0	5.5	3.6	4.2	5.4	4.9	4.4	6.1
	M	16.6	18.3	10.7	11.7	17.8	20.0	13.9	16.2
	SD	4.4	5.3	4.1	4.4	5.7	4.7	4.9	5.7
	M	47.9	48.7	24.0	27.3	54.9	61.9	41.7	46.6
	SD	17.3	15.9	14.4	12.9	15.6	16.9	17.0	18.4
	M	32.6	37.3	19.3	22.9	43.3	46.4	30.3	34.7
	SD	8.6	9.5	6.9	9.0	9.9	9.4	8.8	10.4

CR: cognitive reserve; YA: younger age; OA: older age; LowPF: low phonemic fluency performance; HighPF: high phonemic fluency performance. M: Mean; SD: Standard Deviation; BNT: Boston Naming Test (spontaneous responses); PCV: PC-Vienna System; PASAT: Paced Auditory Serial Addition Test; TMT A: Trial Making Test A; CTT: Color Trails Test; FRT: Facial Recognition Test; JLOT: Judgment of Line Orientation Test. LM: Logical Memory; VR: Visual Reproduction Test; Luria's HAM: Luria's Premotor Functions; Hand Alternative Movements; PF: phonemic fluency.

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ORIGINAL ARTICLE

Cortical Networks Underpinning Compensation of Verbal Fluency in Normal Aging

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Abstract

Elucidating compensatory mechanisms underpinning phonemic fluency (PF) may help to minimize its decline due to normal aging or neurodegenerative diseases. We investigated cortical brain networks potentially underpinning compensation of age-related differences in PF. Using graph theory, we constructed networks from measures of thickness for PF, semantic, and executive–visuospatial cortical networks. A total of 267 cognitively healthy individuals were divided into younger age (YA, 38–58 years) and older age (OA, 59–79 years) groups with low performance (LP) and high performance (HP) in PF: YA-LP, YA-HP, OA-LP, OA-HP. We found that the same pattern of reduced efficiency and increased transitivity was associated with both HP (compensation) and OA (aberrant network organization) in the PF and semantic cortical networks. When compared with the OA-LP group, the higher PF performance in the OA-HP group was associated with more segregated PF and semantic cortical networks, greater participation of frontal nodes, and stronger correlations within the PF cortical network. We conclude that more segregated cortical networks with strong involvement of frontal nodes seemed to allow older adults to maintain their high PF performance. Nodal analyses and measures of strength were helpful to disentangle compensation from the aberrant network organization associated with OA.

Key words: compensation, cortical thickness, graph theory, normal aging, phonemic fluency

Introduction

Language is one of the cognitive functions that is less vulnerable to the effects of aging (Schaie and Willis 1993; Ansado et al. 2013). An explanation for this is that language abilities are broadly distributed across different brain networks (Gernsbacher and Kaschak 2003). However, some language abilities do decline with aging. For instance, verbal fluency is often described as one of the language abilities most vulnerable to the effects of aging (Kavé and Mashal 2012). Previous studies have shown that performance in phonemic fluency (PF), a modality of verbal fluency, is rather stable during the middle-age adulthood, declines around the age of 60, and tends to stabilize again after the age of 65 (Rodriguez-Aranda and Martinussen 2006; Ferreira et al. 2015; Gonzalez-Burgos et al. 2019). This age trajectory of PF may be underlain by compensatory mechanisms that are particularly functional before the age of 60.

There has been an increasing interest in compensatory mechanisms that occur during aging (Cabeza 2002; Grady 2008; Morcom and Johnson 2015; Fitzhugh et al. 2019). Compensation reflects processes through which individuals recruit brain structures, networks, or neural resources in response to brain aging, pathology, or high cognitive demand (Cabeza et al. 2018;

Stern et al. 2020). Common formulations of compensation include enhancement and maintenance of performance (Cabeza et al. 2018; Stern et al. 2020). Further, individuals with higher levels of cognitive reserve (CR) may have a larger range of alternative networks or neural strategies that allow them to maintain cognitive function in a more successful manner than individuals with lower CR (Barulli and Stern 2013; Cabeza et al. 2018; Stern et al. 2020). We previously used graph theory analyses on cognitive data to investigate how CR and network efficiency contribute to PF in middle-aged and elderly individuals (Gonzalez-Burgos et al. 2020). We found that compensation in PF was facilitated by a better performance in semantic and executive–visuospatial abilities (Gonzalez-Burgos et al. 2019; Gonzalez-Burgos et al. 2020). This finding suggests the participation of ipsilateral left language networks and contralateral right frontoparietal networks in the compensation of PF, since semantic abilities have been associated with left inferior temporal, supramarginal, and frontal areas (Zhang et al. 2013; Zhang et al. 2019), and executive–visuospatial abilities have been associated with the right frontoparietal brain network, including prefrontal and supramarginal and other parietal areas (Budisavljevic et al. 2017; Nakajima et al. 2019). However, these neural correlates of compensation of PF were suggested solely from cognitive data (Gonzalez-Burgos et al. 2020), and further research is needed to elucidate whether these anatomical networks are indeed involved in compensation of PF.

The overall goal of the current study was to investigate cortical brain networks potentially underpinning compensation of age-related differences in PF. The first aim was to test whether brain regions associated with PF in previous studies (Costafreda et al. 2006; Birn et al. 2010; Tomasi and Volkow 2012; Zhang et al. 2013; Marsolais et al. 2014; Marsolais et al. 2015; Methqal et al. 2019) comprise a cortical network that is associated with performance in PF in a reference group of younger participants. Similarly, the second aim was to test whether brain regions associated with semantic and executive–visuospatial abilities in previous studies (Budisavljevic et al. 2017; Nakajima et al. 2019) comprise cortical networks that are associated with performance in semantic and executive–visuospatial tests in a reference group of younger participants. The third aim was to investigate compensation of age-related differences in PF in our older group by investigating features of these cortical networks underpinning PF, semantic, and executive–visuospatial cognitive abilities. Hence, our aim was to investigate compensation within the PF cortical network itself as well as ipsilateral compensation through the semantic cortical network and contralateral compensation through the executive–visuospatial cortical network. In this study, compensation refers to the ability to minimize the effect of age in PF in a group of older individuals and maintain high cognitive performance at levels that are comparable to those of younger middle-aged individuals. We hypothesized that older individuals with HP in PF would have a more efficient PF cortical network. Further, more efficient semantic and executive–visuospatial cortical networks would be associated with higher performance in PF in older individuals, likely delineating compensatory processes in normal aging. This study extends previous literature that has been primarily focused on declarative memory (Nyberg et al. 2012; Sala-Llonch et al. 2014; Vaqué-Alcázar et al. 2020) and functional magnetic resonance imaging (MRI) (Anthony and Lin 2018), whereas we investigated compensation in PF and used structural MRI. Unraveling compensatory mechanisms may advance our current understanding of the brain responses to both age-related and pathological processes. This may eventually help designing interventions to minimize or prevent cognitive impairment due to neurodegenerative processes.

Materials and Methods

Participants

A total of 267 participants were selected from the GENIC-database (Group of Neuropsychological Studies of the Canary Islands) (Machado et al. 2018), with ages between 32 and 79 years, and a balanced sex distribution across age (53% females). The sample used in the current study was selected from our previous study focused on cognitive data ($N = 446$, Gonzalez-Burgos et al. 2020), but only participants who had an MRI available were selected ($N = 267$, overlap with sample in Gonzalez-Burgos et al. 2020 is 60%). All participants were native Spanish speakers. Since language is strongly left lateralized, only right-handed participants were included in the current study.

All participants were assessed with a comprehensive neuropsychological protocol. For each participant, cognitive profile and diagnosis were established by at least 2 qualified clinical neuropsychologists, using age-, sex-, and education-adjusted normative data. Inclusion criteria for the current study were: 1) normal cognitive performance in comprehensive neuropsychological assessment (see Ferreira et al. 2015 for detailed information about the protocol) using pertinent clinical normative data (i.e., individuals with mild cognitive impairment or dementia were excluded); 2) preserved functional status and global cognition defined by a Blessed Dementia Scale (BDRS) (Blessed et al. 1968) score <4 and/or a Functional Activity Questionnaire (Pfeffer et al. 1982) score <6 and a Mini-Mental State Examination (Folstein et al. 1975) score ≥ 24; 3) no neurologic, psychiatric or systemic diseases; 4) no history of substance abuse; 5) no abnormal findings such as stroke, tumors, hippocampal sclerosis, etc., in MRI according to an experienced neuroradiologist. Although the BDRS scale cutoff for abnormality is frequently established at ≥ 4 points (Blessed et al. 1968; Erkinjuntti et al. 1988), the "changes in personality, interests, and drive" subscale may influence the BDRS total score and does not necessary reflect impairment in activities of daily living (Machado et al. 2018). With the aim of excluding only individuals with functional impairment, as an exception, we included those participants with total BDRS scores ≥ 4 ($n = 16$) if: 1) 70% or higher percentage of the BDRS total score resulted from changes in personality, interests, and drive subscale and 2) if a score ≤ 1.5 was obtained in the other 2 subscales ("changes in performance of everyday activities" and "changes in habits"). The same procedure has been used in previous studies (Machado et al. 2018; Gonzalez-Burgos et al. 2019).

The current study was approved by the Ethics Committee of the University of La Laguna (Spain), and all participants gave their written informed consent, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Neuropsychological Assessment

The neuropsychological protocol included tests to assess language, processing speed, attention, executive functions, verbal and visual episodic memory, procedural memory, and visuoconstructive, visuoperceptive, and visuospatial functions, as described elsewhere (Ferreira et al. 2015). Among all these tests, the PF test is of relevance to the current study. PF was assessed with the Controlled Oral Word Association Test (Benton et al. 1989). Participants had to recall words that begin with the letters F, A, and S for 1 minute each. Proper nouns, numbers, and derived words were scored as intrusion errors. A total score (F + A + S) was calculated as the number of correct words produced, excluding intrusions and perseverations (repetitions of correct words). The Boston Naming Test (BNT) (Kaplan et al. 1983), Judgment of Line Orientation Test (JLOT) (Benton et al. 1983), Visual Reproduction Test (VRT, from Wechsler Memory Scale – Third Edition) (Wechsler 1997), and Stroop Test (Golden 1978) were also included in this study. The BNT evaluates lexical access by visual confrontation. JLOT, VRT, and the Stroop Test assess visuospatial abilities, visual memory, and executive functions (inhibition), respectively. We selected these tests because a previous publication demonstrated their contribution to performance in PF, possibly underpinning compensatory processes through nonfluency networks (Gonzalez-Burgos et al. 2019). In addition, we report education level and Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) Information subtest as a measure of crystallized intelligence, for characterization of the cohort.

MRI and Automated Image Processing

Participants were scanned using a 3 T General Electric imaging system (General Electric) located at the "Hospital Universitario de Canarias" in Tenerife, Spain. A 3-dimensional T_1-weighted FSPGR (Fast Spoiled Gradient Echo) sequence was acquired in sagittal plane with the following parameters: repetition time/echo time = 8.73/1.74 ms, inversion time = 650 ms, field of view 250 × 250 mm, matrix 250 × 250 mm, flip angle 12°, slice thickness = 1 mm, voxel resolution = 1 × 1 × 1 mm. Full brain and skull coverage was required for the MRI datasets and detailed quality control was carried out on all MR images according to previously published criteria (Simmons et al. 2009). TheHiveDB Database system (Muehlboeck et al. 2014) was used to automatically preprocess the T_1-weighted images with FreeSurfer 6.0.0, following standard procedures (Ferreira et al. 2014). Quality control was performed both on the original T_1-weighted images (Simmons et al. 2009) and the FreeSurfer output. Original images that did not pass quality control were discarded. All FreeSurfer output passed quality control and manual edits were not needed. Among the different measures provided by FreeSurfer, we selected regional estimations of cortical thickness for the current study.

Network Construction and Graph Analysis

The average cortical thickness from selected regions of the Desikan atlas (Desikan et al. 2006) was used as the nodes for network construction (Fig. 1). Three separate cortical networks were constructed to reflect PF, semantic, and executive–visuospatial cortical networks based on regions that have been consistently reported in previous studies (Costafreda et al. 2006; Birn et al. 2010; Tomasi and Volkow 2012; Zhang et al. 2013; Marsolais et al. 2014; Marsolais et al. 2015; Budisavljevic et al. 2017; Methqal et al. 2019; Nakajima et al. 2019). According to these previous studies, the PF cortical network mostly includes areas from the left hemisphere, although it also involves several areas from the right hemisphere. To facilitate interpretations on contralateral compensation, we limited our PF network to areas from the left hemisphere (and reserved the right executive–visuospatial network for the test on contralateral compensation). As depicted in Figure 1, the PF cortical network includes several regions of the left frontal, parietal, and temporal cortex, where the Broca (Pars triangularis), Wernicke (Bankss), and supramarginalis areas are central in well-established models of language functioning (Mesulam 1998). For completeness of information, we also ran complementary analyses for the right side of the PF cortical network (these complementary analysis as well as the nodes included in this subnetwork are shown in Supplementary Fig. S17). The semantic cortical network includes the left inferior temporal, left supramarginal, and areas of the left frontal cortex, and partially overlaps with the PF cortical network. The executive–visuospatial network includes the right prefrontal and supramarginal and other parietal areas. Although this network is expected to be highly specific to our executive–visuospatial tasks of interest, it only included 9 nodes, which may be a concern because graph analyses may be limited on small networks. Hence, we ran complementary analysis on separated larger executive and visuospatial networks (16 and 11 nodes, respectively), at the cost of specificity. These complementary analysis as well as the nodes included in these 2 larger networks are shown in Supplementary Figure S18.

The edges between the nodes were calculated through group-specific association matrices of Pearson correlation coefficients from each pair of nodes (Fig. 2). The matrices were binarized by thresholding the correlation coefficients at a range of densities for the 3 cortical networks (min = 10% to max = 45%, in steps of 1%), ensuring the exclusion of disconnected networks (densities below 10%) and random topologies (densities above 45%, small-world index close to 1). Network topologies were compared across this range of densities. Both self-connections and negative correlations were excluded.

Once the cortical networks were constructed, both nodal and global graph measures were calculated. Nodal measures refer to each specific node, whereas global measures refer to the average across all the nodes. Regarding global measures, we included the "average global efficiency," "average local efficiency," "transitivity," and "average strength" (Rubinov and Sporns 2010). The average global efficiency is the average inverse shortest path length between a node and the rest of the network. The average global efficiency measures how efficiently information is exchanged throughout the network (Latora and Marchiori 2001). The mathematical definition of the average local efficiency is similar to that of the average global efficiency, but the average local efficiency is restricted to a given node and the subgraph created by the node's neighbors. Conceptually, the average local efficiency is related to the clustering coefficient and transitivity measure, which can be regarded as a measure of the local efficiency of information transfer, or of the robustness of the network to deletion of individual nodes (Bullmore and Sporns 2009). The transitivity refers to the fraction of a node's neighbors that are also neighbors of each other in the whole network, normalized by the whole network. It reflects how well the nodes are connected to nearby nodes forming cliques. The average strength is given by the sum of the weights of all edges connected to a node. The average global efficiency, average local efficiency, and transitivity measures were calculated on binary undirected networks across the different densities, and the average strength was calculated on weighted undirected networks (before binarization). In addition, the following nodal measures were calculated: the "nodal global efficiency," the "nodal local efficiency" (Latora and Marchiori 2001), and the "nodal strength" (Barrat et al. 2004). The nodal

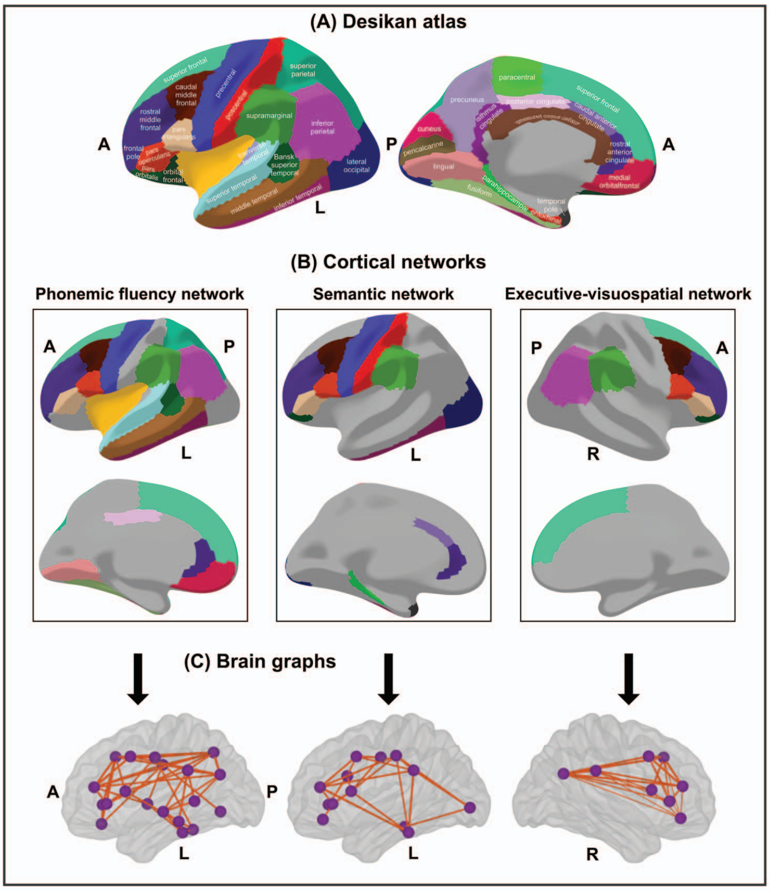

Figure 1. Cortical networks. (A) Desikan atlas; (B) cortical networks, cortical regions included as nodes; (C) brain graphs of the 3 cortical networks at the median density of 27%. Nodes are depicted as purple spheres and edges as orange lines estimated from Pearson correlation coefficients. A, anterior part of the brain; P, posterior part of the brain; L, left; R, right. The R-package ggseg3d was used for visualization (Mowinckel & Vidal-Piñeiro 2019).

global efficiency of a specific node is the average inverse shortest path length between that node and the rest of the network. The nodal local efficiency is the global efficiency of a node calculated on the subgraph created by the node's neighbors. The nodal strength is given by the sum of the weights of all edges connected to a node. Modular analyses were also conducted by applying the Louvain algorithm (Blondel et al. 2008) on weighted undirected networks with a gamma value of 1. The formulae used to calculate all these graph measures are provided in Rubinov and Sporns (2010); Latora and Marchiori (2001); (Barrat et al. (2004). Network construction, measures calculation, and graph analyses were performed using BRAPH (BRain Analysis using graPH theory, www.braph.org, Mijalkov et al. 2017).

Statistical Analysis

Statistical analyses were performed using the R programming environment (Core 2016) and BRAPH (www.braph.org, Mijalkov et al. 2017). We stratified the cohort into groups of younger and older individuals and high performance (HP) and low performance (LP) in PF, semantic (BNT), and executive–visuospatial tasks (JLOT, VRT, and Stroop, z-transformed and combined), using the median values of the age and selected cognitive variables. For the demographic variables, analysis of variance (ANOVA) was used for continuous and dichotomous (dummy) variables, both for main effects and for the interaction between 2 factors (i.e., the interaction between the age and performance groups). The Chi-square test was used for categorical variables. P values in all post hoc analyses were adjusted with the Hochberg's (Hochberg and Benjamini 1990) method for multiple testing. Significant differences were considered when $P \leq 0.05$ (2-tailed). Between-group comparisons of graph measures were conducted through 1000 nonparametric permutations at a range of network densities (10–45%). The 95% confidence intervals of each distribution were used as critical values for testing of the null hypothesis at $P \leq 0.05$ (2-tailed). The false discovery rate

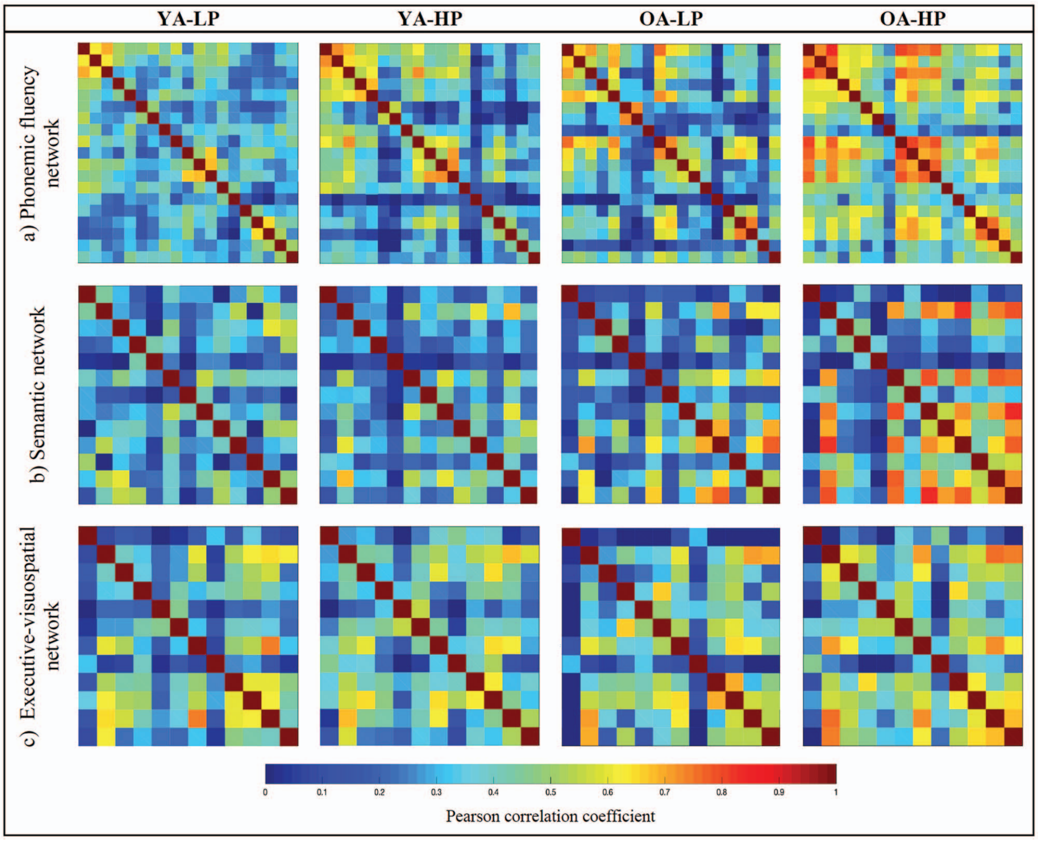

Figure 2. Weighted correlation matrices by study group. PF, semantic and executive–visuospatial networks.

