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

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

Resumen: 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 (fMRI) 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 (differentiation).

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.