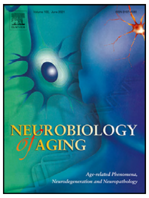
Neurobiology of Aging 117 (2022) 151–164

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org



Cognitive reserve, neurocognitive performance, and high-order resting-state networks in cognitively unimpaired aging

Benxamín Varela-López[a], Álvaro Javier Cruz-Gómez[b], Cristina Lojo-Seoane[c], Fernando Díaz[a], A.X. Pereiro[c], Montserrat Zurrón[a], Mónica Lindín[a], Santiago Galdo-Álvarez[a,*]

[a] *Department of Clinical Psychology and Psychobiology, Universidade de Santiago de Compostela, Galicia, Spain*
[b] *Psychophysiology and Neuroimaging Group, Institute of Biomedical Research Cadiz (INiBICA), Andalusia, Cadiz, Spain*
[c] *Department of Developmental and Educational Psychology, Universidade de Santiago de Compostela, Spain*

ARTICLE INFO

Article history:
Received 24 December 2021
Revised 6 May 2022
Accepted 7 May 2022
Available online 28 May 2022

Keywords:
Cognitive reserve
DAN
FPCN
Healthy aging
Resting-state functional magnetic resonance

ABSTRACT

Cognitive Reserve (CR) is considered a protective factor during the aging process. However, although CR is a multifactorial construct, it has been operationalized in a unitary way (years of formal education or IQ). In the present study, a validated measure to categorize CR holistically (Cognitive Reserve Index Questionnaire) was used to evaluate the resting-state functional connectivity in 77 cognitively unimpaired participants aged 50 years and over with high and low CR, and matched brain global atrophy levels. The connectivity of networks linked to attentional (Dorsal Attention Network -DAN-) and executive (Frontal-Parietal Control Network -FPCN-) processes were evaluated by the combination of Independent Component Analysis and seed-based approaches, since these networks have been proposed as candidates to underlie the protective effect of CR in the aging context. Participants with high CR showed an increase of the connectivity in the FPCN and a decrease in the DAN with respect to the low CR group, correlating with neuropsychological scores and supporting that high CR is related to a better neurocognitive preservation during aging.

1. Introduction

Normal aging is a complex physiological process which involves changes in brain architecture and function (Mak et al., 2017), with several consequences regarding cognition. The cognitive functions most affected by aging are those that require rapid processing or transformation of the information to make a decision, reflected in a decline in speed processing, working memory and executive functioning capacities; however, accumulated knowledge and acquired skills are well maintained into advanced age (Park et al., 2002; Salthouse, 2019).

The effects of aging on cognition depend on the interactions between a broad range of adverse biological and neurophysiological factors and several protective and compensatory processes (Reuter-Lorenz and Park, 2014). Indeed, no linear relationships between clinical manifestations and the pathological severity of the aging process have been detected (Bennett et al., 2006; Bennett et al., 2012; Buchman and Bennett, 2012).

It has been suggested that cognitive reserve (CR) protects against the adverse effects of aging on cognition, increasing tolerance or compensatory capacity throughout aging (Barulli and Stern, 2013). It has been suggested that CR, which can be described as preexisting cognitive processes dependent on genetic and/or environmental factors, enables more efficient performance in cases of pathology or brain impairment (Cabeza et al., 2018; Jones et al., 2011; Stern, 2009) and mitigates the effects of neural decline caused by ageing or age-related diseases by means of increased neural capacity and/or increased neural efficiency (Cabeza et al., 2018).

Research has shown that CR provides some protection against cognitive impairment in normal aging (Giogkaraki et al., 2013) and in older adults with subjective cognitive complaints (Lojo-Seoane et al., 2014, 2018). In addition, CR has been also associated

---

[*] Corresponding author at: Department of Clinical Psychology and Psychobiology, Universidade de Santiago de Compostela, Santiago de Compostela, Galicia, Spain. Tel: +34 881813701, Fax: +34 981521581.
E-mail address: santiago.galdo@usc.es (S. Galdo-Álvarez).