(FDR) adjustment (Genovese et al. 2002) for multiple testing was used at $P \leq 0.05$ (2-tailed) on the nodal measures at the median density (27%).

Results

Table 1 shows the demographic characteristics of the age and PF performance groups. The ANOVA for PF as the outcome variable did not show any significant interaction between the age and performance groups ($P = 0.112$). Subsequent analyses showed that although the older age (OA) group performed worse than the younger age (YA) group in PF; this effect was only observed within the LP groups (younger adults with low PF performance, YA-LP vs. older adults with low PF performance, OA-LP, $P = 0.001$) but not within the HP groups (younger adults with high PF performance, YA-HP vs. older adults with high PF performance, OA-HP, $P = 0.114$) (Fig. 3). Despite the group differences in education level and WAIS-III Information subtest, we did not control for the effect of these 2 variables due to our interest in compensation mechanisms, which are partly facilitated by education level and WAIS-III Information subtest (Gonzalez-Burgos et al. 2020).

Cortical Brain Networks Underpinning PF and Semantic and Executive–Visuospatial Abilities—Analyses in Younger Participants

The first aim of this study was to test whether the brain regions associated to PF in previous studies (Costafreda et al. 2006; Birn et al. 2010; Tomasi and Volkow 2012; Zhang et al. 2013; Marsolais et al. 2014; Marsolais et al. 2015; Methqal et al. 2019) comprise a cortical network that is associated with performance in PF in our reference group of younger participants (32–58 years). To address this aim, we compared the YA-LP group versus YA-HP group, therefore excluding the effect of aging. For simplicity, we constrained our analyses to global graph measures. We found that the average global efficiency was increased, and the transitivity was decreased in the YA-LP group, compared with the YA-HP group (Fig. 4A). This finding demonstrates that this cortical network is associated with performance in PF, therefore likely underpinning PF. There were no significant group differences in the average local efficiency and the average strength. Our complementary analysis for the right nodes of the PF network showed no significant group differences when comparing the same global measures, suggesting that the PF nodes of the right

Table 1 Demographic characteristics and cognitive performance

	YA-LP (*n* = 88)	YA-HP (*n* = 85)	OA-LP (*n* = 47)	OA-HP (*n* = 47)	*P* value
Age	47.7 (5.5)[b,c]	48.5 (6.3)[b,c]	68.4 (5.5)[c]	65.5 (4.9)	<0.001
(Range)	(37–58)	(32–58)	(59–79)	(59–76)	
Sex (women, men)	55/33	39/46	26/21	22/25	0.12
WAIS-III Information subtest	14.4 (5.4)[a,c]	19.3 (5.4)[b]	12.5 (5.3)[c]	19.9 (4.4)	<0.001
Education level					<0.001
Illiteracy	0	0	0	0	
Unfinished primary studies	1	0	9	1	
Completed primary studies	48	16	24	13	
Completed secondary studies	23	24	9	6	
University studies	16	45	5	27	
PF	28.0 (6.2)[a,b,c]	46.0 (9.0)[b]	22.5 (6.2)[c]	43.7 (9.7)	<0.001
BNT	25.5 (3.5)[a,b]	28.0 (2.5)[b]	22.0 (5.2)[c]	26.7 (3.3)	<0.001
JLOT (first half)	13.1 (2.0)[b]	13.7 (1.6)[b]	12.1 (2.5)[c]	13.3 (1.8)	<0.001
Visual Reproduction (Immediate)	82.6 (12.3)[a,b,c]	87.5 (9.9)[b,c]	60.9 (20.1)[c]	74.4 (15.6)	<0.001
Stroop Test (Sheet 3)	37.8 (8.3)[a,b]	43.0 (9.2)[b,c]	27.2 (8.9)[c]	38.3 (8.4)	<0.001

Note: [a] Significantly different from YA-HP.
[b] Significantly different from OA-LP.
[c] Significantly different from OA-HP.

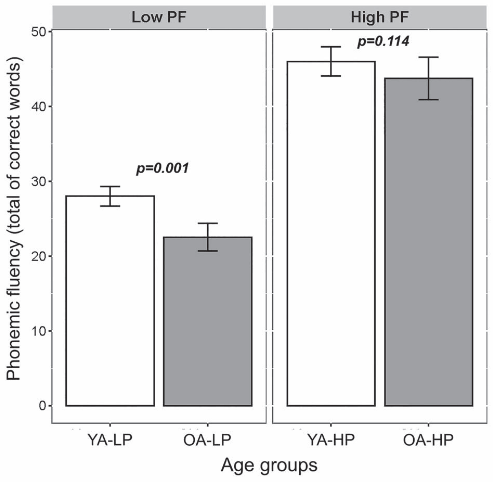

Figure 3. Interaction between age and performance groups with PF as the outcome measure (ANOVA). Bars represent the mean of correct words produced and the jack-knifes represent the 95% confidence intervals. Low PF, low PF performance groups; high PF, high PF performance groups. The OA group performed worse than the YA group in PF but only within the LP groups (younger adults with low PF performance, YA-LP vs. older adults with low PF performance, OA-LP, $F_{3,263} = 136.93$, P = 0.001).

hemisphere are not associated to performance in PF in our cohort (Supplementary Fig. S17).

The second aim of this study was to test whether the brain regions associated to semantic and executive–visuospatial abilities in previous studies (Budisavljevic et al. 2017; Nakajima et al. 2019) comprise cortical networks that are associated with performance in semantic and executive–visuospatial cognitive tasks, also in our reference group of younger participants. To address this aim, we compared the YA-LP group versus YA-HP group, therefore excluding the effect of aging. Regarding the semantic cortical network, the average local efficiency was decreased in the YA-LP group, and we observed a tendency for the average global efficiency to be increased and the transitivity to be decreased in the YA-LP group, compared with the YA-HP group (Fig. 4B). These results suggest (Fig. 4B) that this cortical network is likely underpinning semantic abilities. Regarding the executive–visuospatial cortical network, no differences were observed in any of the global measures when comparing the YA-LP and YA-HP groups (Fig. 4C). Our complementary analysis on larger separate executive and visuospatial networks showed no significant differences when comparing the YA-LP and YA-HP groups across the same global measures (Supplementary Fig. S18). This finding indicates that these cortical networks do not seem to be involved in the executive–visuospatial abilities investigated in the current study. Hence, the executive–visuospatial cortical network was not used for further analyses in this study.

Age-Related Differences in Cortical Networks—Comparison Between Younger and Older Participants

The third aim of this study was to investigate compensation of age-related differences in PF in the older group (59–79 years) by investigating features of the PF cortical network and the semantic cortical network. To do this, we compared the older groups (OA-LP and OA-HP) versus the reference group YA-LP. In order to disentangle the effect of age from compensation effects, we tested for potential differences between the OA-HP and YA-HP groups (age) and between the OA-LP and OA-HP groups (compensation).

PF Cortical Network

The weighted correlation matrices of the PF cortical network are displayed in Figure 2A (see Supplementary Figs S1–S12 for

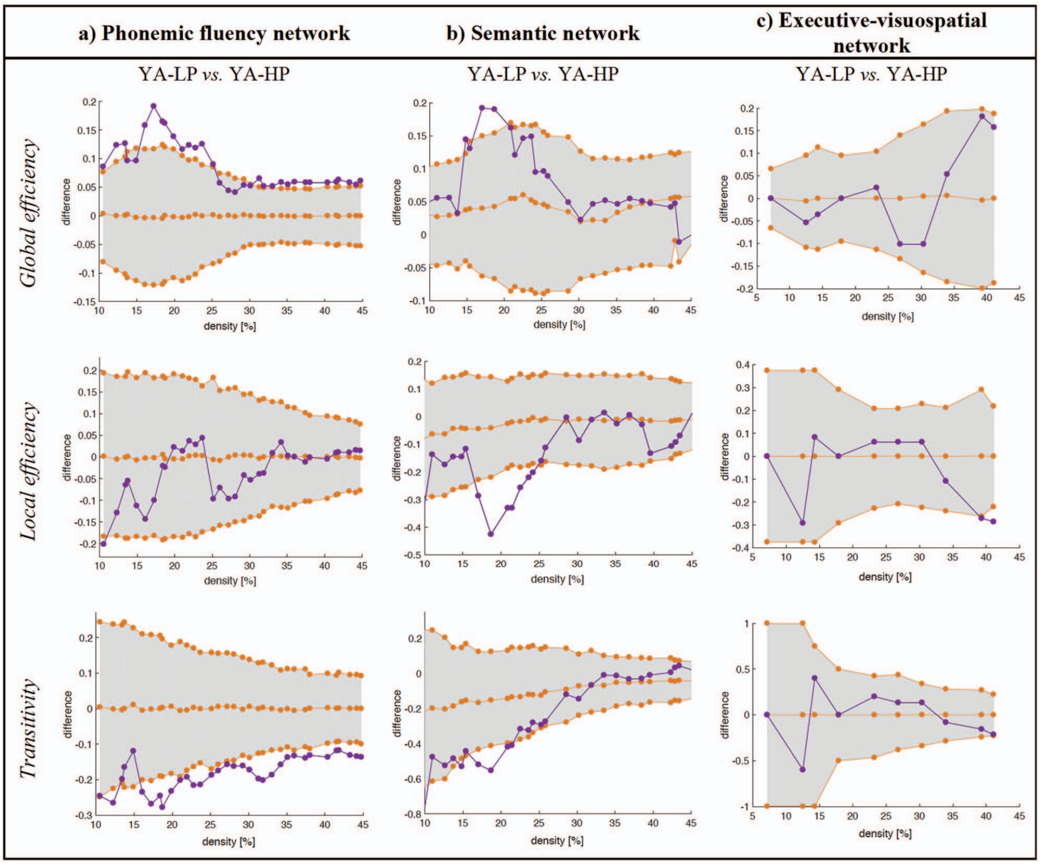

Figure 4. Comparison between the young performance groups (YA-LP vs. YA-HP) across global graph measures. a) Phonemic fluency cortical network. b) Semantic cortical network. c) Executive-visuospatial cortical network. Network densities are displayed on the x-axis from min = 10% to max = 45%, in steps of 1%. Between-group differences in the global graph measures are displayed on the y-axis. The 95% confidence intervals were used as critical values for testing of the null hypothesis at $p \leq 0.05$ (two-tailed), however, graphs show the one-tailed t-test results.

matrices with larger size and labeled regions). Visual inspection of the matrices showed that the YA-LP group had overall weak correlations (Fig. 2A and Supplementary Fig. S1). The YA-HP and OA-LP groups had a more segregated pattern of correlations, with a tendency for some frontal and parietal regions to correlate with each other (Fig. 2A and Supplementary Fig. S2–S3). The OA-HP group had the most segregated pattern of correlations, including strong correlations between several frontal and parietal regions (Fig. 2A and Supplementary Fig. S4). Further, we found distinct modular topologies across groups (Fig. 5). Although a total of 2 modules were identified in all 4 groups, the Broca area was included in the same module than the Wernicke and supramarginalis areas in the younger and older LP groups (YA-LP and OA-LP). In contrast, these regions were included in different modules in the younger and older HP groups (YA-HP and OA-HP).

In the global network analysis, the average global efficiency was decreased and the transitivity was increased in the 2 older groups (OA-LP and OA-HP), when compared with the reference YA-LP group (Fig. 6A). There were no significant group differences in the average local efficiency and the average strength. To disentangle the effects of age from compensation effects, we tested for potential differences between the OA-HP and YA-HP (age) groups and between the OA-LP and OA-HP (compensation) groups. The local efficiency was decreased in the OA-HP group when compared with the YA-HP group, with a tendency toward a reduced global efficiency and an increased transitivity. The average strength was significantly higher in the OA-HP group compared with the YA-HP group (P = 0.035). No differences were observed when comparing the OA-LP and OA-HP groups across any of the graph measures. In the nodal network analysis, the OA-LP group showed decreased nodal global and local efficiency in the lingual and inferior temporal cortex, compared with the reference YA-LP group. The OA-HP group showed decreased nodal global and local efficiency in the lingual and cingulate cortex, and an increased nodal local efficiency and strength

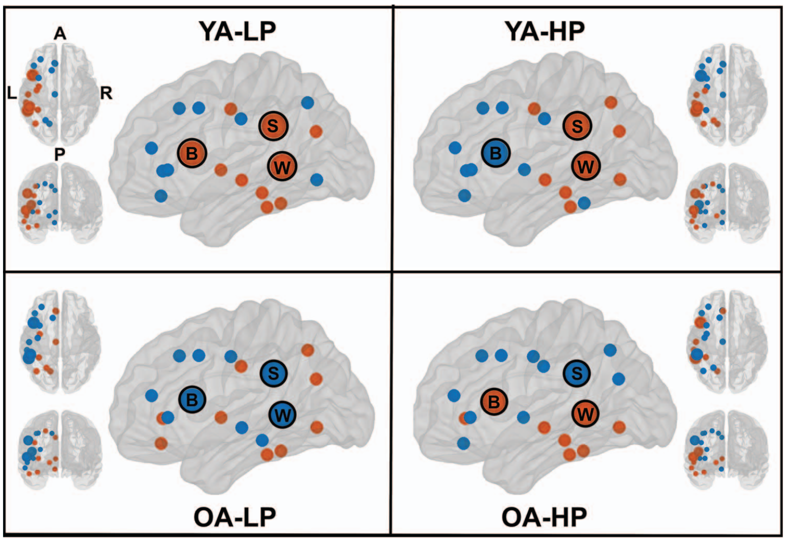

Figure 5. Modules—modular topology within the PF cortical network. Each module is depicted by a different color (blue vs. orange). B, Broca's area; S, supramarginal gyrus; W, Wernicke's area; A, anterior part of the brain; P, posterior part of the brain; L, left; R, right.

in the precentral and supramarginal gyri compared with the reference YA-LP group (Table 2).

In summary, the same pattern of reduced efficiency and increased transitivity was associated with both HP and OA. However, the OA-HP group reached a higher PF performance than the OA-LP group and equaled the performance of the YA-HP group (Fig. 3), likely by keeping a more segregated PF network with greater participation of frontal nodes as compared with temporal or posterior nodes in the OA-LP group and by keeping a high strength in its correlations.

Semantic Cortical Network

We also investigated how global connectivity features of the semantic cortical network contributed to performance in PF in the older groups, potentially illustrating compensation of PF through the semantic cortical network. To do so, global graph measures were calculated within the semantic cortical network by comparing older participants with LP and HP in PF versus the reference YA-LP group. The average global efficiency was decreased and the transitivity and average local efficiency were increased in the OA-LP and OA-HP groups when compared with the reference YA-LP group (Fig. 6*B*). No differences were observed in the average strength (see Supplementary Figs S13–S16 for the weighted correlation matrices). Again, we tested for potential differences between the OA-HP and YA-HP (age) groups and between the OA-LP and OA-HP (compensation) groups, in order to disentangle the effect of age from compensation effects. We observed a tendency toward a reduced global efficiency and an increased transitivity in the OA-HP group when compared with the YA-HP group (Fig. 6*B*). No differences were found when comparing the OA-LP and OA-HP groups across any of the graph measures.

In summary, as demonstrated for the PF cortical network, the same pattern of reduced efficiency and increased transitivity was associated with both HP and OA. However, in contrast to the OA-LP group, individuals in the OA-HP group tended to have a more segregated semantic cortical network (Figs 2*B* and 6*B*).

Discussion

The overall aim of this study was to investigate cortical networks underpinning compensation of PF performance in normal aging. We observed a similar pattern of segregation associated with both HP and OA. Hence, 2 completely opposed levels of PF performance seem to share a common pattern of cortical connectivity. Below we discuss how these similar patterns may underlie different brain mechanisms, suggesting a successful compensation in individuals with HP and an aberrant network organization in individuals with OA and LP. Overall, older adults who performed high in PF had the most segregated PF and semantic cortical networks, involved frontal nodes more strongly, and had a high average strength in the correlations among cortical regions.

We demonstrated that isolated brain areas that have been associated with PF and semantic abilities in previous studies do comprise cortical networks underpinning PF and semantic abilities. In contrast, the right frontoparietal cortical network was not associated with performance in the executive–visuospatial cognitive tests investigated in our study. A possible explanation for this is the use of slightly different tests of executive and visuospatial abilities as well as different age groups in our study and previous studies (Budisavljevic et al. 2017; Nakajima et al. 2019). Another explanation is that the right executive–visuospatial network is a large network that involves regions of the left hemisphere as well (Budisavljevic et al. 2017; Bagarinao et al. 2019; Nakajima et al. 2019). However, we limited our network to the right hemisphere to force the distinction between ipsilateral (semantic network) and contralateral (right executive–visuospatial) compensation. Further,

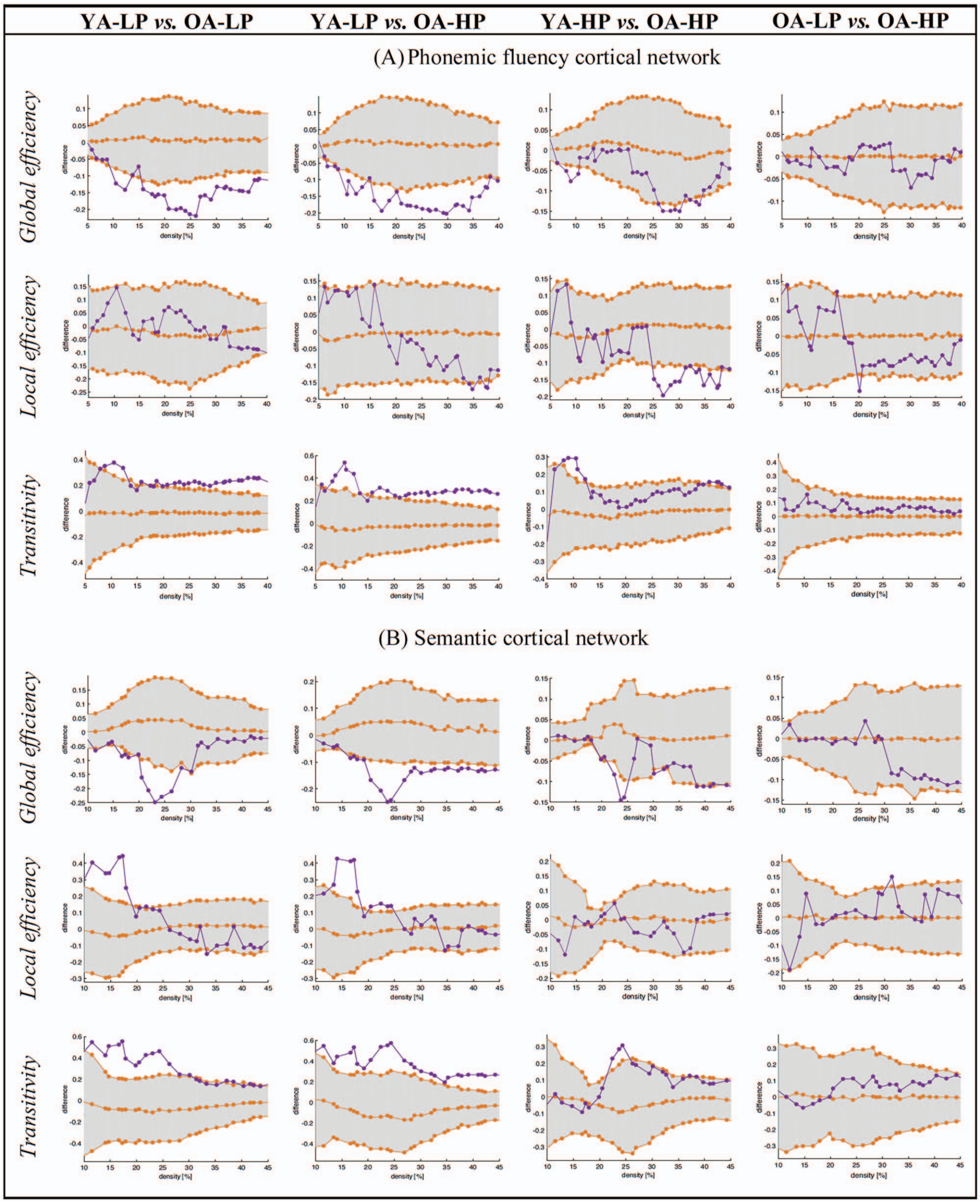

Figure 6. Comparison of the age and PF performance groups across global graph measures. (*A*) Comparison between PF performance and age groups across global graph measures in the PF cortical network. (*B*) Comparison between the PF performance and age groups across global graph measures in the semantic cortical network. Network densities are displayed on the *x*-axis from min = 10% to max = 45%, in steps of 1%. Between-group differences in the global graph measures are displayed on the *y*-axis. The 95% confidence intervals were used as critical values for testing of the null hypothesis at $P \leq 0.05$ (2-tailed); however, graphs show the 1-tailed *t*-test results.