0197-4580/$ – see front matter © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license
(http://creativecommons.org/licenses/by-nc-nd/4.0/)
https://doi.org/10.1016/j.neurobiolaging.2022.05.012

with a lower risk of development of dementia (Bastin et al., 2012; Franzmeier et al., 2017c) and has been shown to be a protective mediator in the conversion from mild cognitive impairment to dementia (Facal et al., 2019).

Considering the dynamic nature of cognitive reserve, that is, it can be modified throughout the lifespan (Fritsch et al., 2007), and as it has been considered to protect against the deleterious effects of normal aging and the development of dementia (Bastin et al., 2012; Franzmeier, et al., 2017d), promoting activities targeting the different proxies included in the Cognitive Reserve Index questionnaire (CRIq) (i.e., education, working activity and leisure time) should be included in potential therapeutic approaches in the context of normal aging and dementia (Anthony & Lin, 2018; Bastin et al., 2012; Franzmeier et al., 2017d).

In addition to the traditional study of normal and pathological aging through the functional magnetic resonance imaging (fMRI) task-activation technique (Hafkemeijer et al., 2012), there is a growing interest from the scientific community regarding the study of the effect of aging on the resting state networks (Hafkemeijer et al., 2012; Mak et al., 2017). Resting state functional resonance imaging (rsfMRI) measures fluctuations in the BOLD signal and can thus map and evaluate the functional brain connectivity (Lee et al., 2013). This technique has been suggested as a promising tool for the study of normal cognition (Hoffman and Morcom, 2018; Mak et al., 2017) and pathological aging (Dennis and Thompson, 2014; Galvin et al., 2011; Hojjati et al., 2017).

Two resting-state networks associated with higher cognitive functions, that is the dorsal attention network (DAN) and the fronto-parietal control network (FPCN), have been found to undergo decline early on in the aging process (Kim, 2019; Murman, 2015).

The DAN is composed by brain regions of the superior parietal lobule, medial intraparietal sulcus, motion-sensitive middle temporal area (MT+), inferior temporal cortex, frontal eyes field and the inferior frontal junction (Kim, 2015; Yeo et al., 2011; Vossel et al., 2014). This network plays an important role in maintaining priority spatial maps for guiding covert and overt attention, saccade planning, observing action and also in visual working memory and thus in memory encoding (Dukelow et al., 2001; Griffis et al., 2015; Huk et al., 2002; Kim, 2019; Vossel et al., 2014). The age-related alteration of DAN functional connectivity may be related to the age-related decline in attention (Betzel et al., 2014; Ferreira and Busatto, 2013; Murman, 2015; Tomasi and Volkow, 2012; Varangis et al., 2019). Moreover, studies of brain metabolism (Alexander et al., 1997; Bastin et al., 2012) and the BOLD signal (Bastin et al., 2012; Franzmeier, et al., 2017b,c) have shown that the level of CR modulates the resting-state functional activity of the DAN in both normal and pathological aging.

The FPCN has been considered a hub for high order functions and cognitive control; by interacting with other structures of the whole brain, it enables rapid, flexible performance of novel tasks (Marek and Dosenbach, 2018). This network is made up of regions that are preferentially involved in maintenance of cognitive control (the anterior prefrontal, insular and cingulate cortices) and regions mainly related to feedback in the context of cognitive control (the dorsolateral prefrontal cortex, the inferior parietal lobe, the caudate nucleus and the lateral cerebellum) (Chiu et al., 2017; Dosenbach et al., 2006; Koziol et al., 2016; Marek and Dosenbach, 2018; Vincent et al., 2008). The FPCN also includes areas involved in language production and comprehension, that is the Brocaś and Wernickeś regions and their right hemisphere equivalents (Laird et al., 2011; Zhu et al., 2014).

The aging-related modification of FPCN activity has been attributed to cognitive decline and to compensatory mechanisms in response to cognitive decline (Jockwitz et al., 2017; Malagurski et al., 2020; Nashiro et al., 2017; Oschmann et al., 2020). The FPCN has also been suggested to at least partly explain the protective effect of CR through the lifespan and during pathological aging (Cole et al., 2012, 2015; Franzmeier et al., 2017b,c; Jiang et al., 2020), as well as in sustaining compensatory mechanisms in early Alzheimerś disease (Elman et al., 2014; Oh et al., 2015).

Some studies have evaluated samples meeting diagnostic criteria of pathological states, including mild cognitive impairment (Bosch et al., 2010; Bozzali et al., 2015; Franzmeier, et al., 2017 a, b, c, d) and/or Alzheimer's dementia (Alexander et al., 1997; Bozzali et al., 2015; Scarmeas et al., 2003; Weiler et al., 2018). However, despite promising results, it is difficult to understand the effects of CR on a brain undergoing extensive neurological changes.

Most studies determine CR from years of education (Weiler et al., 2018), scores on cognitive/intelligence tests (Franzmeier et al., 2017d), or a combination of both (Bastin et al., 2012; Franzmeier et al., 2017 b, c). However, it has been recognised that a global assessment of CR should include other factors, such as occupation and leisure and social activities (Bozzali et al., 2015). Thus, although some studies have categorized CR on the basis of various indicators that act independently (Bennet et al., 2006) or that are included in latent variables (Lojo-Seoane et al., 2014; Siedlecki et al., 2009) or factors (Mitchell et al., 2012), a standard cognitive reserve index is required.

Therefore, the aims of the present study were as follows: (1) to determine the effect of CR, evaluated holistically, by comparing resting state DAN and FPCN connectivity in cognitively unimpaired older adults (participants over 50 years old) divided into 2 groups (high CR and low CR); and (2) to determine whether the effect of CR on the activity of the 2 networks is related to the cognitive performance.

To fulfil the study aims, the CRIq (Nucci et al., 2012) was administrated to participants. This questionnaire provides a standard CR measure in which each piece of information has a weighted value. In line with the Scaffolding Theory of Aging (Park and Reuter-Lorenz, 2009), which postulates that the anterior brain regions have the greatest capacity to functionally reorganize and maintain good levels of cognitive performance during aging, and also considering previous findings on CR (Cole et al., 2012, Cole et al., 2015; Elman et al., 2014; Jiang et al., 2020; Oh et al., 2015), we expected to observe better neuropsychological performance in the high CR group than in the low CR group. Associated with this better performance, it should be possible to observe an increase in the connectivity of anterior brain regions within the 2 networks explored, reflecting an increase in neural capacity during the aging process (Cabeza et al., 2018) and/or a decrease in the connectivity of posterior regions as a result of improved network efficiency (Bastin et al., 2012; Cabeza et al., 2018).

2. Material and methods

2.1. Sample

A total of 77 participants (66 women and 11 men) who had undergone head MRI scanning were selected from a sample of 214 cognitively unimpaired older adults included in the Compostela Aging Study (CompAS), an ongoing longitudinal project to detect cognitive impairment in people aged 50 years and over attending primary care centres in Galicia (north-west Spain) (Juncos-Rabadán et al. 2012).

None of the participants had prior diagnosis of dementia, psychiatric or neurological disorders, severe illness, deafness or blindness; they were not receiving chemotherapy and they did not have

Table 1
Demographic and neuropsychological variable scores (means and standard deviation in parentheses) obtained by the two groups CR+ (High cognitive reserve) and CR- (Low cognitive reserve), and group comparison (t values, df: degrees of freedom)