Table 2 Nodal graph measures in the PF network

Measure and region		YA-LP	OA-LP	FDR-adjusted P value
Global nodal efficiency				
Left lingual		0.398	0	<0.05
Left inferior temporal		0.542	0	<0.05
Local nodal efficiency				
Left lingual		1	0	<0.05
Strength				NS
		YA-LP	**OA-HP**	
Global nodal efficiency				
Left posterior cingulate		0.630	0	<0.05
Local nodal efficiency				
Left lingual	1	0	<0.05	
Left rostral anterior cingulate	1	0	<0.05	
Left precentral gyrus	0	0.764	<0.05	
Nodal strength				
Left precentral gyrus		6.222	10.637	<0.05
Left supramarginal gyrus		6.137	11.084	<0.05

Note: NS, nonsignificant ($P > 0.05$).

we restricted our right frontoparietal network to brain areas associated with the specific executive and visuospatial tasks that were previously shown to contribute to performance in PF (Gonzalez-Burgos et al. 2019, 2020). Although this restricted network is expected to be highly specific to our executive–visuospatial tasks of interest, graph analyses may be limited when conducted on small networks. Moreover, the inclusion of larger executive and visuospatial networks could increase the sensitivity and ability to find significant associations with performance in PF. However, we could not demonstrate such an association in our complementary analyses, where we tested larger right-sided executive and visuospatial networks.

Compensation can occur as a more efficient use of a specific brain network, which in our study was illustrated by network characteristics within the PF cortical network. Compensation can also occur through recruitment of other brain networks, which in our study was illustrated by network characteristics of an ipsilateral language network that is the semantic cortical network. The recruitment of a network with shared brain regions could be explained by the association between PF and other linguistic functions (Lezak et al. 2004; Gonzalez-Burgos et al. 2019). How contralateral networks such as the right executive–visuospatial network contribute to the compensation of age-related differences in PF remains to be investigated in future studies. While we limited our study to right-handed individuals as a proxy of language lateralization to the left hemisphere (Mazoyer et al. 2014), an interesting prospect is to investigate whether recruitment of contralateral networks is more prominent in individuals with a more bilateral pattern of language lateralization (Catani et al. 2007).

The main finding in this study is that the same pattern of reduced efficiency and increased transitivity in PF and semantic cortical networks was associated with both HP and OA. This finding is partially contrary to our hypothesis, which anticipated that higher performance would be associated with higher efficiency. Despite the contradictory finding on the specific measures of efficiency, it is possible that the combination of network characteristics in the HP group is indeed related to overall higher network efficiency, which was associated with higher performance. Below we discuss this interpretation further. The finding showing that groups with HP and groups with OA achieved different levels of performance in PF suggests that the implication of our study is that a common pattern of cortical connectivity may underlie different brain mechanisms. Interpreting network features in combination with level of cognitive performance is thus important. In particular, OA was associated with lower performance in PF. Hence, reduced efficiency and increased transitivity associated with lower performance in older individuals is in line with our hypothesis and suggests that this pattern of network organization is aberrant or inefficient (Logan et al. 2002; Park et al. 2004; Reuter-Lorenz and Cappell 2008; Grady 2008; Meunier et al. 2014; Cabeza et al. 2018; Vaqué-Alcázar et al. 2020). Previous studies have also reported reduced efficiency (Achard and Bullmore 2007; Sala-Llonch et al. 2014; Sala-Llonch et al. 2015) and increased transitivity (Marques et al. 2016; Farahani et al. 2019) in aging, indicating loss of specificity and effectiveness (Baltes et al. 1980; Baltes and Lindenberger 1997; Sleimen-Malkoun et al. 2014; Sleimen-Malkoun et al. 2014; Hülür et al. 2015; Pereira et al. 2018).

However, not all individuals age in the same way, highlighting between-subject variability in cognitive aging (Ferreira et al. 2017). This is clearly illustrated in our current study by a substantial number of older individuals who managed to maintain a high level of performance in PF (the OA-HP group), which was as high as the level of performance in the YA-HP group. Hence, reduced efficiency and increased transitivity associated with HP in older individuals suggests that this pattern of network organization can also be effective, possibly underlying compensatory mechanisms. This interpretation is further supported by the finding of reduced efficiency and increased transitivity associated with HP in young individuals with HP in PF (the YA-HP group). In the next paragraphs we elaborate on several findings that allowed us to further disentangle this overall network similarities related to both higher performance and OA.

Despite the overall network similarities, several findings allowed us to discriminate between compensation and aberrant network organization. We identified 2 modules in each of our 4 groups. However, the groups had distinct topological organization. The modular analyses showed that the Broca area, Wernicke area, and the supramarginal gyri were clustered in 2 separate modules in the groups with a HP. These 3 areas are central in well-established models of language functioning (Mesulam 1998). However, PF is a task primarily belonging to the so-called motor (Broca) dimension of the language function (as opposed to the sensorial —Wernicke—or transcortical—supramarginalis—dimensions). This finding in conjunction with a greater participation of frontal nodes and a higher average strength in the OA-HP group suggests that the close connectivity of the Broca area with neighboring frontal regions is preferential in order to produce HP in PF (the Broca area was segregated from Wernicke and/or supramarginalis areas in HP groups, and nodal results revealed the role of frontal nodes in the OA-HP group). Hence, this combination of features seems to illustrate a more efficient network that is associated with a higher performance, as anticipated by our hypothesis. A more segregated frontal hub with strong close connections seems to favor the higher performance in PF, which would be reflected by an increased transitivity and reduced average efficiency measures (path lengths of the frontal hub with distant brain areas may be increased due to the high segregation of the frontal hub). The findings of increased strength support this interpretation. The interaction among neighboring brain regions to reduce metabolic and wiring cost is greater in individuals with high CR (Bullmore and Sporns 2012; Marques et al. 2016; Franzmeier et al. 2018; Lee et al. 2019), who have more efficient compensatory mechanisms (Gonzalez-Burgos et al. 2020) and perform higher in PF tests (Crossley et al. 1997; Tombaugh 1999; Auriacombe et al. 2001; Roldan-Tapia et al. 2012; Gonzalez-Burgos et al. 2019; Balduino et al. 2019). The frontal lobe has been postulated as a scaffold in compensatory processes (Park and Reuter-Lorenz 2009), based on the contribution of frontal regions such as the precentral gyrus to HP in older individuals (Park and Reuter-Lorenz 2009). Despite overall age-related structural and cognitive differences reported in previous studies using the same cohort than in the current study (Ferreira et al. 2015; Ferreira et al. 2016; Machado et al. 2018; Gonzalez-Burgos et al. 2019; Cedres et al. 2019; Nemy et al. 2020), we found that a group of older participants achieved HP, comparable to that of younger adults, which presumably reflects compensatory mechanisms.

In contrast, long-distance connectivity of the Broca area seems to be less efficient and is associated with LP in PF (the Broca area was in the same community than both the Wernicke and supramarginalis areas in LP groups, and nodal results revealed the role of temporal and occipital nodes in the OA-LP group). Hence, HP in PF seems to be underpinned by a highly intraconnected subnetwork with short-distance connections, primarily including the Broca and other frontal areas. Contrarily, LP in PF seems to be characterized by the presence of a long-distance subnetwork including the Broca and other posterior brain areas such as Wernicke and supramarginal areas. Although long-distance connections can transfer information in a fast and noiseless way by reducing the path length (Buzsáki et al. 2004; Bullmore and Sporns 2012), the cost of long-distance connections can exceed its value (Achard and Bullmore 2007; Bullmore and Sporns 2012; van den Heuvel and Sporns 2013; van den Heuvel and Sporns 2019). Our findings of reduced efficiency and increased transitivity in the OA-LP group suggest that these long-distance connections are not direct in this group, which may have caused LP in PF.

This study has some limitations. We analyzed cross-sectional data; hence, our age-related differences in cognitive performance may partially be explained by cohort effects. We used a structural atlas that includes large regions (Desikan et al. 2006), and our PF network includes large regions of interest of the left hemisphere. Our current results could thus be compared with future analyses using smaller parcellations, which may perhaps provide a more fine-grained illustration of nodal contributions to compensation in PF. In addition, functional MRI and longitudinal designs may help substantiating our current results and further discriminate compensation from aberrant network organization associated to OA. Another issue is that we approached compensatory mechanisms by investigating the language function, in particular, verbal fluency. Future studies should extend our current analyses to other language components and non-language cognitive functions, to inform on whether compensation is task-dependent or is a universal process (Stern et al. 2018). Finally, the software we used for graph analyses only provides the possibility to perform group comparisons. Although this is the most common form of analysis in graph studies, an approach based on correlations could introduce advantages when it comes to modeling the contribution of the semantic network to performance in PF. Future work should thus explore methods that can generate individual networks (Tijms et al. 2012), enabling correlations between graph measures and performance in PF and age as continuous variables.

Distinguishing between compensation and aberrant network organization is challenging (Shafto and Tyler 2014). Our study provides data that may help to improve this distinction. We suggest that modular analyses complemented with nodal analyses and measures of strength may help to disentangle compensation from the aberrant network organization associated with OA. Altogether, we conclude that more segregated cortical networks with a strong involvement of frontal nodes seems to allow older adults to maintain their HP in PF. Advancing our current understanding of mechanisms underlying cognitive compensation will have direct implications for the treatment and prevention of cognitive decline in normal aging and pathological processes.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Author Contributions

Principal investigator: Prof. J.B.

L.G.B.: data curation, conceptualization, methodology writing—original draft preparation; J.P.: methodology, software, writing—original draft preparation; R.M.: methodology, writing—original draft preparation; J.B.: conceptualization, writing—reviewing and editing; E.W.: methodology, writing—reviewing and editing, supervision; D.F.: conceptualization, methodology, writing—reviewing and editing, supervision, funding. All authors contributed to manuscript revision and read and approved the submitted version.

Notes

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References

Achard S, Bullmore E. 2007. Efficiency and cost of economical brain functional networks. Friston KJ, editor. *PLoS Comput Biol*. 3(2):e17.

Ansado J, Marsolais Y, Methqal I, Alary F, Joanette Y. 2013. The adaptive aging brain: evidence from the preservation of communication abilities with age. *Eur J Neurosci*. 37: 1887–1895.

Anthony M, Lin F. 2018. A systematic review for functional neuroimaging studies of cognitive reserve across the cognitive aging spectrum. *Arch Clin Neuropsychol*. 33(8):937–948.

Auriacombe S, Fabrigoule C, Lafont S, Jacqmin-Gadda H, Dartigues J-F. 2001. Letter and category fluency in normal elderly participants: a population-based study. *Aging Neuropsychol Cogn*. 8(2):98–108.

Bagarinao E, Watanabe H, Maesawa S, Mori D, Hara K, Kawabata K, Yoneyama N, Ohdake R, Imai K, Masuda M, et al. 2019. Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. *Sci Rep*. 9(1):11352.

Balduino E, de Melo BAR, de Sousa Mota da Silva L, Martinelli JE, Cecato JF. 2019. The “SuperAgers” construct in clinical practice: neuropsychological assessment of illiterate and educated elderly. *Int Psychogeriatr*. 32(2):191–198.

Baltes PB, Cornelius SW, Spiro A, Nesselroade JR, Willis SL. 1980. Integration versus differentiation of fluid/crytallized intelligence in old age. *Dev Psychol*. 16(6):625–635.

Baltes PB, Lindenberger U. 1997. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging*. 12(1):12–21.

Barrat A, Barthélemy M, Pastor-Satorras R, Vespignani A. 2004. The architecture of complex weighted networks. *Proc Natl Acad Sci U S A*. 101(11):3747–3752.

Barulli D, Stern Y. 2013. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*. 17:502–509

Benton A, Hamsher K, Sivan A. 1989. In: Associates A, editor. *Multilingual aphasia examination*. 2nd ed. Iowa City, IA: AJA Associates. University of Iowa.

Benton A, Hamsher S, Varney O, Spreen N. 1983. *Contributions to neuropsychological assessment: a clinical manual*. New York: Oxford University Press.

Birn RM, Kenworthy L, Case L, Caravella R, Jones TB, Bandettini PA, Martin A. 2010. Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. *NeuroImage*. 49(1):1099–1107.

Blessed G, Tomlinso BE, Roth M. 1968. Association between quantitative measures of dementia and of senile change in cerebral grey matter of elderly subjects. *Br J Psychiatry*. 114(512):797–811.

Blondel VD, Guillaume J-L, Lambiotte R, Lefebvre E. 2008. Fast unfolding of communities in large networks. *J Stat Mech*. 2008(10):P10008.

Budisavljevic S, Dell’Acqua F, Zanatto D, Begliomini C, Miotto D, Motta R, Castiello U. 2017. Asymmetry and structure of the fronto-parietal networks underlie visuomotor processing in humans. *Cereb Cortex*. 27:1532–1544.

Bullmore E, Sporns O. 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 10(3):186–198.

Bullmore E, Sporns O. 2012. The economy of brain network organization. *Nat Rev Neurosci*. 13(5):336–349.

Buzsáki G, Geisler C, Henze DA, Wang X-J. 2004. Interneuron diversity series: circuit complexity and axon wiring economy of cortical interneurons. *Trends Neurosci*. 27(4):186–193.

Cabeza R. 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging*. 17(1):85–100.

Cabeza R, Albert M, Belleville S, Craik FIM, Duarte A, Grady CL, Lindenberger U, Nyberg L, Park DC, Reuter-Lorenz PA, et al. 2018. Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat Rev Neurosci*. 19(11):701–710.

Catani M, Allin MPG, Husain M, Pugliese L, Mesulam MM, Murray RM, Jones DK 2007. Symmetries in human brain language pathways correlate with verbal recall. *PNAS*. 104:17163–17168.

Cedres N, Machado A, Molina Y, Diaz-Galvan P, Hernández-Cabrera JA, Barroso J, Westman E, Ferreira D. 2019. Subjective cognitive decline below and above the age of 60: a multivariate study on neuroimaging, cognitive, clinical, and demographic measures. *J Alzheimer Dis*. 68:295–309.

Core TR. 2016. *R: a language and environment for statistical computing*. Vienna, Austria.

Costafreda SG, Fu CHY, Lee L, Everitt B, Brammer MJ, David AS. 2006. A systematic review and quantitative appraisal of fMRI studies of verbal fluency: role of the left inferior frontal gyrus. *Hum Brain Mapp*. 27(10):799–810.

Crossley M, D’Arcy C, Rawson NS. 1997. Letter and category fluency in community-dwelling Canadian seniors: a comparison of normal participants to those with dementia of the Alzheimer or vascular type. *J Clin Exp Neuropsychol*. 19(1):52–62.

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, et al. 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 31(3):968–980.

Erkinjuntti T, Hokkanen L, Sulkava R, Palo J. 1988. The Blessed Dementia Scale as a screening test for dementia. *Int J Geriatr Psychiatry*. 3(4):267–273.

Farahani FV, Karwowski W, Lighthall NR. 2019. Application of graph theory for identifying connectivity patterns in human brain networks: a systematic review. *Front Neurosci*. 13:585.

Ferreira D, Bartrés-Faz D, Nygren L, Rundkvist LJ, Molina Y, Machado A, Junqué C, Barroso J, Westman E. 2016. Different reserve proxies confer overlapping and unique endurance to cortical thinning in healthy middle-aged adults. *Behav Brain Res*. 311:375–383.

Ferreira D, Correia R, Nieto A, Machado A, Molina Y, Barroso J. 2015. Cognitive decline before the age of 50 can be detected with sensitive cognitive measures. *Psicothema*. 27(3):216–222.

Ferreira D, Machado A, Molina Y, Nieto A, Correia R, Westman E, Barroso J. 2017. Cognitive variability during middle-age: possible association with neurodegeneration and cognitive reserve. *Front Aging Neurosci*. 9(188):1–14.

Ferreira D, Molina Y, Machado A, Westman E, Wahlund L-O, Nieto A, Correia R, Junqué C, Díaz-Flores L, Barroso J. 2014. Cognitive decline is mediated by gray matter changes during middle age. *Neurobiol Aging*. 35(5):1086–1094.

Fitzhugh MC, Braden BB, Sabbagh MN, Rogalsky C, Baxter LC. 2019. Age-related atrophy and compensatory neural networks in reading comprehension. *J Int Neuropsychol Soc*. 25(6):569–582.

Folstein MF, Folstein SE, McHugh PR. 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 12(3):189–198.

Franzmeier N, Hartmann J, Taylor ANW, Araque-Caballero MÁ, Simon-Vermot L, Kambeitz-Ilankovic L, Bürger K, Catak C, Janowitz D, Müller C, et al. 2018. The left frontal cortex supports reserve in aging by enhancing functional network efficiency. *Alzheimer Res Ther*. 10(1):28.

Genovese CR, Lazar NA, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*. 15(4):870–878.

Gernsbacher MA, Kaschak MP. 2003. Neuroimaging studies of language production and comprehension. *Annu Rev Psychol*. 54:91–114.

Golden CJ. 1978. *Stroop Colour and Word Test: a manual for clinical and experimental uses*. Chicago: Stoelting Company.

Gonzalez-Burgos L, Barroso J, Ferreira D. 2020. Cognitive reserve and network efficiency as compensatory mechanisms of the effect of aging on phonemic fluency. *Aging*. 12(22):23351–23378.

Gonzalez-Burgos L, Hernández-Cabrera JA, Westman E, Barroso J, Ferreira D. 2019. Cognitive compensatory mechanisms in normal aging: a study on verbal fluency and the contribution of other cognitive functions. *Aging*. 11(12): 4090–4106.

Grady CL. 2008. Cognitive neuroscience of aging. *Ann N Y Acad Sci*. 1124(1):127–144.

van den Heuvel MP, Sporns O. 2013. Network hubs in the human brain. *Trends Cogn Sci*. 17(12):683–696.

van den Heuvel MP, Sporns O. 2019. A cross-disorder connectome landscape of brain dysconnectivity. *Nat Rev Neurosci*. 20(7):435–446.

Hochberg Y, Benjamini Y. 1990. More powerful procedures for multiple significance testing. *Stat Med*. 9(7):811–818.

Hülür G, Ram N, Willis SL, Warner Schaie K, Gerstorf D. 2015. Cognitive dedifferentiation with increasing age and proximity of death: within-person evidence from the Seattle longitudinal study. *Psychol Aging*. 30(2):311–323.

Kaplan EF, Goodglass H, Weintraub S. 1983. *The Boston Naming Test*. 2nd ed. Philadelphia: Lea & Febiger.

Kavé G, Mashal N. 2012. Age-related differences in word-retrieval but not in meaning generation. *Aging Neuropsychol Cogn*. 19(4):515–529.

Latora V, Marchiori M. 2001. Efficient behavior of small-world networks. *Phys Rev Lett*. 87(19):198701.

Lee DH, Lee P, Seo SW, Roh JH, Oh M, Oh JS, Oh SJ, Kim JS, Jeong Y. 2019. Neural substrates of cognitive reserve in Alzheimer’s disease spectrum and normal aging. *Neuroimage*. 186: 690–702.

Lezak M, Howieson DB, Loring DW. 2004. *Neuropsychological assessment*. 4th ed. New York: Oxford University Press.

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*. 33(5):827–840.

Machado A, Barroso J, Molina Y, Nieto A, Díaz-Flores L, Westman E, Ferreira D. 2018. Proposal for a hierarchical, multidimensional, and multivariate approach to investigate cognitive aging. *Neurobiol Aging*. 71:179–188.

Marques P, Moreira P, Magalhães R, Costa P, Santos N, Zihl J, Soares J, Sousa N. 2016. The functional connectome of cognitive reserve. *Hum Brain Mapp*. 37(9):3310–3322.

Marsolais Y, Methqal I, Joanette Y. 2015. Marginal neurofunctional changes in high-performing older adults in a verbal fluency task. *Brain Lang*. 140:13–23.

Marsolais Y, Perlbarg V, Benali H, Joanette Y. 2014. Age-related changes in functional network connectivity associated with high levels of verbal fluency performance. *Cortex*. 58:123–138.

Mazoyer B, Zago L, Jobard G, Crivello F, Joliot M, Perchey G, Mellet E, Petit L, Tzourio-Mazoyer N. 2014. Gaussian mixture modeling of hemispheric lateralization for language in a large sample of healthy individuals balanced for handedness. *PLoS One*. 9(6):e101165.

Mesulam MM. 1998. From sensation to cognition. *Brain*. 121(Pt 6):1013–1052.

Methqal I, Marsolais Y, Wilson MA, Monchi O, Joanette Y. 2019. More expertise for a better perspective: task and strategy-driven adaptive neurofunctional reorganization for word production in high-performing older adults. *Aging Neuropsychol Cogn*. 26(2):190–221.

Meunier D, Stamatakis EA, Tyler LK. 2014. Age-related functional reorganization, structural changes, and preserved cognition. *Neurobiol Aging*. 35(1):42–54.

Mijalkov M, Kakaei E, Pereira JB, Westman E, Volpe G. 2017. BRAPH: a graph theory software for the analysis of brain connectivity. Hayasaka S, editor. *PLoS One*. 12(8):e0178798.

Morcom AM, Johnson W. 2015. Neural reorganization and compensation in aging. *J Cogn Neurosci*. 27(7):1275–1285.

Mowinckel AM, Vidal-Piñeiro D. 2019. Visualisation of brain statistics with R-packages ggseg and ggseg3d. *arXiv:191208200*.

Muehlboeck J-S, Westman E, Simmons A. 2014. TheHiveDB image data management and analysis framework. *Front Neuroinf*. 7:49.

Nakajima R, Kinoshita M, Shinohara H, Nakada M. 2019. The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging Behav*. 14(6):2817–2830.

Nemy M, Cedres N, Grothe MJ, Muehlboeck J-S, Lindberg O, Nedelska Z, Stepankova O, Vyslouzilova L, Eriksdotter M, Barroso J, et al. 2020. Cholinergic white matter pathways make a stronger contribution to attention and memory in normal aging than cerebrovascular health and nucleus basalis of Meynert. *NeuroImage*. 211:116607.

Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. 2012. Memory aging and brain maintenance. *Trends Cogn Sci*. 16(5):292–305.

Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR. 2004. Aging reduces neural specialization in ventral visual cortex. *PNAS*. 101(35):13091–13095.

Park DC, Reuter-Lorenz P. 2009. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. 60:173–196.

Pereira JB, van Westen D, Stomrud E, Strandberg TO, Volpe G, Westman E, Hansson O. 2018. Abnormal structural brain connectome in individuals with preclinical Alzheimer's disease. *Cereb Cortex*. 28(10):3638–3649.

Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. 1982. Measurement of functional activities in older adults in the community. *J Gerontol*. 37(3):323–329.

Reuter-Lorenz PA, Cappell KA. 2008. Neurocognitive aging and the compensation hypothesis. *Curr Dir Psychol Sci*. 17(3):177–182.

Rodriguez-Aranda C, Martinussen M. 2006. Age-related differences in performance of phonemic verbal fluency measured by Controlled Oral Word Association Task (COWAT): a meta-analytic study. *Dev Neuropsychol*. 30(2):697–717.

Roldan-Tapia L, Garcia J, Canovas R, Leon I. 2012. Cognitive reserve, age, and their relation to attentional and executive functions. *Appl Neuropsychol Adult*. 19(1):2–8.

Rubinov M, Sporns O. 2010. Complex network measures of brain connectivity: uses and interpretations. *NeuroImage*. 52(3):1059–1069.

Sala-Llonch R, Bartrés-Faz D, Junqué C. 2015. Reorganization of brain networks in aging: a review of functional connectivity studies. *Front Psychol*. 6:663.

Sala-Llonch R, Junqué C, Arenaza-Urquijo EM, Vidal-Piñeiro D, Valls-Pedret C, Palacios EM, Domènech S, Salvà A, Bargalló N, Bartrés-Faz D. 2014. Changes in whole-brain functional networks and memory performance in aging. *Neurobiol Aging*. 35(10):2193–2202.

Schaie KW, Willis SL. 1993. Age difference patterns of psychometric intelligence in adulthood: generalizability within and across ability domains. *Psychol Aging*. 8(1):44–55.

Shafto MA, Tyler LK. 2014. Language in the aging brain: the network dynamics of cognitive decline and preservation. *Science*. 346(6209):583–587.

Simmons A, Westman E, Muehlboeck S, Mecocci P, Vellas B, Tsolaki M, Kloszewska I, Wahlund L-O, Soininen H, Lovestone S, et al. 2009. MRI measures of Alzheimer's disease and the AddNeuroMed study. *Ann N Y Acad Sci*. 1180:47–55.

Sleimen-Malkoun R, Temprado J-J, Hong SL. 2014. Aging induced loss of complexity and dedifferentiation: consequences for coordination dynamics within and between brain, muscular and behavioral levels. *Front Aging Neurosci*. 6:140.

Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, Ewers M, Franzmeier N, Kempermann G, Kremen WS, et al. 2020. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's Dementia*. 16(9):1305–1311.

Stern Y, Gazes Y, Razlighi Q, Steffener J, Habeck C. 2018. A task-invariant cognitive reserve network. *NeuroImage*. 178:36–45.

Tijms BM, Series P, Willshaw DJ, Lawrie SM. 2012. Similarity-based extraction of individual networks from gray matter MRI scans. *Cereb Cortex*. 22(7):1530–1541.

Tomasi D, Volkow ND. 2012. Resting functional connectivity of language networks: characterization and reproducibility. *Mol Psychiatry*. 17(8):841–854.

Tombaugh T. 1999. Normative data stratified by age and education for two measures of verbal fluency FAS and animal naming. *Arch Clin Neuropsychol*. 14(2):167–177.

Vaqué-Alcázar L, Sala-Llonch R, Abellaneda-Pérez K, Coll-Padrós N, Valls-Pedret C, Bargalló N, Ros E, Bartrés-Faz D. 2020. Functional and structural correlates of working memory performance and stability in healthy older adults. *Brain Struct Funct*. 225(1):375–386.

Wechsler D. 1997. *Wechsler Memory Scale – technical manual*. 3rd ed. San Antonio, TX: The Psychological Corporation.

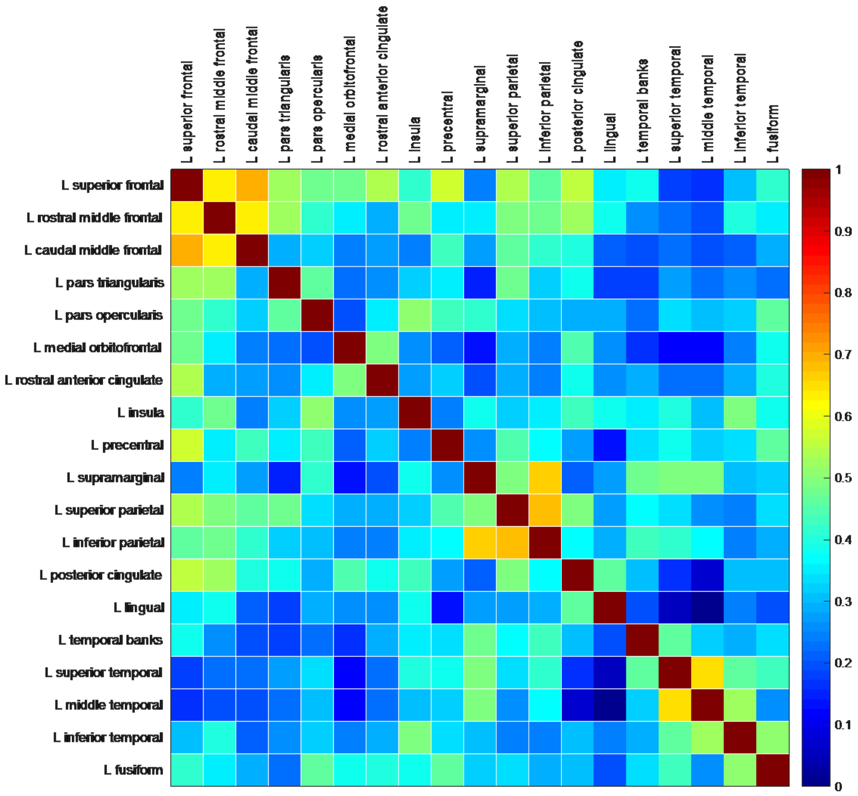
Zhang H, Eppes A, Diaz MT. 2019. Task difficulty modulates age-related differences in the behavioral and neural bases of language production. *Neuropsychologia*. 124:254–273.

Zhang H, Sachdev PS, Wen W, Kochan NA, Crawford JD, Brodaty H, Slavin MJ, Reppermund S, Kang K, Trollor JN. 2013. Grey matter correlates of three language tests in non-demented older adults. Zang Y-F, editor. *PLoS One*. 8(11):e80215.

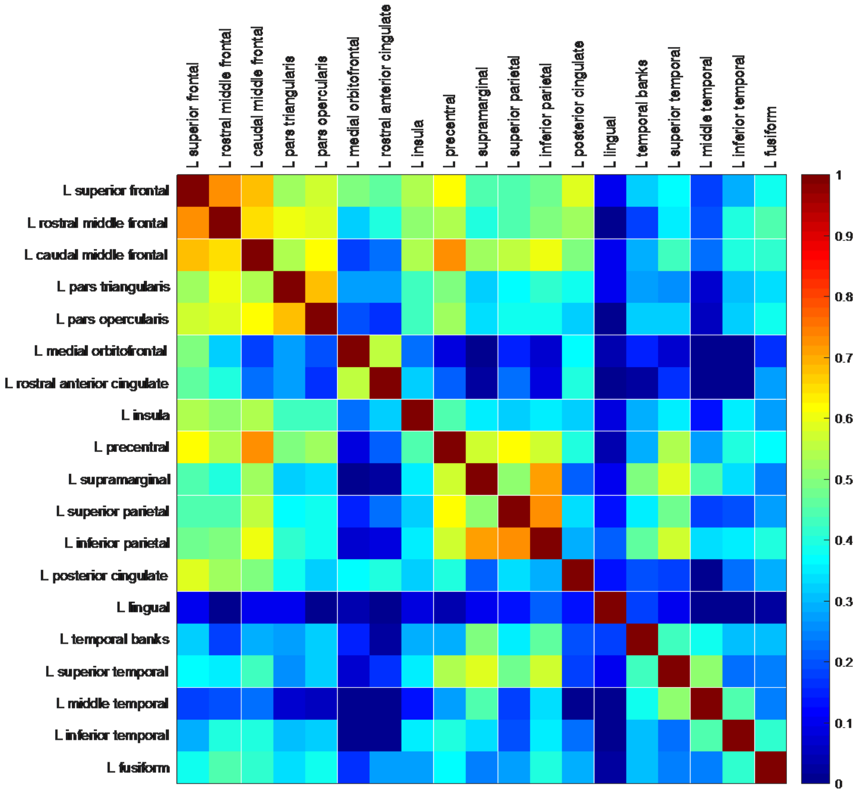
Supplementary Material

Cortical networks underpinning compensation of verbal fluency in normal aging.

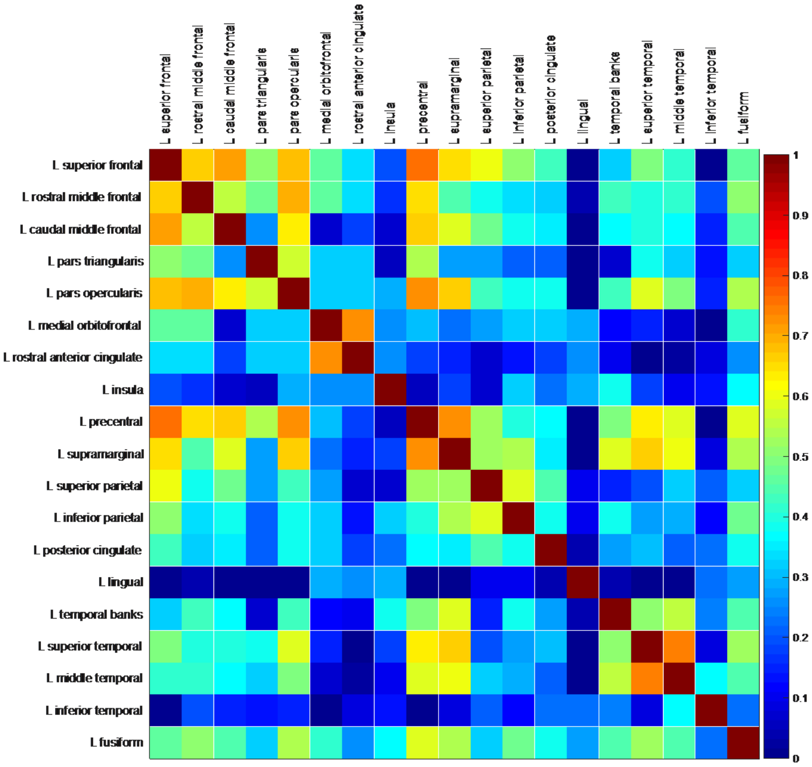
Lissett Gonzalez-Burgos[1,2]; Joana B. Pereira[2], Rosaleena Mohanty[2], José Barroso[1], Eric Westman[2,3], and Daniel Ferreira[1,2]*



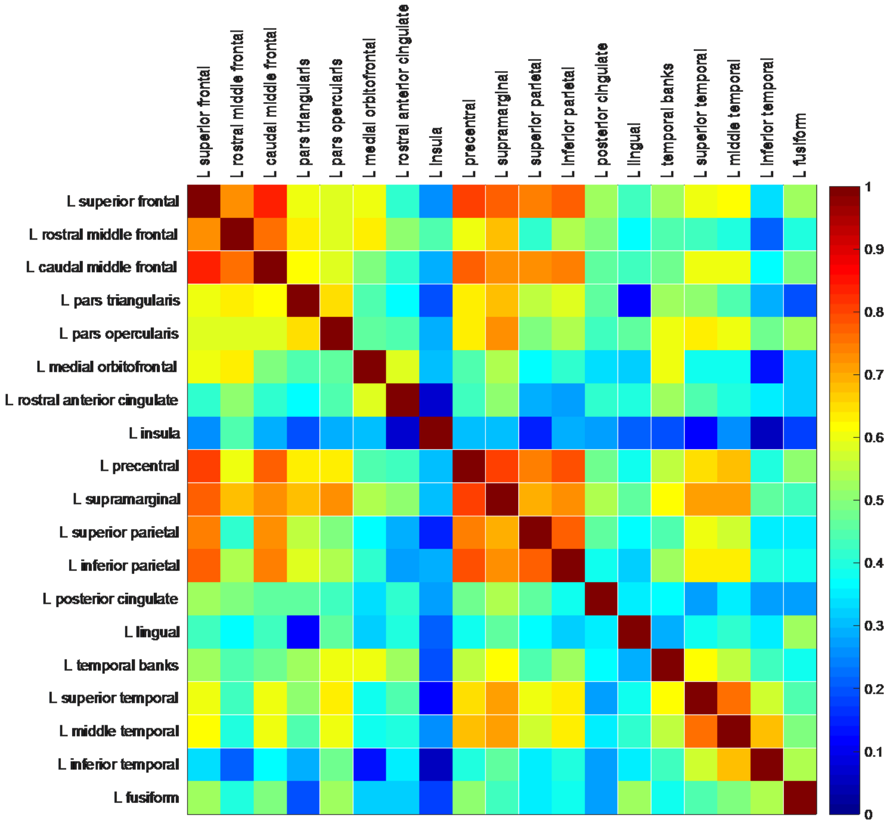
Supplementary Figure S1. Weighted correlation matrix, phonemic fluency network (YA-LP). YA, younger age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



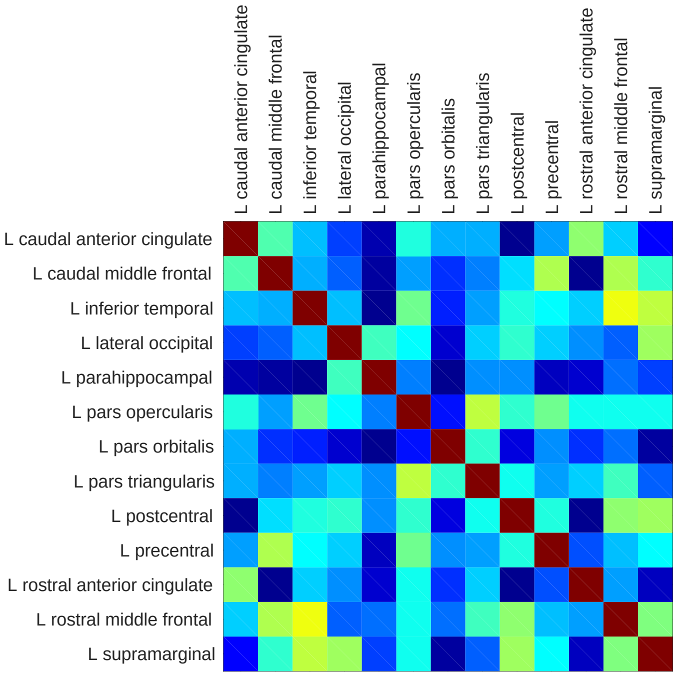
Supplementary Figure S2. Weighted correlation matrix, phonemic fluency network (YA-HP). YA, younger age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



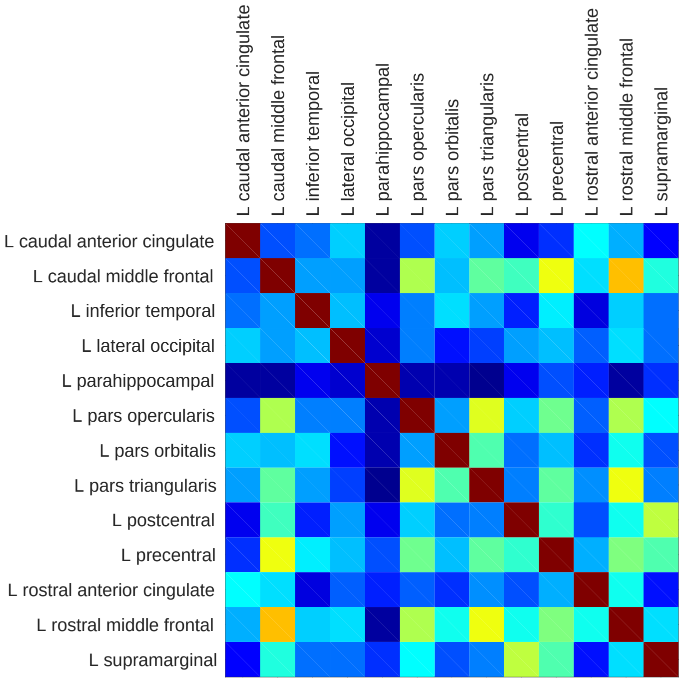
Supplementary Figure S3. Weighted correlation matrix, phonemic fluency network (OA-LP). OA, older age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



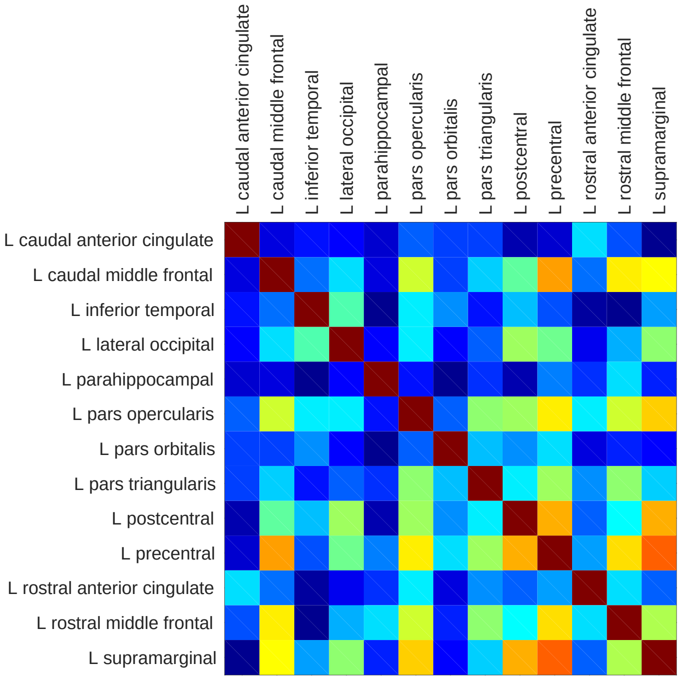
Supplementary Figure S4. Weighted correlation matrix, phonemic fluency network (OA-HP). OA, older age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



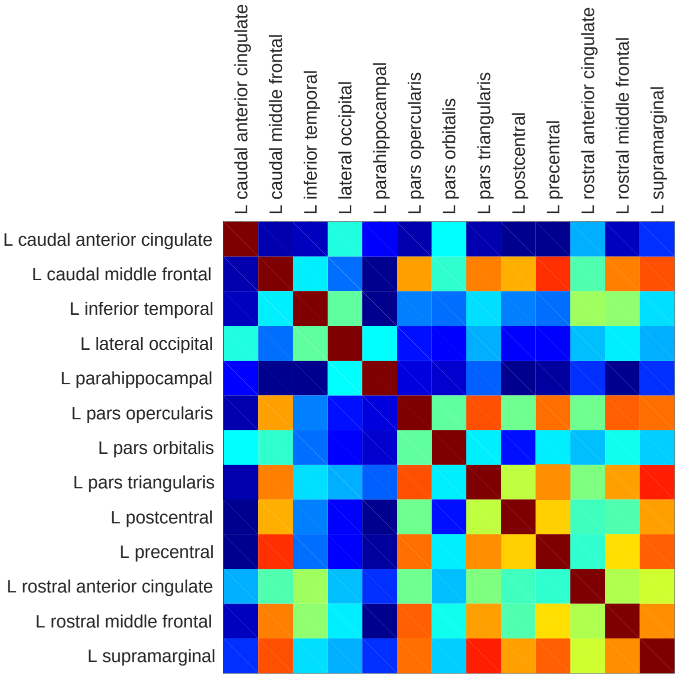
Supplementary Figure S5. Weighted correlation matrix, semantic network (YA-LP). YA, younger age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



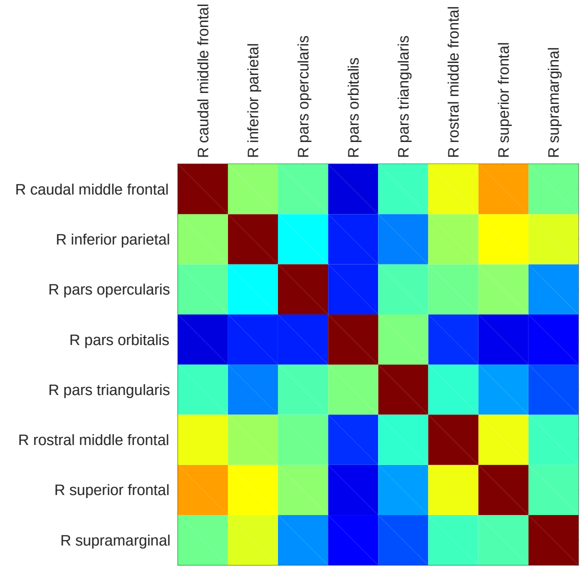
Supplementary Figure S6. Weighted correlation matrix, semantic network (YA-HP). YA, younger age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



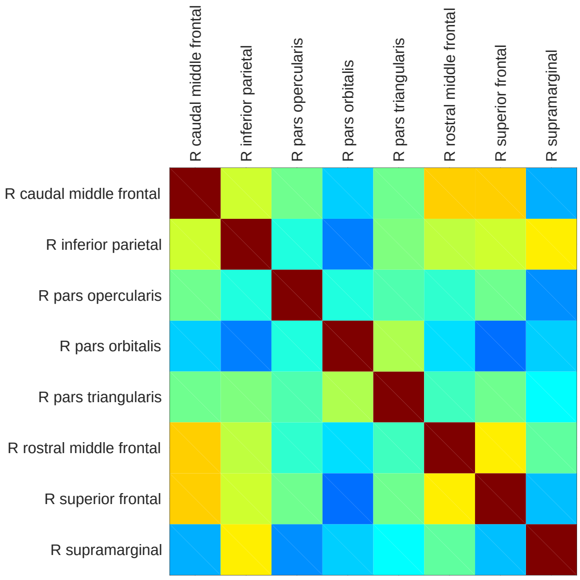
Supplementary Figure S7. Weighted correlation matrix, semantic network (OA-LP). OA, older age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