Variable	Group CR+(n = 38)	Group CR-(n = 39)	Group comparisont-values, df
Age (years)	64.13 (7.67)	65.65 (7.37)	0.52, 75
Gender	30 women/8 men	36 women/3 men	2.806, 1
BV/CSF Index	42.15 (23.18)	39.06 (23.38)	-0.581, 75
Years of formal education	17.55 (4.08)	7.38 (2.87)	-12.60[a], 66.24
MMSE	29.05 (1.13)	27.53 (1.84)	-4.34[a], 63.46
CAMCOG-R Total	97.55 (4.10)	89.33 (5.10)	-7.80[a], 72.43
CAMCOG-R Attention-Calculation	8.36 (0.85)	6.92 (1.70)	-4.71[a], 56.13
CAMCOG-R Memory	23.44 (2.08)	21.28 (2.13)	-4.49[a], 75
CAMCOG-R Executive functions	23.73 (2.61)	18.66 (3.75)	-6.89[a], 68.01
CVLT Immediate Free Recall	56.86 (8.50)	49.25 (8.00)	-4.04[a], 75
CVLT Short-Delayed Free Recall	12.73 (2.45)	10.43 (2.26)	-4.27[a], 75
CVLT Long-Delayed Free Recall	13.10 (2.29)	11.30 (2.24)	-3.46[a], 75
WAIS-III Vocabulary	53.68 (7.65)	37.23 (12.00)	-7.14[a], 64.72
BDAE	55.55 (4.84)	46.76 (6.10)	-6.97[a], 75
CRIq Total score	128.31 (9.67)	86.89 (2.24)	-28.02[a], 61.89

Key: BDAE, Boston diagnostic aphasia examination; BV/CSF, Global brain atrophy index; CAMCOG-R, Cambridge cognitive examination-revised; CRIq, cognitive reserve index questionnaire; CVLT, California verbal learning test; MMSE, mini-mental state examination; WAIS-III= Wechsler adult intelligence scale.

[a] $p < 0.001$

alcohol or other substance use disorder. All participants gave their written informed consent prior to participation in the study. The research was approved by the Galician Ethics Committee for Clinical Research and was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and revised in Seoul 2008.

Each participant underwent extensive evaluation, including review of their medical history and neuropsychological assessment. The following assessments/tools were used during study: (1) Spanish version of the CRIq (http://www.cognitivereserveindex.org). The CRIq is a semi-structured interview of 24 item that quantifies CR through information regarding the individual's entire adult life. The questionnaire combines information about education (such as years of formal schooling and/or courses completed), working activity (number of years of dedication in different work activities according to their cognitive complexity) and leisure time (e.g., reading newspapers and books, going to the cinema or theatre, gardening, social activities, trips) for holistic categorization of the CR construct. (2) General cognitive functioning was evaluated by the Spanish version of the Mini-Mental State Examination MMSE (Lobo et al., 1999, with norms for age and education) and by the Spanish version of the Cambridge Cognitive Examination (CAMCOG-R, total score) (Roth et al., 1999; with norms for age and education, Pereiro et al., 2015). (3) Memory was assessed using the corresponding subscale of CAMCOG-R and the Spanish version of the California Verbal Learning Test (CVLT) (Benedet and Alejandre, 1998; Delis et al., 1987) with scores in Immediate free recall, Short-delayed free recall and Long-delayed free recall. (4) Attention and Executive functions were evaluated using the corresponding subscales of the CAMCOG-R. E) Language was assessed using the Vocabulary subscale of the Wechsler intelligence scale (WAIS-III, Wechsler, 2002) and the abbreviated form of the Spanish version of the Boston Diagnostic Aphasia Examination (BDAE) – Spanish version (Goodglass and Kaplan, 1996).

All participants were classified as cognitively unimpaired adults according to norms for age and years of education. Participants were classified as having a high level of CR or low level of CR according to the percentile distribution of the total CRIq scores from the 214 unimpaired participants (source sample): high cognitive reserve (CR+), when the scoring was equal to or greater than 75th percentile, and low cognitive reserve (CR-), when the scoring was equal to or less than 25th percentile. Furthermore, following the recommendations of the Reserve and Resilience initiative (https://reserveandresilience.com), both groups were matched on a measure of age-related brain change that has been linked to cognitive decline, that is the Brain Volume/Cerebrospinal Fluid Index (BV/CSF index; Orellana et al., 2016), a validated proxy for the global measurement of brain atrophy, was obtained (see Data preprocessing section). This index has been strongly associated with age and also distinguishes between groups of participants with different clinical status, as cognitively unimpaired or with Mild Cognitive Impairment or Alzheimer Dementia (Orellana et al., 2016).

Demographic and neuropsychological profiles of both groups are shown in Table 1.

2.2. MRI acquisition parameters

Magnetic resonance imaging (MRI) was performed with a Philips 3T Achieva scanner (Philips Medical System). A sagittal T1-weighted 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (repetition time/echo time = 7.45 ms/3.40 ms, flip angle = 8º; 180 slices, voxel size = 1 × 1 × 1 mm, field of view = 240 × 240 mm^2, matrix size = 240 × 240 mm) and functional magnetic resonance images were acquired with a gradient echo-planar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast (repetition time/echo time = 2000 ms / 30 ms, flip angle = 87º; 37 interleaved slices, voxel size = 3 × 3 × 3.5 mm, field of view = 240 × 240 mm^2, matrix size = 80 × 80 mm) during open-eyes resting state (while a fixation cross was presented, following previous recommendations; Patriat et al., 2013). Four dummy scans were automatically discarded before image acquisition to prevent signals arising from progressive saturation. Head movements of the participants were minimized by using a vacuum cushion during the MRI data acquisition.

2.3. Data pre-processing and functional connectivity analysis

Both structural and functional images were pre-processed and analysed using the CONN 19c (https://www.nitrc.org/projects/conn; Whitfield-Gabrieli and Nieto-Castanon, 2012) and SPM12 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) toolboxes implemented in Matlab R2019a. In addition, the high-resolution sagittal 3-dimensional T1-weighted MPRAGE sequences (1 × 1 × 1 mm^3) were processed with the FreeSurfer v6.0.0 program (https://surfer.nmr.mgh.harvard.edu/), to obtain the BV/CSF index (where the total brain