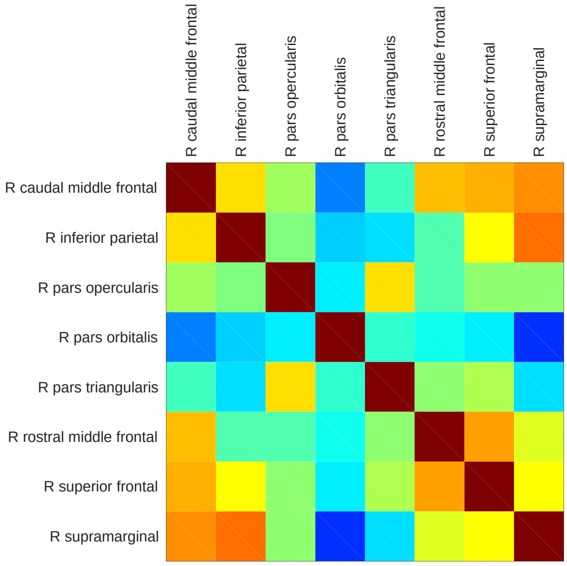
Supplementary Figure S8. Weighted correlation matrix, semantic network (OA-HP). OA, older age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



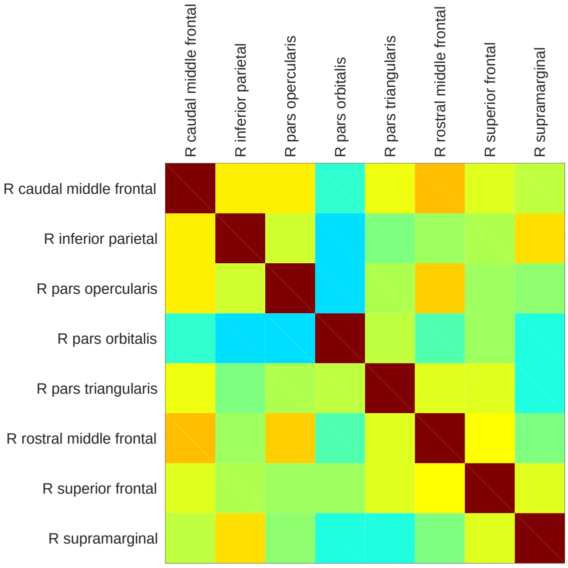
Supplementary Figure S9. Weighted correlation matrix, fronto-parietal network (YA-LP). YA, younger age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



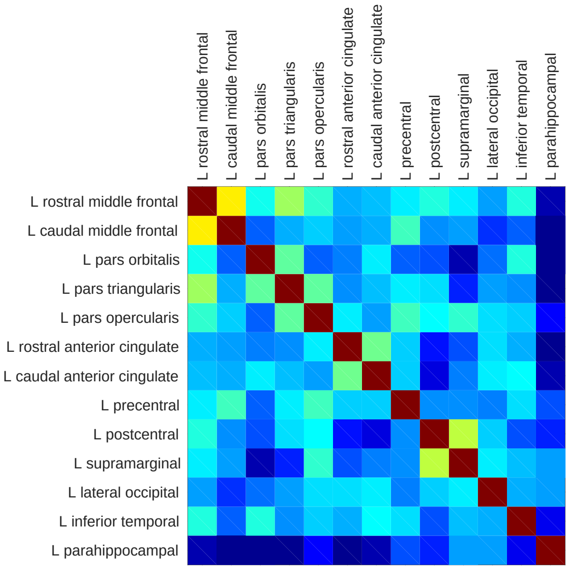
Supplementary Figure S10. Weighted correlation matrix, fronto-parietal network (YA-HP). YA, younger age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



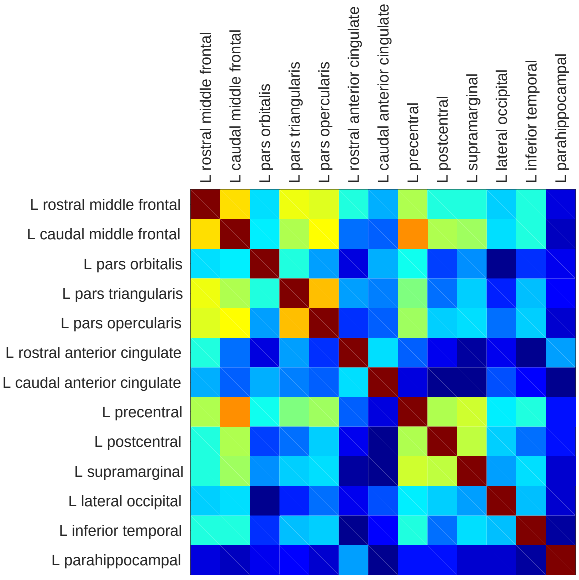
Supplementary Figure S11. Weighted correlation matrix, fronto-parietal network (OA-LP). OA, older age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



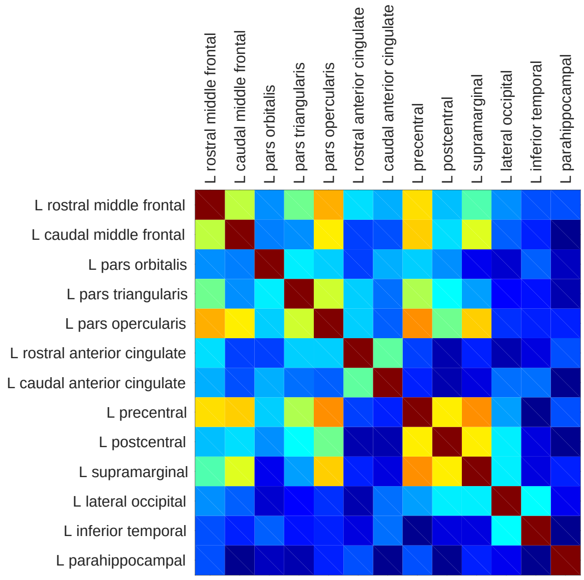
Supplementary Figure S12. Weighted correlation matrix, fronto-parietal network (OA-HP). OA, older age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



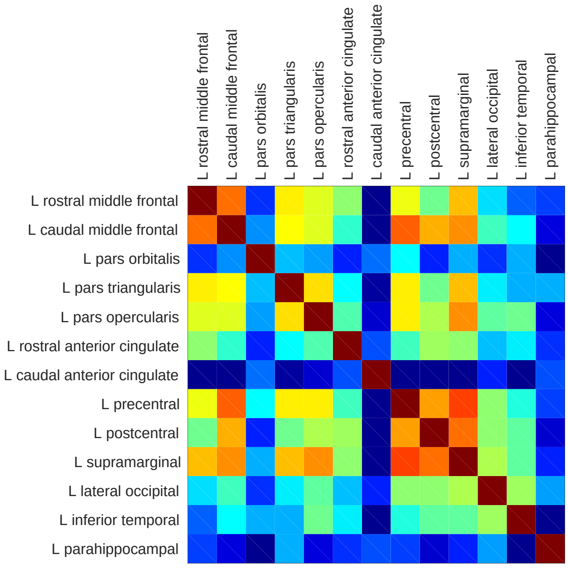
Supplementary Figure S13. Weighted correlation matrix, semantic network in phonemic fluency performance groups (YA-LP). YA, younger age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



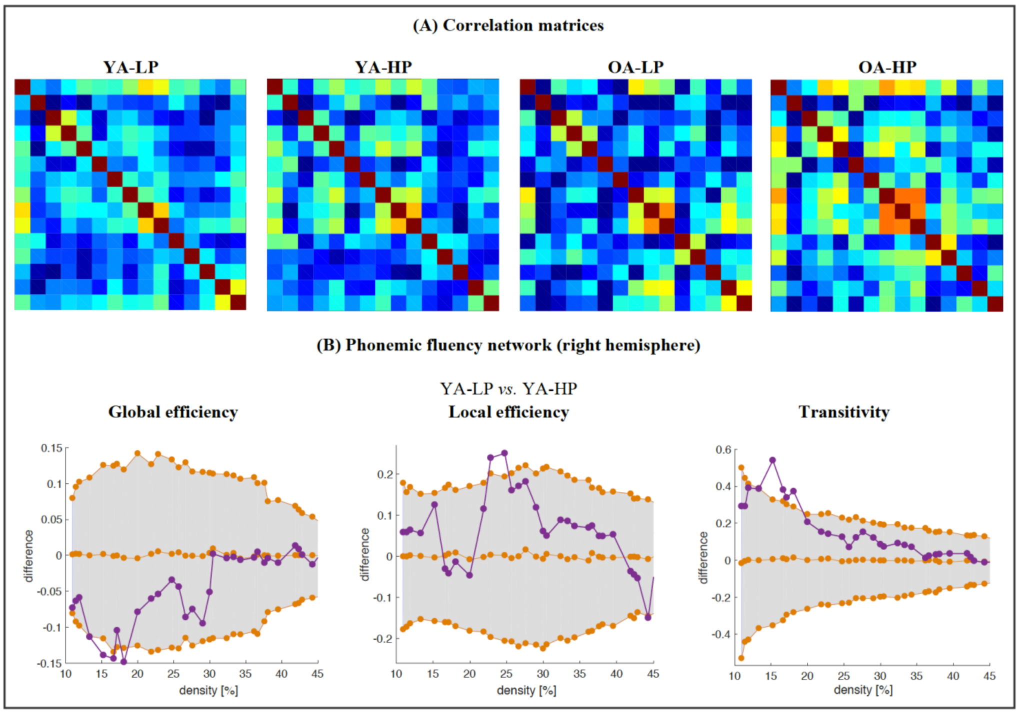
Supplementary Figure S14. Weighted correlation matrix, semantic network in phonemic fluency performance groups (YA-HP). YA, younger age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



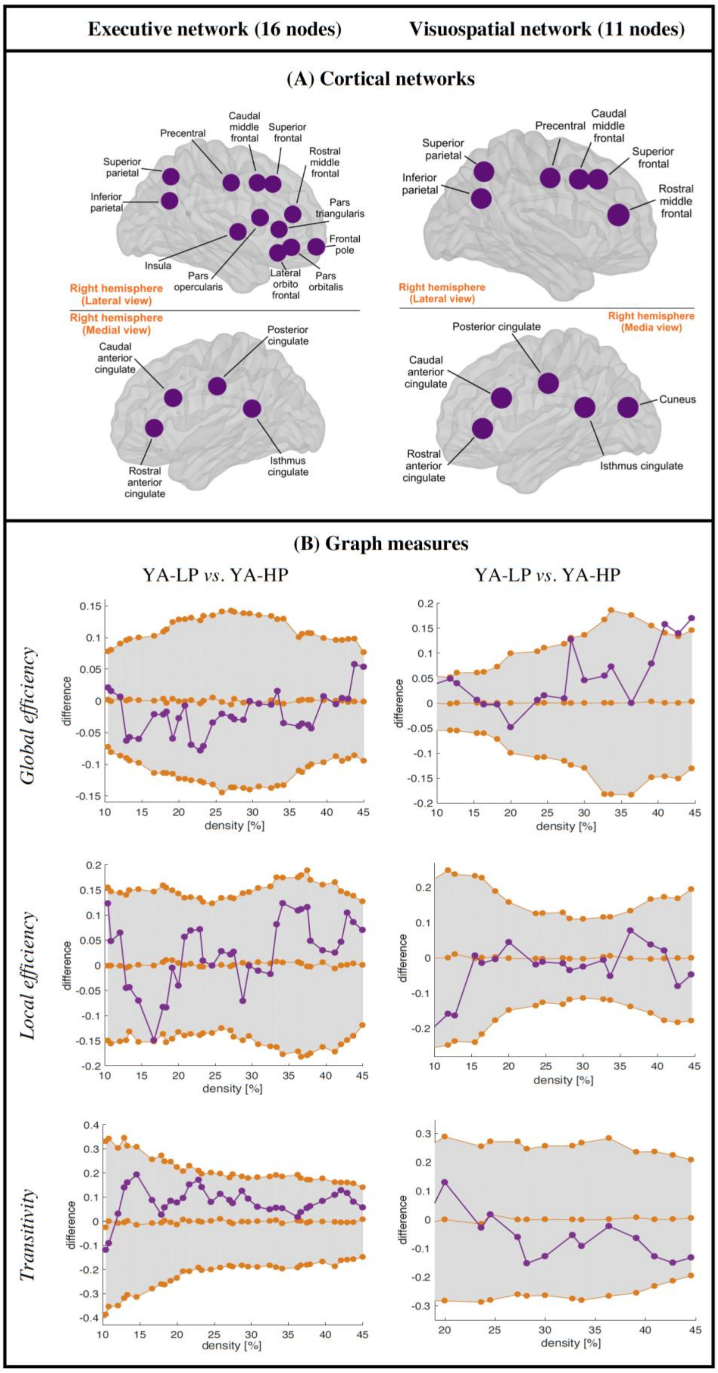
Supplementary Figure S15. Weighted correlation matrix, semantic network in phonemic fluency performance groups (OA-LP). OA, older age. LP, low performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



Supplementary Figure S16. Weighted correlation matrix, semantic network in phonemic fluency performance groups (OA-HP). OA, older age. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations.



Supplementary Figure S17. **Phonemic fluency network (right hemisphere).** Regions included: superior frontal, pars orbitalis, pars triangularis, pars opercularis, precentral, insula, superior parietal, inferior parietal, inferior temporal, lingual, fusiform, rostral anterior cingulate, caudal anterior cingulate, posterior cingulate, isthmus cingulate, all these from the right hemisphere. (A) Weighted correlation matrices of the phonemic fluency network (right hemisphere) in phonemic fluency performance groups. YA, younger age. LP, low performance. HP, high performance. The color bar indicates the strength of the Pearson correlation coefficients: colder colors represent weaker correlations, while warmer colors represent stronger correlations. (B) Comparison between the young performance groups (YA-LP vs. YA-HP) across global graph measures. Network densities are displayed on the x-axis from min = 10% to max = 45%, in steps of 1%. Between-group differences in the global graph measures are displayed on the y-axis. The 95% confidence intervals were used as critical values for testing of the null hypothesis at $p \leq 0.05$ (two-tailed), however graphs show the one-tailed t-test results. There were no significant group differences in the *average strength* (YA-LP = 3.95; YA-HP = 3.80, *p*-value (two-tailed) = 0.808).


Executive network (16 nodes)
Visuospatial network (11 nodes)
(A) Cortical networks
Precentral
Caudal middle frontal
Superior frontal
Rostral middle frontal
Superior parietal
Inferior parietal
Pars triangularis
Frontal pole
Insula
Pars opercularis
Lateral orbito frontal
Pars orbitalis
Right hemisphere (Lateral view)
Right hemisphere (Medial view)
Caudal anterior cingulate
Posterior cingulate
Rostral anterior cingulate
Isthmus cingulate
Precentral
Caudal middle frontal
Superior parietal
Superior frontal
Inferior parietal
Rostral middle frontal
Right hemisphere (Lateral view)
Right hemisphere (Media view)
Posterior cingulate
Caudal anterior cingulate
Cuneus
Rostral anterior cingulate
Isthmus cingulate
(B) Graph measures
YA-LP vs. YA-HP
YA-LP vs. YA-HP
Global efficiency
Local efficiency
Transitivity
difference
density [%]
10
15
20
25
30
35
40
45

Supplementary Figure S18. **Comparison between the younger age – low performance and younger age - high performance groups (YA-LP vs. YA-HP) across global graph measures in the larger executive and visuospatial networks. (A)** *Cortical networks, cortical regions included as nodes. (B) Network densities are displayed on the x-axis from min = 10% to max = 45%, in steps of 1%. Between-group differences in the global graph measures are displayed on the y-axis. The 95% confidence intervals were used as critical values for testing of the null hypothesis at p≤0.05 (two-tailed), however graphs show the one-tailed t-test results.* There were no significant group differences in the *average strength* (Executive network, YA-LP = 0.502, YA-HP = 0.9960; *p* (two-tailed) = 4.523. Visuospatial network, YA-LP = 3.477, YA-HP = 3.304; *p* (two-tailed) = 0.735).

STUDY IV

Functional Connectivity and Compensation of Phonemic Fluency in Aging

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Keywords (max 8): resting-state, functional MRI, functional connectivity, verbal fluency, phonemic fluency, cognitive reserve, compensation, healthy aging

ABSTRACT

Neural compensatory mechanisms associated with broad cognitive abilities have been studied. However, those associated with specific cognitive subdomains (e.g., verbal fluency) remain to be investigated in healthy aging. Here, we delineate: **(a)** neural substrates of verbal (phonemic) fluency, and **(b)** compensatory mechanisms mediating the association between these neural substrates and phonemic fluency. We analyzed resting-state functional magnetic resonance imaging from 133 right-handed, cognitively normal individuals who underwent the Controlled Oral Word Association Test (COWAT) to record their phonemic fluency. We evaluated functional connectivity in an established and extended language network comprising Wernicke*,* Broca*,* thalamic and anti-correlated modules. **(a)** We conducted voxel-wise multiple linear regression to identify the brain areas associated with phonemic fluency. **(b)** We used mediation effects of cognitive reserve, measured by the Wechsler Adult Intelligence Scale – Information subtest, upon the association between functional connectivity and phonemic fluency tested to investigate compensation. We found that: **(a)** Greater functional connectivity between the Wernicke module and brain areas within the anti-correlated module was associated with better performance in phonemic fluency, **(b)** Cognitive reserve was an unlikely mediator in younger adults. In contrast, cognitive reserve was a partial mediator of the association between functional connectivity and phonemic fluency in older adults, likely representing compensation to counter the effect of aging. We conclude that in healthy aging, higher performance in phonemic fluency at older ages could be attributed to greater functional connectivity partially facilitated by higher cognitive reserve, presumably reflecting compensatory mechanisms to minimize the effect of aging.

1. INTRODUCTION

Despite changes to brain integrity with aging, some functions such as language processes remain remarkably preserved (Ansado et al. 2013; Schaie and Willis 1993). One theory for the maintenance of language function in light of age-related brain atrophy is the engagement of compensatory brain networks (Park and Reuter-Lorenz 2009). The impact of age-related atrophy on various cognitive domains is well-documented (D. Ferreira et al. 2014; Lowe et al. 2019; Raz and Rodrigue 2006; Sungura et al. 2020). Hence, investigating how compensatory mechanisms in specific cognitive domains (e.g., language) counteract the onslaught of aging may articulate ways to improve everyday functioning of older adults.

Traditionally, the characterization of the language network in the brain has been limited to the Broca's area (inferior frontal) and Wernicke's area (superior temporal), which are associated with the functions of language production and language comprehension, respectively (Mesulam 1998). However, recent resting-state functional connectivity and lesion studies have implicated the contribution of a more extended network in language processing (Birn et al. 2010; Costafreda et al. 2006; Marsolais et al. 2014; Marsolais, Methqal, and Joanette 2015; Methqal et al. 2019; Tomasi and Volkow 2012; Zhang et al. 2013). In the elderly, decline in language functions such as experiencing difficulty in retrieval of words is common and could be an early indicator of presence of pathology (Henry and Crawford 2004). Such deficits can be captured by cognitive tests evaluating verbal fluency, particularly sensitive towards frontal lobe functions, critical for retrieval, free recall and executive functions (Azuma 2004; Cabeza and Dennis 2012; Henry and Crawford 2004; Jurado et al. 2000; Robinson et al. 2012).

One of the subdomains of verbal fluency is phonemic fluency, which is commonly used in clinical practice and research. Phonemic fluency tests require participants to say as many words as possible beginning with a specific letter (e.g., F, E) usually within one minute.

Phonemic fluency has been found to be relatively stable during aging in comparison to other fluency domains (Elgamal, Roy, and Sharratt 2011; Foldi et al. 2003; Gonzalez-Burgos et al. 2019; Troyer 2000). Although verbal fluency is typically measured based on the number of timely acceptable answers, alternative qualitative measures have been proposed, including clustering (groupings or contiguous words in the same sub-category) and switching (changing groupings) to infer the nature of the deficit (Troyer, Moscovitch, and Winocur 1997; Troyer 2000). Impaired clustering reflects compromised temporal cortex, while impaired switching reflects compromised dorsolateral and superior medial frontal regions (Troyer et al. 1998). A fall in switching performance is evident in advanced ages (Pereira et al. 2018; Troyer, Moscovitch, and Winocur 1997) and is associated with impaired working memory. In contrast, the stability in phonemic fluency performance has been linked with the contribution of other cognitive domains (Troyer et al. 1998), including a more efficient use of ipsilateral language networks (Gonzalez-Burgos, Barroso, and Ferreira 2020), and perhaps involving a greater capacity to recruit contralateral frontoparietal networks (Gonzalez-Burgos et al. 2019). Resting-state MRI-based functional connectivity studies have identified four modules related to performance in phonemic fluency (Tomasi and Volkow 2012), including the Broca module, Wernicke module, thalamic module and anti-correlated module.

Although not entirely characterized, ipsilateral language networks and contralateral frontoparietal networks may form the basis for compensation and the stability in phonemic fluency, which could be facilitated by higher levels of cognitive reserve (Gonzalez-Burgos, Barroso, and Ferreira 2020). Cognitive reserve is “the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult” (Bartrés-Faz et al. 2020). Individuals with higher cognitive reserve produce more words in phonemic fluency (Auriacombe et al. 2001; Balduino et al. 2020; Crossley, D’arcy, and Rawson 1997; Roldán-Tapia et al. 2012; Tombaugh, Kozak, and

Rees 1999), have greater neural efficiency (Bartrés-Faz et al. 2009; Fernández-Cabello et al. 2016), and thus, have greater potential for compensation. The closest direct measure of cognitive reserve is based on functional brain processes (Bartrés-Faz et al. 2020), addressed with methods such as functional magnetic resonance imaging (MRI). Despite the wealth of research on identifying and characterizing distinct aspects of verbal fluency, limited neuroimaging studies have investigated the neural correlates of phonemic fluency, specifically in the context of cognitive reserve (Boyle et al. 2020; Rodríguez-Aranda et al. 2020).

To this end, we aimed to study the neural functional substrates of phonemic fluency and potential compensatory mechanisms facilitated by cognitive reserve, which would contribute to high performance in phonemic fluency across age groups. Firstly, we characterized resting-state functional MRI-based functional connectivity within the four modules previously related with phonemic fluency (Tomasi and Volkow 2012). By including these four modules, we extended beyond the traditional Broca's and Wernicke's brain areas and tested for both within and outside network effects, which may be relevant for investigating compensation. We described functional connectivity patterns in younger and older adults as well as tested for potential differences in functional connectivity between the two age groups. Secondly, we tested for the association between functional connectivity within the four modules and phonemic fluency. Finally, we examined the mediation effect of cognitive reserve on the relationship between functional connectivity and performance in phonemic fluency, separately in younger and older adults. We hypothesized that: (a) younger adults would show greater functional connectivity in the four modules previously related with phonemic fluency than older adults; (b) functional connectivity particularly in Broca's module (language production center) would be associated with performance in phonemic fluency; and (c) cognitive reserve would mediate the relationship between functional connectivity involving both linguistic and non-linguistic brain areas and performance in phonemic fluency, especially in older adults, hence indicating compensation of the effect of age in phonemic fluency.

2. METHODS

2.1 Participants

A group of 149 cognitively normal healthy individuals were selected from a community-based longitudinal cohort, GENIC (Group of Neuropsychological Studies of the Canary Islands) (D. Ferreira et al. 2015). For the current study, individuals were selected at the earliest timepoint (not necessarily baseline visit) where a functional MRI was available along with the following inclusion criteria: (a) age ≥ 35 years; (b) right-handed; (c) normal performance in comprehensive neuropsychological assessment using pertinent clinical normative data (i.e. individuals with mild cognitive impairment or dementia were excluded); (d) preserved global cognitive and functional status operationalized as a Mini-Mental State Examination score (MMSE) ≥ 24, a Blessed Dementia Scale (BDRS) score < 4 and/or a Functional Activity Questionnaire score < 6); (e) no neurologic, psychiatric or systemic diseases; (f) no history of substance abuse;(g) no abnormal findings in MRI (e.g. stroke, tumors, hippocampal sclerosis, etc.), as assessed by an experienced neuroradiologist (L.D-F); and (h) a balanced distribution of sex (44.9% female). Although the BDRS scale cut-off for abnormality is frequently established at ≥ 4 points (Blessed, Tomlinson, and Roth 1968; Erkinjuntti et al. 1988), the 'changes in personality, interests and drive' subscale may influence the BDRS total score and does not necessary reflect impairment in activities of daily living (Machado et al. 2018). With the aim of excluding only individuals with functional impairment, as an exception, we included those participants with total BDRS scores ≥ 4 (N=8) if: (a) 70% or higher percentage of the BDRS total score resulted from ‘changes in personality, interests and drive’ subscale; and (b) if a score ≤ 1.5 was obtained in the other two subscales (‘changes in performance of everyday activities’ and ‘changes in habits’). The same procedure has been used in previous studies (Gonzalez-Burgos et al. 2019; Machado et al. 2018). This study was reviewed and approved by the ethics committee of the University of La Laguna, Spain. All participants provided their written and informed consent for participation in this study.

2.2 Neuropsychological assessments

All individuals underwent an extensive neuropsychological battery, which assessed multiple cognitive domains (language, processing speed, attention, executive functions, episodic memory, procedural memory, visuoconstructive, visuoperceptive and visuospatial functions). To investigate the hypothesis of the current study, we focused on verbal fluency as the primary outcome. Phonemic fluency, a subdomain of verbal fluency, was measured with the Controlled Oral Word Association Test (COWAT) (Benton, Hamsher, and Sivan 1989). Individuals were instructed to recall words beginning with the letters F, A, and S, in a span of one minute for each letter. Intrusions (proper nouns, numbers, derived words) and perseverations (repetitions of correct words) were considered as errors and were excluded. The total number of correct words was counted and a total score (sum of words for F, A, S) was calculated as the measure of phonemic fluency. Cognitive reserve has been conventionally represented by sociobehavioral proxies (e.g., education, IQ, occupation, etc.). While such proxies may not be able to capture any specific functional mechanisms, they capture experiences contributing toward the development of cognitive reserve. In this study, we chose Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Information Subtest (Wechsler 1997), a measure of crystalized intelligence, to represent cognitive reserve as it has been demonstrated (a) to better capture achievements and usage of educational opportunities compared to years of education (Correia et al. 2015), and (b) to have a greater mediation effect between neural correlates of cognition, when treated as a measure of cognitive reserve compared to other sociobehavioral proxies (WAIS-III Vocabulary, Cognitive Reserve Questionnaire, years of education) [Ferreira aet al., 2016] (D. Ferreira et al. 2016) in the current cohort.

2.3 Neuroimaging

All scans were acquired on a 3.0 T GE scanner (General Electric, Milwaukee, WI, USA) with an eight channel high resolution head coil situated at the *Hospital Universitario de Canarias* in Tenerife, Spain. Structural MRI were 3-D T1-weighted fast spoiled gradient echo (FSPGR) scans, acquired sagitally with the following parameters: repetition time (TR) = 8.73 ms, echo time (TE) = 1.74 ms, inversion time (TI) = 650 ms, field of view 250 × 250 mm, matrix 250 × 250 mm, flip angle 12°, slice thickness = 1 mm and voxel resolution = 1 × 1 × 1 mm^3. Six minutes of resting-state functional MRI were collected using single-shot gradient recalled echo-planar T2*-weighted imaging with the following parameters: TR = 2000 ms, 180 time-points, TE = 22.1 ms, field of view = 240 × 240 mm, flip angle = 90°, matrix = 64 × 64, slice thickness = 4 mm, voxel dimensions 3.75 × 3.75 × 4 mm^3 and 36 slices on AC-PC orientation. Participants were instructed to relax with their eyes closed while staying awake and head padding were provided to prevent head motion during scanning.

2.4 Functional connectivity analyses

Functional MRI were preprocessed with the following steps: the initial six functional volumes were discarded to ensure stabilization of magnetization, the remainder functional volumes were slice time corrected to account for temporal differences in the interleaved acquisition, the volumes were realigned to the mean of all functional volumes for motion correction and to obtain the motion parameters, the mean functional volume was realigned and linearly co-registered to the structural MRI with a rigid body transformation, the structural MRI was segmented into tissue classes (gray matter, white matter and cerebrospinal fluid), the structural MRI was normalized to the standard Montreal Neurological Institute (MNI) space to learn the transformation, the motion-corrected functional MRI volumes were normalized to the MNI space using the learned transformation, and spatially smoothed with 8 mm full width at half maximum Gaussian kernel using Statistical Parametric Mapping software version 12 (https://www.fil.ion.ucl.ac.uk/spm/), all automated through a database system (Muehlboeck, Westman, and Simmons 2014). Then, functional MRI were temporally filtered (Gaussian band-pass between 0.01 - 0.1 Hz, implemented with Oxford Centre for Functional MRI of the Brain Laboratory Software Library, version 5.0.9, https://fsl.fmrib.ox.ac.uk/fsl/). All scans were assessed visually (raw and registered images) and quality control was based on motion parameters (cases with motion >3 mm or 3° were excluded) and framewise displacement (FWD).

For each module of the language network, the first eigenvariate of the average time course in the involved regions was extracted. Similar time courses were extracted for the white matter and the lateral ventricles. The two latter time courses, the global brain signal changes over time (Li et al. 2019), their derivatives, movement parameters (three translation and three rotation) and corresponding squared values were included as nuisance covariates in the statistical general linear model. Serial correlations were estimated with a restricted maximum likelihood algorithm using an intrinsic autoregressive model during parameter estimation. The effects of interest were tested by linear contrasts, generating statistical parametric T maps in each subject. A contrast image was generated that identified regions significantly correlated to the selected brain region/module after removal of sources of spurious variance at the individual level.

2.5 Statistical analyses

To address the aims of this study, we divided the data into two age groups, with a threshold at 60 years: a reference control group with younger adults (age < 60 years) and a group with the older adults (age >= 60 years). We conducted both qualitative and quantitative analyses to examine group characteristics, group differences, associations with phonemic fluency and cognitive reserve mediations potentially reflecting compensatory mechanisms. All the analyses were performed using MATLAB R2014b (The MathWorks, Inc., Natick, Massachusetts, United States).

2.5.1 Mean functional connectivity in younger and older adults

Functional connectivity patterns specific to each module and age group were identified through voxelwise one-sample *t*-test, revealing brain regions with functional connectivity greater than the global mean value. Multiple comparisons correction was performed with Family-wise Error (FWE) $p \leq 0.001$. Sex was included as a potential covariate and the whole procedure was repeated for each of the four modules of the language network.

2.5.2 Group differences in functional connectivity between younger and older adults

To examine the differences in functional connectivity between the younger adults and older adults, we conducted voxelwise two-sample *t*-test at the group-level. The purpose of this analysis was to reveal brain regions showing higher functional connectivity in the younger adults relative to the older adults and vice-versa. Multiple comparisons correction was performed with FWE $p \leq 0.05$. This whole procedure was repeated for each of the four modules of the language network.

2.5.3 Neural correlates of phonemic fluency

We conducted voxelwise multiple linear regression to investigate the association between functional connectivity and phonemic fluency in the combined cohort including both younger and older adults for greater statistical power. The significance of the obtained clusters was based on whether they achieved an extent threshold corresponding to a whole-brain FWE-corrected $p \leq 0.05$ and a cluster-forming threshold of uncorrected $p \leq 0.001$. Given that such a parametric clusterwise inference approach may inflate the false positive rate based on the assumptions of Gaussian random field theory (Eklund, Nichols, and Knutsson 2016), we verified the association between functional connectivity and phonemic fluency with a non-parametric approach (SnPM13.1.08), which is free of such assumptions (Nichols and Holmes 2002). Here, permutation testing (5000 permutations) determined the significance of the obtained clusters that achieved an extent threshold corresponding to FWE-corrected $p \leq 0.05$ and a cluster-forming threshold of FWE-corrected $p \leq 0.05$. Finally, we reported the clusters achieving significance in parametric and validated by nonparametric clusterwise inference approaches. Cluster-level functional connectivity was computed as the first eigenvariate over the whole significant cluster which was used for subsequent post-hoc analyses. We accounted for the timepoint of the visit (baseline versus follow-up) to control for potential learning effects in phonemic fluency. Additionally, to understand the contribution of language function to phonemic fluency, we controlled for other cognitive functions which may also underlie phonemic fluency in independent parametric models. Specifically, we controlled for cognitive flexibility/executive control (assessed by reaction time in Vienna Reaction test), verbal memory (assessed by learning across three trials in TAVEC: Test de Aprendizaje Verbal España-Complutense) or processing speed (assessed by time for completion of the Color Trails Test – Part 2) (D. Ferreira et al. 2015).

2.5.4 Mediation effects of cognitive reserve

We examined potential mediation effects of cognitive reserve on the association between functional connectivity and phonemic fluency. We first conducted a mediation analysis in the combined cohort, irrespective of age, to understand the relationship of cognitive reserve with cluster-level functional connectivity and phonemic fluency. Once demonstrated that cognitive reserve can modify the association between functional connectivity and phonemic fluency, we investigated whether this effect may be more prominent in older individuals, thus, delineating compensatory effects. In particular, we tested the direct involvement of functional connectivity as well as the indirect involvement of functional connectivity mediated by cognitive reserve (WAIS-III Information subtest) in relation to phonemic fluency (Baron and Kenny 1986). We implemented the mediation model through a series of linear regression models comprising four tests. Path *a*: association of functional connectivity with cognitive reserve; path *b*: association of cognitive reserve with phonemic fluency; direct path *c*: association of functional connectivity with phonemic fluency, and indirect path *c'*: association of functional connectivity and cognitive reserve with phonemic fluency. If associations for paths *a*, *b*, or *c* are non-significant, then cognitive reserve is an unlikely mediator. If associations for paths *a*, *b*, and *c* are significant, then path *c'* would indicate either a partial mediation (significant association of functional connectivity with phonemic fluency when controlled for cognitive reserve) or a full mediation (non-significant association of functional connectivity with phonemic fluency when controlled for cognitive reserve) effect of cognitive reserve.

3. RESULTS

3.1 Participants

From the initial cohort of 149 individuals, data from two individuals were excluded after initial quality control of the scans (due to short scan length, limited FOV). Based on the motion parameters, data from fourteen (older) individuals were excluded (mean FWD > 0.25 mm). **Table 1** shows the demographic and clinical characteristics of the remainder 133 individuals included for further analyses. There were no significant differences in the sex distribution ($p = 1$), WAIS-III Information subtest ($p = 0.5$), and FWD ($p = 0.07$) between the younger adults and older adults. However, there were significant differences between the two groups in MMSE ($p < 0.001$), and phonemic fluency ($p = 0.003$; $p = 0.06$ when controlled for MMSE).

Table 1

Demographics and clinical characteristics of the study cohort

	Younger Adults	**Older Adults**	**Differences: younger vs older (*p*)**	**Full Cohort**
N	60	73	-	133
Baseline (BL) vs. follow-up (FU) visit (BL/FU)	3/57	20/53	-	23/110
Age (years)	52.1 ± 4.6 [40, 59]	67.7 ± 5.5 [60, 82]	**<0.0001**	60.7 ± 9.3 [40, 82]
Sex (%F)	43.3	43.8	1	43.6
MMSE	29.8 ± 0.6 [27, 30]	29.1 ± 1.3 [25, 30]	**<0.001**	29.4 ± 1.1 [25, 30]
Phonemic fluency (words)	39.9 ± 10.8 [16 69]	33.5 ± 13.7 [11, 72]	**0.003**	36.4 ± 12.8 [11, 72]
WAIS-III Information	17.4 ± 5.2 [7, 25]	16.7 ± 6.3 [5, 27]	0.5	17.1 ± 5.8 [5, 27]
FWD (mm)	0.07 ± 0.03 [0.03, 0.16]	0.07 ± 0.02 [0.03, 0.13]	0.07	0.07 ± 0.02 [0.03, 0.16]

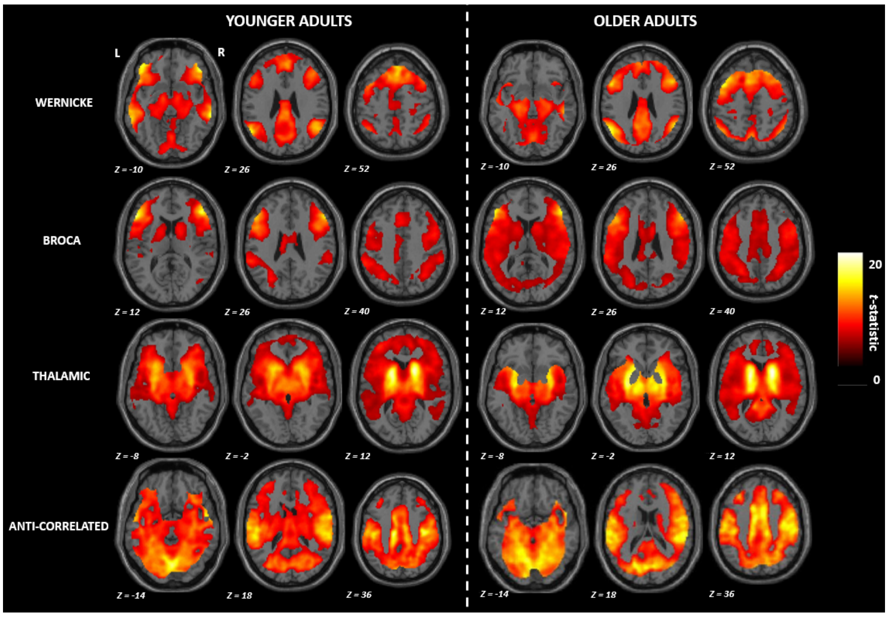
Note: N = sample size; F = female; MMSE = mini mental state exam; WAIS-III = Wechsler Adult Intelligence Scale; FWD = framewise displacement. All continuous variables are reported as mean ± standard deviation [range]. In bold, $p \leq 0.05$ for easier discrimination.

3.2 Mean functional connectivity in younger and older adults

Figure 1 shows the mean functional connectivity maps (FWE corrected $p \leq 0.001$) for each module of the language network by age groups. Based on qualitative visual inspection, two patterns emerged: (a) in the Wernicke and the Broca modules, the younger adults demonstrated a distinct pattern of functional connectivity localized to specific brain areas while the older adults demonstrated a diffuse pattern of functional connectivity involving additional brain regions; (b) in the thalamic and the anti-correlated modules, the younger adults demonstrated involvement of greater number of brain regions relative to the older adults. All of these differences persisted after adjusting for sex as a potential covariate.

Figure 1

Group mean maps observed in the functional connectivity of the language network



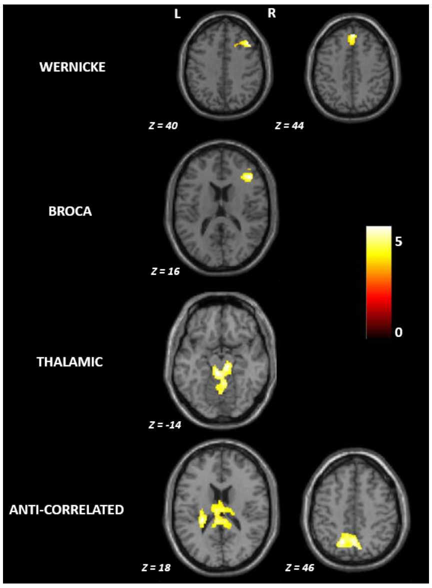
Note: R = right; L = left. All brain maps are visualized at familywise error corrected $p \leq 0.001$.

3.3 Group differences in functional connectivity between younger and older adults

Figure 2 and **Table 2** summarize the findings on differences in functional connectivity between the younger and the older adults. In all four modules, we observed higher functional connectivity in younger than older adults (FWE-corrected $p \leq 0.05$). Higher functional connectivity was seen in the younger adults involving: (a) the right middle and superior frontal gyrus for the Wernicke module; (b) the right middle frontal gyrus for the Broca module; (c) the brainstem for the thalamic module; and (d) the left parietal operculum and superior parietal lobule for the anti-correlated module. For the contrast testing for brain regions showing higher functional connectivity in older adults than in younger adults, we did not find any significant effects in any module.

Figure 2

Group differences in functional connectivity between younger and older adults in the language network



Note: R = right; L = left. All brain maps are visualized at familywise error corrected $p \leq 0.05$.

Table 2

Group differences observed between younger and older adults in functional connectivity of the language network

Module	Peak Region	MNI coordinates (x, y, z)	Z-score	FWE corrected *p*
Wernicke	R middle frontal gyrus	44, 22, 40	5.37	0.001
	R superior frontal gyrus	4, 42, 44	5.25	0.001
Broca	R middle frontal gyrus	44, 32, 16	4.9	0.007
Thalamic	Brainstem	-4, -34, -14	4.54	0.032
Anti-correlated	L parietal operculum	-26, -32, 18	4.84	0.012
	L superior parietal lobule	-16, -60, 46	4.66	0.025

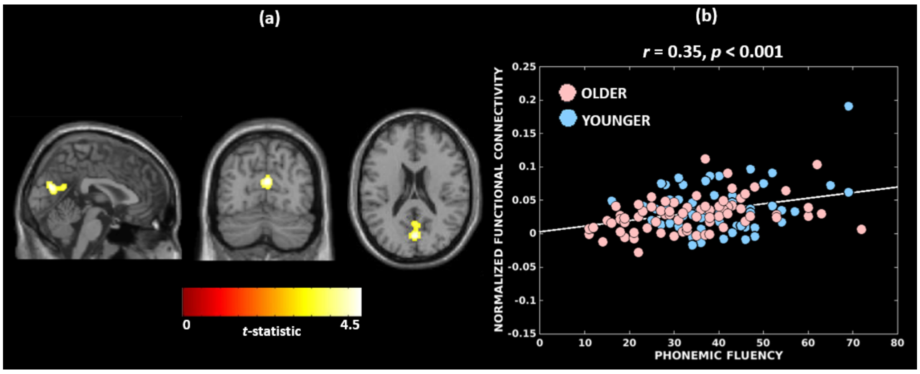
Note: R = right; L = left; MNI = Montreal Neurological Institute; FWE = familywise error.

3.4 Neural correlates of phonemic fluency

Figure 3 and **Table 3** report the association found between functional connectivity of the Wernicke module and phonemic fluency in the combined cohort. The associated cluster that was deemed significant after parametric (341 voxels, FWE-corrected p = 0.033) and further validated with non-parametric (393 voxels, FWE-corrected p = 0.030) testing was observed at cuneus (peak at MNI 2, -72, 20). Functional connectivity over the whole cluster, computed post-hoc as the first eigenvariate, accounted for 82.8% of the variance. Specifically, greater functional connectivity of the Wernicke module involving ipsilateral and contralateral cuneus and extending to precuneus, calcarine cortex and lingual gyrus (**Figure 3A**), was significantly associated with higher phonemic fluency at the cluster-level (r = 0.35, p < 0.001). Notably, older adults with lower functional connectivity presented poorer phonemic fluency compared to the younger adults (**Figure 3B**). When evaluating the effect of non-language cognitive functions to phonemic fluency, we observed from the parametric models that the association between functional connectivity of the Wernicke module and phonemic fluency was not significant when controlled for reaction time in Vienna Reaction test (N=116; FWE corrected p-values: peak-level $p = 0.2$; cluster-level $p = 0.4$) but was significant when controlled for learning in TAVEC (N=124; FWE corrected p-values: peak-level $p = 0.021$; cluster-level $p = 0.019$; peak region = contralateral and ipsilateral cuneus) and time for completion of the Color Trails Test – Part 2 (N=126; FWE corrected p-values: peak-level $p = 0.015$; cluster-level $p = 0.001$; peak region = contralateral and ipsilateral cuneus). We did not observe any significant associations between functional connectivity and phonemic fluency for the Broca, thalamic or anti-correlated modules.

Figure 3

Neural substrates associated with phonemic fluency in the combined cohort



Note: **(a)** A greater functional connectivity of the Wernicke module involving bilateral cuneus (peak) correlates with higher performance in phonemic fluency; The brain maps are visualized at cluster-level familywise error corrected $p \leq 0.05$. **(b)** Association between cluster-level functional connectivity of the Wernicke module and phonemic fluency in younger and older adults.

Table 3

Correlates and mediator of phonemic fluency

Language Module	Wernicke		
Functional connectivity correlates			
Peak region	Contralateral and ipsilateral cuneus		
MNI coordinates for peak region (x, y, z)	2, -72, 20		
Parametric cluster size (voxels)	341		
Parametric FWE corrected *p*-value	0.033		
Non-parametric cluster size (voxels)	393		
Non-parametric FWE corrected *p*-value	0.03		
***r* (*p*-value)**	0.35 (< 0.001)		
Cognitive reserve as a mediator			
Coefficient for Path	**Combined Cohort**	**Younger Adults**	**Older Adults**
***a* (*p*-value)**	2.2 (0.03)	0.2 (0.8)	2.9 (0.005)
***b* (*p*-value)**	7.4 (<0.001)	2.7 (0.01)	7.4 (<0.001)
***c* (*p*-value)**	4.4 (<0.001)	1.9 (0.06)	3.8 (<0.001)
***c'* (*p*-value)**	3.7 (0.003)	1.9 (0.06)	2.4 (0.02)

Note: MNI = Montreal Neurological Institute; FWE = familywise error; *r* = correlation coefficient; *a* = corresponds to the model testing association between cluster-level functional connectivity and cognitive reserve; *b* = corresponds to the model testing association between cognitive reserve and phonemic fluency; *c* = corresponds to the model testing association between cluster-level functional connectivity and phonemic fluency (direct path); *c'* = corresponds to the model testing association between cluster-level functional connectivity, cognitive reserve together and phonemic fluency (indirect path).

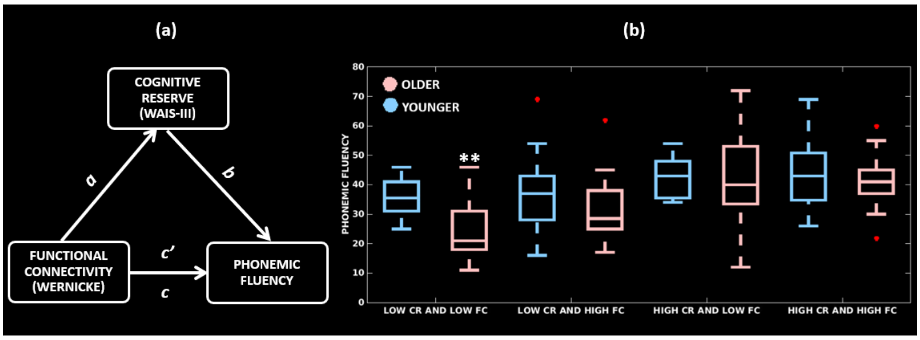
3.4 Mediation effects of cognitive reserve

First, we wanted to demonstrate that cognitive reserve mediates the association between functional connectivity of the Wernicke module and performance in phonemic fluency. This analysis was performed in the combined cohort (younger and older groups pooled together). We did not run any model for the Broca, thalamic and anti-correlated modules because functional connectivity in these modules did not correlate with performance in phonemic fluency. **Figure 4A** and **Table 3** present the mediation model for the Wernicke module within the significant cluster that correlated with phonemic fluency. We found a significant association between: greater functional connectivity of the Wernicke module and higher cognitive reserve (coefficient $a = 2.2$, $p = 0.03$); higher cognitive reserve and higher performance in phonemic fluency (coefficient $b = 7.4$, $p < 0.001$); greater functional connectivity of the Wernicke module and higher performance in phonemic fluency (direct path coefficient $c = 4.4$, $p < 0.001$); greater functional connectivity of the Wernicke module and higher performance in phonemic fluency when controlled for cognitive reserve (indirect path coefficient $c' = 3.7$, $p = 0.003$). Thus, cognitive reserve was found to be a partial mediator between functional connectivity of the Wernicke module and phonemic fluency in the combined cohort.

Once demonstrated that cognitive reserve mediates the association between the cluster-level functional connectivity and phonemic fluency, we wanted to investigate whether this effect is differential in younger and older adults (**Table 3)**, with a greater mediation effect in older adults, hence delineating compensation. In the younger adults, there was no significant association between functional connectivity of the Wernicke module and cognitive reserve (coefficient $a = 0.2$, $p = 0.8$). This non-significant result indicated that the mediation effect of cognitive reserve is unlikely in the younger adults. Contrarily, in older adults, there was a significant association between: greater functional connectivity of the Wernicke module and higher cognitive reserve (coefficient $a = 2.9$, $p = 0.005$); higher cognitive reserve and higher performance in phonemic fluency (coefficient $b = 7.4$, $p < 0.001$); and greater functional connectivity of the Wernicke module and higher performance in phonemic fluency (direct path coefficient $c = 3.8$, $p < 0.001$). Finally, the association between functional connectivity of the Wernicke module and phonemic fluency, when controlled for cognitive reserve was significant (indirect path coefficient $c' = 2.4$, $p = 0.02$). This result indicates that cognitive reserve was a partial mediator between functional connectivity of the Wernicke module and phonemic fluency in older adults.

Figure 4

Mediation effects of cognitive reserve



Note: **(a)** Mediation model testing cognitive reserve as a mediator between cluster-level functional connectivity of the Wernicke module and phonemic fluency; *a*: association of functional connectivity with cognitive reserve; *b*: association of cognitive reserve with phonemic fluency; direct path *c’*: association of functional connectivity with phonemic fluency, and indirect path *c*: association of functional connectivity and cognitive reserve with phonemic fluency. **(b)** Distribution of cluster-level functional connectivity of the Wernicke module (independent variable, two groups based on the median-split), cognitive reserve (mediator, two groups based on the median-split) and phonemic fluency (dependent variable); CR = cognitive reserve; FC = functional connectivity; **significantly lower phonemic fluency compared to all other groups ($p \leq 0.01$).

Figure 4B highlights the mediation effect of cognitive reserve levels on the association between the cluster-level functional connectivity of the Wernicke module and phonemic fluency. Across the low/high (median-split) cognitive reserve and low/high (median-split) functional connectivity groups, (a) older adults with low cognitive reserve and low functional connectivity showed the poorest phonemic fluency compared to all of the other groups ($p \leq 0.01$), but (b) older adults with high cognitive reserve showed phonemic fluency comparable to their younger counterparts, indicating ability to compensate for the effect of aging in phonemic fluency.

4. DISCUSSION

Cognitive status is instrumental in maintenance of functional independence in the elderly. Decline in cognitive status could arise due to age-related pathology - manifesting as gradual cognitive decline, or due to disease-related pathology - manifesting as a more prominent cognitive decline. Irrespective of the pathology, the underlying brain structure and/or function are the conventional determinants of cognitive health. Complementing these determinants are the constructs of brain reserve (corresponding to structure) (Coffey et al. 1999) and cognitive reserve (corresponding to function) (Stern 2002), whose presence (or lack thereof) could maintain (or negatively affect) cognitive performance. For example, older individuals could be (a) super agers, with high reserve and preserved brain structure and function, showing preserved cognition (de Godoy et al. 2020); (b) normal agers, with altered brain structure and function, showing gradual cognitive decline; or (c) poor agers, with low reserve and significantly altered brain structure and function and significant cognitive decline (Solé-Padullés et al. 2009). Altogether, a balance among structure, function and reserve most likely regulates an individual’s ability to compensate in the face of pathology. In the present study, using functional MRI, we demonstrated the association of functional connectivity with the cognitive subdomain of verbal fluency and how cognitive reserve mediates this association, likely reflecting compensation in normal aging.

It must be stipulated that the construct of reserve has been described and reported predominantly in relation to broad measures of cognition, with greater emphasis on memory (Opdebeeck, Martyr, and Clare 2016; Steffener and Stern 2012; Nyberg et al. 2012). It is unclear whether distinct measures of cognition could be associated with specific compensatory mechanisms as it pertains to reserve (Stern et al. 2018). Understanding of cognitive domain-specific compensation is important as not all cognitive domains evolve similarly with aging. Thus, in our current work, we focused specifically on verbal fluency, while future studies should investigate other language and non-language cognitive functions to further inform on universal versus cognitive domain-specific compensation. In particular, we investigated the specific domain of phonemic fluency and tested the hypothesis that older individuals with high cognitive reserve can maintain phonemic fluency possibly by recruiting both linguistic and non-linguistic networks (Gonzalez-Burgos, Barroso, and Ferreira 2020). In the current study, we validated this hypothesis by showing that greater functional connectivity of the Wernicke module with non-Wernicke structures (ipsilateral and contralateral cuneus, precuneus, calcarine cortex and lingual gyrus) was associated with higher performance in phonemic fluency. Further, this association was not mediated by cognitive reserve in the younger adults but was mediated by cognitive reserve in the older adults, thus, presumably representing compensation in the elderly. Our findings are relevant as verbal fluency is significantly impaired in several dementia types including Alzheimer's disease (Henry, Crawford, and Phillips 2004), shows early changes in mild cognitive impairment (Murphy, Rich, and Troyer 2006), is sensitive to subjective cognitive decline (Nikolai et al. 2018), and is even suggested as a potential screening tool (McDonnell et al. 2020). Further, subdomains of verbal fluency such as phonemic and semantic fluency evolve differentially over time, even in healthy aging (Gonzalez-Burgos et al. 2019; Stolwyk et al. 2015; Rodríguez-Aranda et al. 2020). Relative stability of phonemic fluency over aging, thus, raises the question of whether reserve-facilitated compensatory mechanisms might have a role in its reduced susceptibility to decline. Below we contextualize our findings, discuss the potential implications, and outline future directions.

We investigated an extended language network, beyond the classically identified Wernicke's and Broca's areas, by including the Wernicke's, Broca's, thalamic and anti-correlated modules (Tomasi and Volkow 2012). Across these four modules, we observed four spatially distinct patterns of functional connectivity with involvement of frontal, temporal, parietal and subcortical brain regions, therefore extending beyond traditional Wernicke's and Broca's areas. This is consistent with the notion that language processing is supported by multiple and distributed sub-networks (modules) rather than individual specialized brain regions (Fedorenko and Thompson-Schill 2014). Functional connectivity pattern in each of these modules also differed between age groups. On the one hand, we found involvement of additional brain regions in older adults relative to younger adults within the Wernicke and Broca modules. On the other hand, we found involvement of fewer brain regions in older adults relative to younger adults in the thalamic and anti-correlated modules (**Figure 1**). Such a differential pattern has often been attributed to aging (Cabeza and Dennis 2012; Logan et al. 2002) and observed in other brain networks including visual (Park et al. 2004; Geerligs et al. 2014) and motor (Carp et al. 2011) networks. Irrespective of the module, we found that older adults had diminished functional connectivity compared to the younger adults (**Figure 2**). This implies that the older brains are more vulnerable to breakdown of within-module connectivity (L. K. Ferreira and Busatto 2013; Damoiseaux 2017; Sala-Llonch, Bartrés-Faz, and Junqué 2015), thus, increasing the likelihood of need for compensation at older age.

Firstly, out of the four investigated functional modules, we identified that functional connectivity of the Wernicke module was a correlate of phonemic fluency in the combined cohort (**Figure 3**). However, this finding is incongruent with our hypothesis that functional connectivity involving the Broca's area (inferior frontal gyri) would be associated with phonemic fluency. The Broca's area, part of the Broca module in our study, has been implicated in language production (Meinzer et al. 2009). In contrast, Wernicke's area (superior temporal gyri), part of the Wernicke module in this study, is traditionally known to be involved in language comprehension. This discordance could have three explanations: (a) the Wernicke module is broader than and extends beyond the Wernicke's area, comprising additionally temporal, parietal, and frontal brain regions. Particularly, the contribution of the (inferior, middle, superior) frontal regions has been implicated in phonemic fluency task activation, both in cognitively normal (Wagner et al. 2014) and aphasic patients (Perani et al. 2003); (b) even if the Wernicke's area may predispose the Wernicke module to be predominantly associated with semantic fluency (for semantic and lexical abilities), the module could still be important for phonemic fluency. Comparing semantic and phonemic fluency in cognitively normal individuals has shown a prominent separation between the semantic categories of animate and inanimate entities within phonemic fluency (Schwartz et al. 2003). Therefore, it is possible that phonemic fluency is not purely phonemic and has a pervasive semantic facilitation; (c) contrary to the traditional view, the role of Wernicke's area may indeed extend to language production, perhaps not in facilitating the motor movements required for production but rather in enabling the knowledge needed to articulate prior to production (Binder 2015), attributing a similar role to the Wernicke module. Altogether, we suggest that in our current cohort of cognitively normal individuals, where all participants demonstrated normal levels of performance in phonemic fluency, variability in phonemic fluency is not primarily related to the normal functioning of Broca's area but on the efficient recruitment of non-Broca areas belonging to Wernicke and anti-correlated modules.

Secondly, we observed the functional connectivity of the Wernicke module with non-Wernicke regions to be correlated with phonemic fluency (**Figure 3A**). In fact, we observed engagement of regions from the anti-correlated module including both ipsilateral and contralateral cuneus, precuneus, calcarine cortex and lingual gyrus, which show a negatively correlated BOLD activity to that of the Wernicke module (Tomasi and Volkow 2012). Cuneus, calcarine cortex and lingual gyrus are core to visual processing while precuneus is key for the default mode network, hence involved in attention and memory. This association between functional connectivity and phonemic fluency was not significant when adjusting for cognitive flexibility but persisted when adjusting for verbal memory and processing speed, validating that the observed association is specific to language processing to a certain degree. This implies that phonemic fluency elicited connectivity of language-specific task-positive (Wernicke module) and concomitantly task-negative (anti-correlated module) networks, suggesting the dichotomized functional organization in the brain (Fox et al. 2005). Overall, these findings underline the importance of investigating not only within-network but also outside-network connectivity.

Finally, our findings divulged cognitive reserve as a partial mediator of the relationship between functional connectivity (of Wernicke with anti-correlated module) and phonemic fluency in the combined cohort (**Figure 4**). Further investigation revealed that cognitive reserve is an unlikely mediator of phonemic fluency in younger adults while it is a partial mediator in older adults, thus, emphasizing the need of compensation at an older age. Notably, older adults with low cognitive reserve and low functional connectivity exhibited significantly lower phonemic fluency, whereas older adults with high cognitive reserve performed significantly better and comparable to the younger adults regardless of functional connectivity, thus, demonstrating the occurrence of compensation at an older age. Neuroanatomically, these effects were localized in the calcarine cortex, lingual gyrus and precuneus. The contributions of structures from the anti-correlated module (calcarine cortex, lingual gyrus, precuneus), have been shown to be part of the network topography expressing differential deactivation in aging (Stern et al. 2005). Given the involvement of Wernicke and the corresponding anti-correlated modules specific to phonemic fluency, future studies should examine correlates and compensation underlying other specific modalities of verbal fluency (semantic, action) and other language components or cognitive domains, to further understand whether the involvement of calcarine cortex, lingual gyrus and precuneus is specific to phonemic fluency, verbal fluency, or compensation of cognition in general.

This study has some limitations. As this is a cross-sectional study, we could not track longitudinal trajectories and changes in phonemic fluency and compensation. Although we divided our cohort into younger and older adults based on age, the younger group represented a late midlife age profile. Future studies should include an early midlife age group to detect the earliest changes in neural/compensatory mechanisms and cognition. We included imaging data and corresponding phonemic fluency performance at the first available timepoint, which was not necessarily the baseline timepoint. This may have induced a learning effect in phonemic fluency that we tried to circumvent by accounting for potential learning effects in our statistical models. Further, we observed a significantly lower (although normal) global cognition (MMSE) in the older adults than in younger adults. The age effect on global cognition is a common finding in the aging literature (Bravo and Hébert 1997; Tombaugh and McIntyre 1992). Our result regarding age-related differences in phonemic fluency likely reflects an overall decline in cognition, as illustrated by the finding of non-significant age differences in phonemic fluency when controlling for MMSE. Hence, future studies in pathologies primarily affecting phonemic fluency are needed to further understand compensatory processes specific to pathology affecting phonemic fluency. As a proxy for cognitive reserve, we used the WAIS-III Information subtest, while there exist other proxies based on factors such as education, occupation, lifestyle, etc. However, the WAIS-III Information subtest was recently demonstrated to better capture premorbid ability, being superior to other proxies of cognitive in the current cohort (D. Ferreira et al. 2016; Correia et al. 2015), and is also validated as an appropriate measure of reserve longitudinally (Elkana et al. 2019). Finally, in contrast to most studies on compensation using task-based functional MRI, we used resting-state MRI to derive the neural correlates of verbal fluency and investigate potential compensatory mechanisms. Although resting-state data would help us elucidate task-invariant networks, it may be limited in the specificity of accurately deriving the most relevant neural correlates of cognition functions.

In conclusion, we delineated that functional connectivity involving brain areas shared by the Wernicke (linguistic) and anti-correlated (non-linguistic) modules was associated with phonemic fluency in aging. This association was mediated by cognitive reserve in the older adults but not in the younger adults, indicating compensation to the effect of aging in phonemic fluency in the elderly. Extending our current analyses to other language and non-language cognitive functions is important and expected to provide a deeper understanding of universal versus domain-specific compensatory mechanisms.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

RM: conceptualization, data preparation, data analysis, manuscript writing and revision; LGB: conceptualization, data collection, data preparation, data analysis, manuscript writing and revision; LDF: data curation and manuscript revision; JSM: data preparation, data processing; JB: data collection, manuscript revision and funding; DF: conceptualization, data collection, supervision and manuscript revision; EW: supervision, manuscript revision and funding. All authors have read the approved the submitted manuscript.

DATA AVAILABILITY STATEMENT

The data used for this study may be available upon reasonable request to the authors.

REFERENCES

Ansado, Jennyfer, Yannick Marsolais, Ikram Methqal, Flamine Alary, and Yves Joanette. 2013. “The Adaptive Aging Brain: Evidence from the Preservation of Communication Abilities with Age.” *European Journal of Neuroscience* 37 (12): 1887–95.

Auriacombe, Sophie, Colette Fabrigoule, Sylviane Lafont, Hélène Jacqmin-Gadda, and Jean-François Dartigues. 2001. “Letter and Category Fluency in Normal Elderly Participants: A Population-Based Study.” *Aging, Neuropsychology, and Cognition* 8 (2): 98–108.

Azuma, Tamiko. 2004. “Working Memory and Perseveration in Verbal Fluency.” *Neuropsychology* 18 (1): 69.

Balduino, Everton, Brian Alvarez Ribeiro de Melo, Larissa de Sousa Mota da Silva, José Eduardo Martinelli, and Juliana Francisca Cecato. 2020. “The ‘SuperAgers’ Construct in Clinical Practice: Neuropsychological Assessment of Illiterate and Educated Elderly.” *International Psychogeriatrics* 32 (2): 191–98.

Baron, Reuben M, and David A Kenny. 1986. “The Moderator–mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations.” *Journal of Personality and Social Psychology* 51 (6): 1173.

Bartrés-Faz, David, Syvie Belleville, Marc Cantillon, Gael Chetelat, Sean Clouston, and Yaakov Stern. 2020. “Whitepaper: Defining and Investigating Cognitive Reserve, Brain Reserve and Brain Maintenance.” *Alzheimers Dement.*

Bartrés-Faz, David, Cristina Solé-Padullés, Carme Junqué, Lorena Rami, Beatriz Bosch, Núria Bargalló, Carles Falcón, Raquel Sánchez-Valle, and José Luis Molinuevo. 2009. “Interactions of Cognitive Reserve with Regional Brain Anatomy and Brain Function during a Working Memory Task in Healthy Elders.” *Biological Psychology* 80 (2): 256–59.

Benton, A L, K d Hamsher, and A Sivan. 1989. "Multilingual Aphasia Examination. Iowa City, IA: AJA Associates." *NEUROPSYCHOLOGY, BLOCKING, SCHIZOPHRENIA* 59.

Binder, Jeffrey R. 2015. "The Wernicke Area: Modern Evidence and a Reinterpretation." *Neurology* 85 (24): 2170–75.

Birn, Rasmus M, Lauren Kenworthy, Laura Case, Rachel Caravella, Tyler B Jones, Peter A Bandettini, and Alex Martin. 2010. "Neural Systems Supporting Lexical Search Guided by Letter and Semantic Category Cues: A Self-Paced Overt Response FMRI Study of Verbal Fluency." *Neuroimage* 49 (1): 1099–1107.

Blessed, Garry, Bernard E Tomlinson, and Martin Roth. 1968. "The Association between Quantitative Measures of Dementia and of Senile Change in the Cerebral Grey Matter of Elderly Subjects." *The British Journal of Psychiatry* 114 (512): 797–811.

Boyle, Rory, Lee Jollans, Laura M Rueda-Delgado, Rossella Rizzo, Görsev G Yener, Jason P McMorrow, Silvin P Knight, Daniel Carey, Ian H Robertson, and Derya D Emek-Savaş. 2020. "Brain-Predicted Age Difference Score Is Related to Specific Cognitive Functions: A Multi-Site Replication Analysis." *Brain Imaging and Behavior*, 1–19.

Bravo, Gina, and Réjean Hébert. 1997. "Age-and Education-specific Reference Values for the Mini-Mental and Modified Mini-Mental State Examinations Derived from a Non-demented Elderly Population." *International Journal of Geriatric Psychiatry* 12 (10): 1008–18.

Cabeza, Roberto, and Nancy A Dennis. 2012. "Frontal Lobes and Aging." *Principles of Frontal Lobe Function. 2d Ed. New York: Oxford University Press. P*, 628–52.

Carp, Joshua, Joonkoo Park, Andrew Hebrank, Denise C Park, and Thad A Polk. 2011. "Age-Related Neural Dedifferentiation in the Motor System." *PloS One* 6 (12): e29411.

Cedres, Nira, Alejandra Machado, Yaiza Molina, Patricia Diaz-Galvan, Juan Andres

Hernández-Cabrera, Jose Barroso, Eric Westman, and Daniel Ferreira. 2019. “Subjective Cognitive Decline below and above the Age of 60: A Multivariate Study on Neuroimaging, Cognitive, Clinical, and Demographic Measures.” *Journal of Alzheimer’s Disease* 68 (1): 295–309.

Coffey, C Edward, J A Saxton, G Ratcliff, R N Bryan, and J F Lucke. 1999. “Relation of Education to Brain Size in Normal Aging: Implications for the Reserve Hypothesis.” *Neurology* 53 (1): 189.

Correia, Rut, Antonieta Nieto, Daniel Ferreira, María Sabucedo, and Jose Barroso. 2015. “Fund of Information Is More Strongly Associated with Neuropsychological Functioning than Education in Older Spanish Adults.” *Archives of Clinical Neuropsychology* 30 (4): 310–21.

Costafreda, Sergi G, Cynthia H Y Fu, Lucy Lee, Brian Everitt, Michael J Brammer, and Anthony S David. 2006. “A Systematic Review and Quantitative Appraisal of FMRI Studies of Verbal Fluency: Role of the Left Inferior Frontal Gyrus.” *Human Brain Mapping* 27 (10): 799–810.

Crossley, Margaret, Carl D’arcy, and Nigel S B Rawson. 1997. “Letter and Category Fluency in Community-Dwelling Canadian Seniors: A Comparison of Normal Participants to Those with Dementia of the Alzheimer or Vascular Type.” *Journal of Clinical and Experimental Neuropsychology* 19 (1): 52–62.

Damoiseaux, Jessica S. 2017. “Effects of Aging on Functional and Structural Brain Connectivity.” *Neuroimage* 160: 32–40.

Eklund, Anders, Thomas E Nichols, and Hans Knutsson. 2016. “Cluster Failure: Why FMRI Inferences for Spatial Extent Have Inflated False-Positive Rates.” *Proceedings of the National Academy of Sciences* 113 (28): 7900–7905.

Elgamal, Safa A, Eric A Roy, and Michael T Sharratt. 2011. “Age and Verbal Fluency: The

Mediating Effect of Speed of Processing." *Canadian Geriatrics Journal: CGJ* 14 (3): 66.

Elkana, Odelia, Shani Soffer, Osnat Reichman Eisikovits, Noga Oren, Vered Bezalel, and Elissa L Ash. 2019. "WAIS Information Subtest as an Indicator of Crystallized Cognitive Abilities and Brain Reserve among Highly Educated Older Adults: A Three-Year Longitudinal Study." *Applied Neuropsychology: Adult*, 1–7.

Erkinjuntti, T, Laura Hokkanen, R Sulkava, and J Palo. 1988. "The Blessed Dementia Scale as a Screening Test for Dementia." *International Journal of Geriatric Psychiatry* 3 (4): 267–73.

Fedorenko, Evelina, and Sharon L Thompson-Schill. 2014. "Reworking the Language Network." *Trends in Cognitive Sciences* 18 (3): 120–26.

Fernández-Cabello, Sara, Cinta Valls-Pedret, Matthias Schurz, Dídac Vidal-Piñeiro, Roser Sala-Llonch, Nuria Bargallo, Emilio Ros, and David Bartrés-Faz. 2016. "White Matter Hyperintensities and Cognitive Reserve during a Working Memory Task: A Functional Magnetic Resonance Imaging Study in Cognitively Normal Older Adults." *Neurobiology of Aging* 48: 23–33.

Ferreira, Daniel, David Bartrés-Faz, Linn Nygren, Leigh J Rundkvist, Yaiza Molina, Alejandra Machado, Carme Junqué, José Barroso, and Eric Westman. 2016. "Different Reserve Proxies Confer Overlapping and Unique Endurance to Cortical Thinning in Healthy Middle-Aged Adults." *Behavioural Brain Research* 311: 375–83.

Ferreira, Daniel, Rut Correia, Antonieta Nieto, Alejandra Machado, Yaiza Molina, and José Barroso. 2015. "Cognitive Decline before the Age of 50 Can Be Detected with Sensitive Cognitive Measures." *Psicothema* 27 (3): 216–22.

Ferreira, Daniel, Yaiza Molina, Alejandra Machado, Eric Westman, Lars-Olof Wahlund, Antonieta Nieto, Rut Correia, Carme Junqué, Lucio Díaz-Flores, and José Barroso.

2014. “Cognitive Decline Is Mediated by Gray Matter Changes during Middle Age.” *Neurobiology of Aging* 35 (5): 1086–94.

Ferreira, Luiz Kobuti, and Geraldo F Busatto. 2013. “Resting-State Functional Connectivity in Normal Brain Aging.” *Neuroscience & Biobehavioral Reviews* 37 (3): 384–400.

Foldi, Nancy S, Nancy Helm-Estabrooks, Joel Redfield, and Debra Gail Nickel. 2003. “Perseveration in Normal Aging: A Comparison of Perseveration Rates on Design Fluency and Verbal Generative Tasks.” *Aging, Neuropsychology, and Cognition* 10 (4): 268–80.

Fox, Michael D, Abraham Z Snyder, Justin L Vincent, Maurizio Corbetta, David C Van Essen, and Marcus E Raichle. 2005. “The Human Brain Is Intrinsically Organized into Dynamic, Anticorrelated Functional Networks.” *Proceedings of the National Academy of Sciences* 102 (27): 9673–78.

Geerligs, Linda, Natasha M Maurits, Remco J Renken, and Monicque M Lorist. 2014. “Reduced Specificity of Functional Connectivity in the Aging Brain during Task Performance.” *Human Brain Mapping* 35 (1): 319–30.

Godoy, Laiz Laura de, Cesar Augusto Pinheiro Ferreira Alves, Juan Sebastian Martin Saavedra, Adalberto Studart-Neto, Ricardo Nitrini, Claudia da Costa Leite, and Sotirios Bisdas. 2020. “Understanding Brain Resilience in Superagers: A Systematic Review.” *Neuroradiology*, 1–21.

Gonzalez-Burgos, Lissett, José Barroso, and Daniel Ferreira. 2020. “Cognitive Reserve and Network Efficiency as Compensatory Mechanisms of the Effect of Aging on Phonemic Fluency.” *Aging* 12.

Gonzalez-Burgos, Lissett, Juan Andrés Hernández-Cabrera, Eric Westman, José Barroso, and Daniel Ferreira. 2019. “Cognitive Compensatory Mechanisms in Normal Aging: A Study on Verbal Fluency and the Contribution of Other Cognitive Functions.” *Aging*

(Albany NY) 11 (12): 4090.

Henry, Julie D, and John R Crawford. 2004. “A Meta-Analytic Review of Verbal Fluency Performance Following Focal Cortical Lesions.” *Neuropsychology* 18 (2): 284.

Henry, Julie D, John R Crawford, and Louise H Phillips. 2004. “Verbal Fluency Performance in Dementia of the Alzheimer’s Type: A Meta-Analysis.” *Neuropsychologia* 42 (9): 1212–22.

Jurado, M Angeles, Maria Mataro, Katia Verger, Federic Bartumeus, and Carme Junque. 2000. “Phonemic and Semantic Fluencies in Traumatic Brain Injury Patients with Focal Frontal Lesions.” *Brain Injury* 14 (9): 789–95.

Korhonen, Onerva, Heini Saarimäki, Enrico Glerean, Mikko Sams, and Jari Saramäki. 2017. “Consistency of Regions of Interest as Nodes of FMRI Functional Brain Networks.” *Network Neuroscience* 1 (3): 254–74.

Li, Jingwei, Ru Kong, Raphael Liegeois, Csaba Orban, Yanrui Tan, Nanbo Sun, Avram J Holmes, Mert R Sabuncu, Tian Ge, and B T Thomas Yeo. 2019. “Global Signal Regression Strengthens Association between Resting-State Functional Connectivity and Behavior.” *NeuroImage* 196: 126–41.

Logan, Jessica M, Amy L Sanders, Abraham Z Snyder, John C Morris, and Randy L Buckner. 2002. “Under-Recruitment and Nonselective Recruitment: Dissociable Neural Mechanisms Associated with Aging.” *Neuron* 33 (5): 827–40.

Lowe, Alexander J, Casey Paquola, Reinder Vos de Wael, Manesh Girn, Sara Lariviere, Shahin Tavakol, Benoit Caldairou, Jessica Royer, Dewi V Schrader, and Andrea Bernasconi. 2019. “Targeting Age-related Differences in Brain and Cognition with Multimodal Imaging and Connectome Topography Profiling.” *Human Brain Mapping* 40 (18): 5213–30.

Machado, Alejandra, José Barroso, Yaiza Molina, Antonieta Nieto, Lucio Díaz-Flores, Eric

Westman, and Daniel Ferreira. 2018. “Proposal for a Hierarchical, Multidimensional, and Multivariate Approach to Investigate Cognitive Aging.” *Neurobiology of Aging* 71: 179–88.

Marsolais, Yannick, Ikram Methqal, and Yves Joanette. 2015. “Marginal Neurofunctional Changes in High-Performing Older Adults in a Verbal Fluency Task.” *Brain and Language* 140: 13–23.

Marsolais, Yannick, Vincent Perlbarg, Habib Benali, and Yves Joanette. 2014. “Age-Related Changes in Functional Network Connectivity Associated with High Levels of Verbal Fluency Performance.” *Cortex* 58: 123–38.

McDonnell, Michelle, Lauren Dill, Stella Panos, Stacy Amano, Warren Brown, Shadee Giurgius, Gary Small, and Karen Miller. 2020. “Verbal Fluency as a Screening Tool for Mild Cognitive Impairment.” *International Psychogeriatrics* 32 (9): 1055–62.

Meinzer, Marcus, Tobias Flaisch, Lotte Wilser, Carsten Eulitz, Brigitte Rockstroh, Tim Conway, Leslie Gonzalez-Rothi, and Bruce Crosson. 2009. “Neural Signatures of Semantic and Phonemic Fluency in Young and Old Adults.” *Journal of Cognitive Neuroscience* 21 (10): 2007–18.

Mesulam, M-Marsel. 1998. “From Sensation to Cognition.” *Brain: A Journal of Neurology* 121 (6): 1013–52.

Methqal, Ikram, Yannick Marsolais, Maximiliano A Wilson, Oury Monchi, and Yves Joanette. 2019. “More Expertise for a Better Perspective: Task and Strategy-Driven Adaptive Neurofunctional Reorganization for Word Production in High-Performing Older Adults.” *Aging, Neuropsychology, and Cognition* 26 (2): 190–221.

Muehlboeck, J, Eric Westman, and Andrew Simmons. 2014. “TheHiveDB Image Data Management and Analysis Framework.” *Frontiers in Neuroinformatics* 7: 49.

Murphy, Kelly J, Jill B Rich, and Angela K Troyer. 2006. “Verbal Fluency Patterns in Amnestic

Mild Cognitive Impairment Are Characteristic of Alzheimer's Type Dementia." *Journal of the International Neuropsychological Society* 12 (4): 570–74.

Nichols, Thomas E, and Andrew P Holmes. 2002. "Nonparametric Permutation Tests for Functional Neuroimaging: A Primer with Examples." *Human Brain Mapping* 15 (1): 1–25.

Nikolai, Tomas, Ondrej Bezdicek, Hana Markova, Hana Stepankova, Jiri Michalec, Miloslav Kopecek, Monika Dokoupilova, Jakub Hort, and Martin Vyhnalek. 2018. "Semantic Verbal Fluency Impairment Is Detectable in Patients with Subjective Cognitive Decline." *Applied Neuropsychology: Adult* 25 (5): 448–57.

Nyberg, Lars, Martin Lövdén, Katrine Riklund, Ulman Lindenberger, and Lars Bäckman. 2012. "Memory Aging and Brain Maintenance." *Trends in Cognitive Sciences* 16 (5): 292–305.

Opdebeeck, Carol, Anthony Martyr, and Linda Clare. 2016. "Cognitive Reserve and Cognitive Function in Healthy Older People: A Meta-Analysis." *Aging, Neuropsychology, and Cognition* 23 (1): 40–60.

Park, Denise C, Thad A Polk, Rob Park, Meredith Minear, Anna Savage, and Mason R Smith. 2004. "Aging Reduces Neural Specialization in Ventral Visual Cortex." *Proceedings of the National Academy of Sciences* 101 (35): 13091–95.

Park, Denise C, and Patricia Reuter-Lorenz. 2009. "The Adaptive Brain: Aging and Neurocognitive Scaffolding." *Annual Review of Psychology* 60: 173–96.

Perani, D, S F Cappa, M Tettamanti, M Rosa, P Scifo, A Miozzo, A Basso, and F Fazio. 2003. "A FMRI Study of Word Retrieval in Aphasia." *Brain and Language* 85 (3): 357–68.

Pereira, Andressa Hermes, Ana Bresolin Gonçalves, Maila Holz, Hosana Alves Gonçalves, Renata Kochhann, Yves Joanette, Nicolle Zimmermann, and Rochele Paz Fonseca. 2018. "Influence of Age and Education on the Processing of Clustering and Switching in

Verbal Fluency Tasks.” *Dementia & Neuropsychologia* 12 (4): 360–67.

Raz, Naftali, and Karen M Rodrigue. 2006. “Differential Aging of the Brain: Patterns, Cognitive Correlates and Modifiers.” *Neuroscience & Biobehavioral Reviews* 30 (6): 730–48.

Robinson, Gail, Tim Shallice, Marco Bozzali, and Lisa Cipolotti. 2012. “The Differing Roles of the Frontal Cortex in Fluency Tests.” *Brain* 135 (7): 2202–14.

Rodríguez-Aranda, Claudia, Susana A Castro-Chavira, Ragna Espenes, Fernando A Barrios, and Torgil Riise Vangberg. 2020. “The Role of Moderating Variables on BOLD FMRI Response during Semantic Verbal Fluency and Finger Tapping in Active and Educated Healthy Seniors.”

Roldán-Tapia, Lola, Juan García, Rosa Cánovas, and Irene León. 2012. “Cognitive Reserve, Age, and Their Relation to Attentional and Executive Functions.” *Applied Neuropsychology: Adult* 19 (1): 2–8.

Sala-Llonch, Roser, David Bartrés-Faz, and Carme Junqué. 2015. “Reorganization of Brain Networks in Aging: A Review of Functional Connectivity Studies.” *Frontiers in Psychology* 6: 663.

Schaie, K Warner, and Sherry L Willis. 1993. “Age Difference Patterns of Psychometric Intelligence in Adulthood: Generalizability within and across Ability Domains.” *Psychology and Aging* 8 (1): 44.

Schwartz, Sophie, Juliana Baldo, Roger E Graves, and Peter Brugger. 2003. “Pervasive Influence of Semantics in Letter and Category Fluency: A Multidimensional Approach.” *Brain and Language* 87 (3): 400–411.

Solé-Padullés, Cristina, David Bartrés-Faz, Carme Junqué, Pere Vendrell, Lorena Rami, Imma C Clemente, Beatriu Bosch, Amparo Villar, Núria Bargalló, and M Angeles Jurado. 2009. “Brain Structure and Function Related to Cognitive Reserve Variables in Normal

Aging, Mild Cognitive Impairment and Alzheimer's Disease." *Neurobiology of Aging* 30 (7): 1114–24.

Steffener, Jason, and Yaakov Stern. 2012. "Exploring the Neural Basis of Cognitive Reserve in Aging." *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 1822 (3): 467–73.

Stern, Yaakov. 2002. "What Is Cognitive Reserve? Theory and Research Application of the Reserve Concept."

Stern, Yaakov, Yunglin Gazes, Qolomreza Razlighi, Jason Steffener, and Christian Habeck. 2018. "A Task-Invariant Cognitive Reserve Network." *Neuroimage* 178: 36–45.

Stern, Yaakov, Christian Habeck, James Moeller, Nikolaos Scarmeas, Karen E Anderson, H John Hilton, Joseph Flynn, Harold Sackeim, and Ronald Van Heertum. 2005. "Brain Networks Associated with Cognitive Reserve in Healthy Young and Old Adults." *Cerebral Cortex* 15 (4): 394–402.

Stolwyk, Renerus, Bavani Bannirchelvam, Claudine Kraan, and Katrina Simpson. 2015. "The Cognitive Abilities Associated with Verbal Fluency Task Performance Differ across Fluency Variants and Age Groups in Healthy Young and Old Adults." *Journal of Clinical and Experimental Neuropsychology* 37 (1): 70–83.

Sungura, Richard, Callen Onyambu, Emmanuel Mpolya, E Sauli, and John-Mary Vianney. 2020. "The Extended Scope of Neuroimaging and Prospects in Brain Atrophy Mitigation: A Systematic Review." *Interdisciplinary Neurosurgery*, 100875.

Tomasi, Dardo, and Nora D Volkow. 2012. "Resting Functional Connectivity of Language Networks: Characterization and Reproducibility." *Molecular Psychiatry* 17 (8): 841–54.

Tombaugh, Tom N, Jean Kozak, and Laura Rees. 1999. "Normative Data Stratified by Age and Education for Two Measures of Verbal Fluency: FAS and Animal Naming." *Archives of Clinical Neuropsychology* 14 (2): 167–77.

Tombaugh, Tom N, and Nancy J McIntyre. 1992. “The Mini-mental State Examination: A Comprehensive Review.” *Journal of the American Geriatrics Society* 40 (9): 922–35.

Troyer, Angela K. 2000. “Normative Data for Clustering and Switching on Verbal Fluency Tasks.” *Journal of Clinical and Experimental Neuropsychology* 22 (3): 370–78.

Troyer, Angela K, Morris Moscovitch, and Gordon Winocur. 1997. “Clustering and Switching as Two Components of Verbal Fluency: Evidence from Younger and Older Healthy Adults.” *Neuropsychology* 11 (1): 138.

Troyer, Angela K, Morris Moscovitch, Gordon Winocur, Michael P Alexander, and D O N Stuss. 1998. “Clustering and Switching on Verbal Fluency: The Effects of Focal Frontal- and Temporal-Lobe Lesions.” *Neuropsychologia* 36 (6): 499–504.

Wagner, Stefanie, Alexandra Sebastian, Klaus Lieb, Oliver Tüscher, and André Tadić. 2014. “A Coordinate-Based ALE Functional MRI Meta-Analysis of Brain Activation during Verbal Fluency Tasks in Healthy Control Subjects.” *BMC Neuroscience* 15 (1): 19.

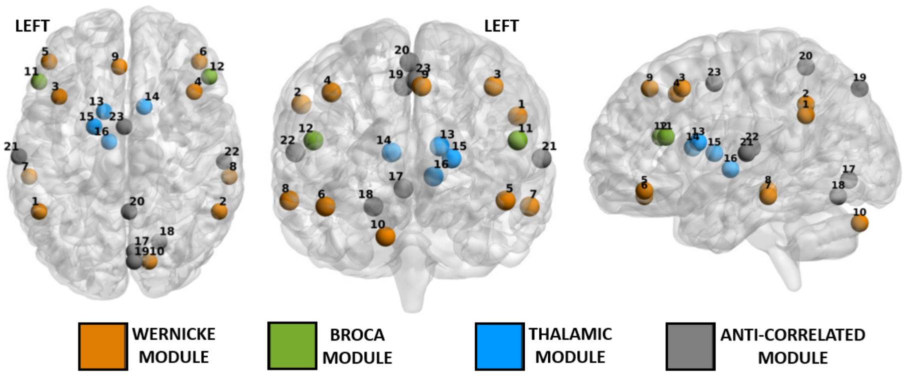
Wechsler, D. 1997. “WAIS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio, Texas.”

Zhang, Haobo, Perminder S Sachdev, Wei Wen, Nicole A Kochan, John D Crawford, Henry Brodaty, Melissa J Slavin, Simone Reppermund, Kristan Kang, and Julian N Trollor. 2013. “Grey Matter Correlates of Three Language Tests in Non-Demented Older Adults.” *PLoS One* 8 (11): e80215.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1

Organization of the four modules in the extended language network



Notes: Labels corresponding to the indices of the brain regions can be found listed in Supplementary Table 1. The visualizations were generated with BrainNet Viewer (Xia, Mingrui, Jinhui Wang, and Yong He. "BrainNet Viewer: a network visualization tool for human brain connectomics." *PloS one* 8, no. 7 (2013): e68910).

Supplementary Table 1

Spatial coordinates of the extended language network

Index	Brain region	Brodmann Area	MNI x (mm)	MNI y (mm)	MNI z (mm)
Wernicke Module					
1	Wernicke's area	39/40	-51	-51	30
2	Right inferior parietal	40	57	-51	36
3	Middle frontal	46	-39	18	45
4	Pars opercularis	44	42	21	42
5	Left pars orbitalis	47	-45	39	-12
6	Right pars orbitalis	47	45	39	-15
7	Left inferior temporal	21/20	-57	-30	-15
8	Right inferior temporal	21/20	63	-30	-12
9	Superior frontal	8	-3	36	45
10	Cerebellum	crus	15	-81	-30
Broca Module					
11	Broca's area	45	-51	27	18
12	Pars triangularis	45	51	30	18
Thalamic Module					
13	Left caudate	-	-12	9	15
14	Right caudate	-	12	12	12
15	Putamen/globus pallidus	-	-18	0	9
16	Ventral thalamus	-	-9	-9	0
Anti-correlated Module					
17	Striate	17	6	-75	-6
18	Extrastriate	18	21	-69	-15
19	Posterior parietal	7	6	-81	45
20	Superior Parietal	5	3	-51	57
21	Left superior temporal	42	-63	-18	9
22	Right superior temporal	42	60	-21	12
23	Cingulate	24	0	0	48

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