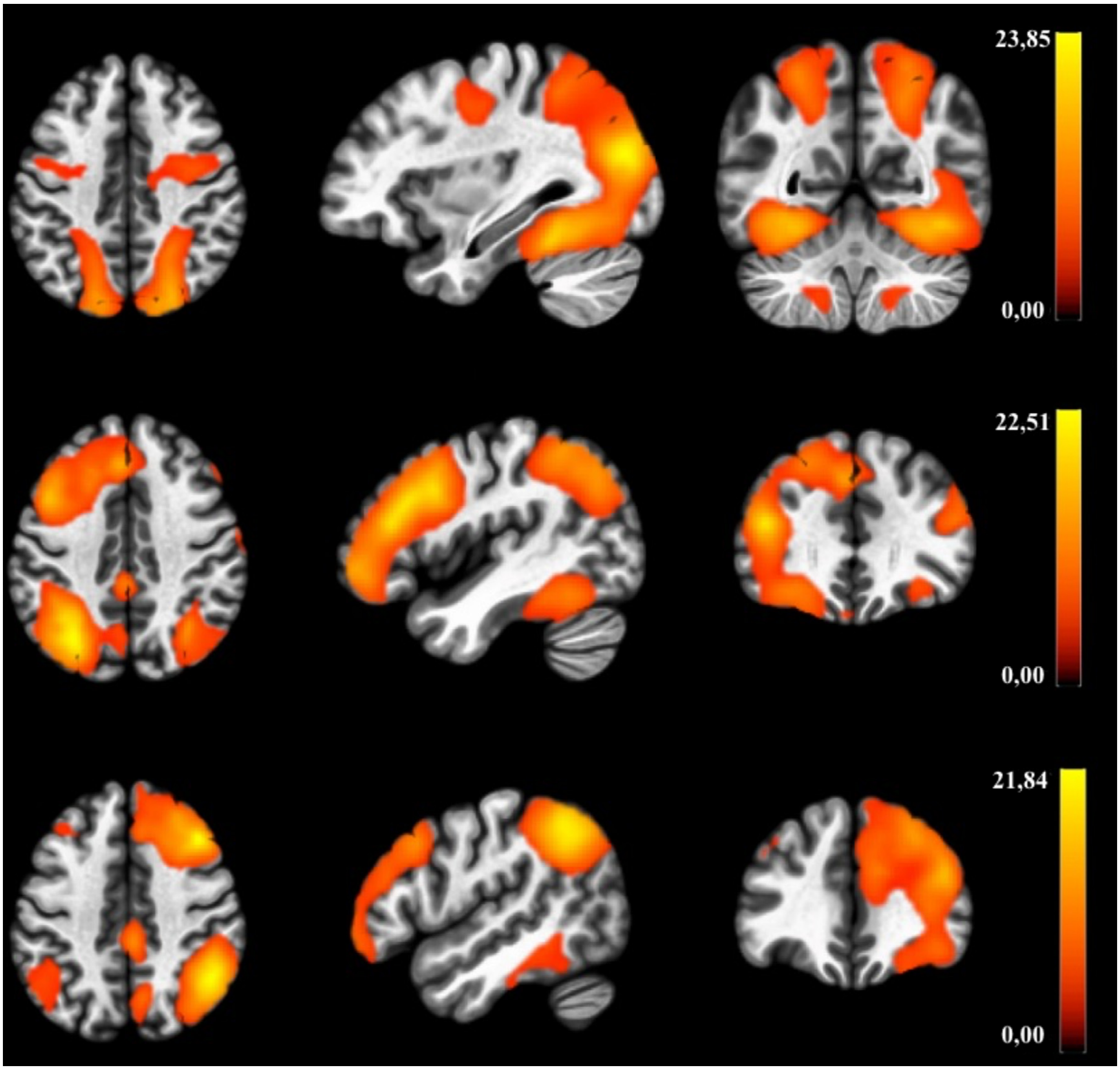


Fig. 1. The 3 independent components derived from the whole sample. DAN (top), left FPCN (middle) and right FPCN (bottom). Color bars correspond to t-scores. "(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)"

volume is put in relation to the total CSF volume). Considering that this index is significantly associated with total intracranial volume (TIV), volume measurements were adjusted using the estimated total intracranial volume (eTIV) using the formula, adjusted_volume = volume_observed – b * (eTIV – mean_eTIV) where mean_eTIV is the average eTIV of all participants and b is the coefficient of regression between the volume observed and the eTIV (Voevodskaya, 2014).

We followed the default pre-processing pipeline of the CONN toolbox, which included functional realignment and unwarping, functional centring of the image to (0, 0, 0) coordinates, slice-timing correction, functional outlier detection, simultaneous functional direct segmentation and normalization to MNI space, structural centring to (0, 0, 0) coordinates, simultaneous structural segmentation and normalization to MNI space and spatial smoothing with a kernel of 8 mm FWHM.

Potential confounding effects of the estimated BOLD signal (noise components from white matter and cerebrospinal areas, estimated subject-motion parameters, scrubbing and rest effects) were estimated and removed separately for each voxel, participant and session, using Ordinary Least Squares regression to project each BOLD signal time series to the sub-space orthogonal to all potential confounding effects as part of the de-noising step (Behzadi et al., 2007; Friston et al., 1996; Power et al., 2014; Whitfield-Gabrieli and Nieto-Castanon, 2012).

CONN's default de-noising pipeline implements an anatomical component-based noise correction procedure (aCompCor), which can extract white matter and cerebral spinal fluid noise components (Behzadi et al., 2007). This procedure was chosen rather than global signal regression because aCompCor has demonstrated higher levels of specificity and sensitivity for positive correlations while addressing negative correlations (Chai et al., 2012). This procedure is combined with quantification of participant motion and identification of outlier scans in the Artifact Rejection Toolbox (Shirer et al., 2015; Whitfield-Gabrieli and Nieto-Castanon, 2012). The Artifact Rejection Toolbox was set to the 97th percentile setting, with the mean global-signal deviation threshold at $z = \pm 5$ and the participant-motion threshold at 0.9 mm. Motion and outlier information were included as covariates in the first-level analyses. Linear regression of the potential confounds and temporal band-pass filter of 0.008–0.09 Hz were applied to the data to exclude signal frequencies outside of the range of expected BOLD signals, reduce the impact of participant motion, extract white matter and cerebral spinal fluid noise components, account for com-

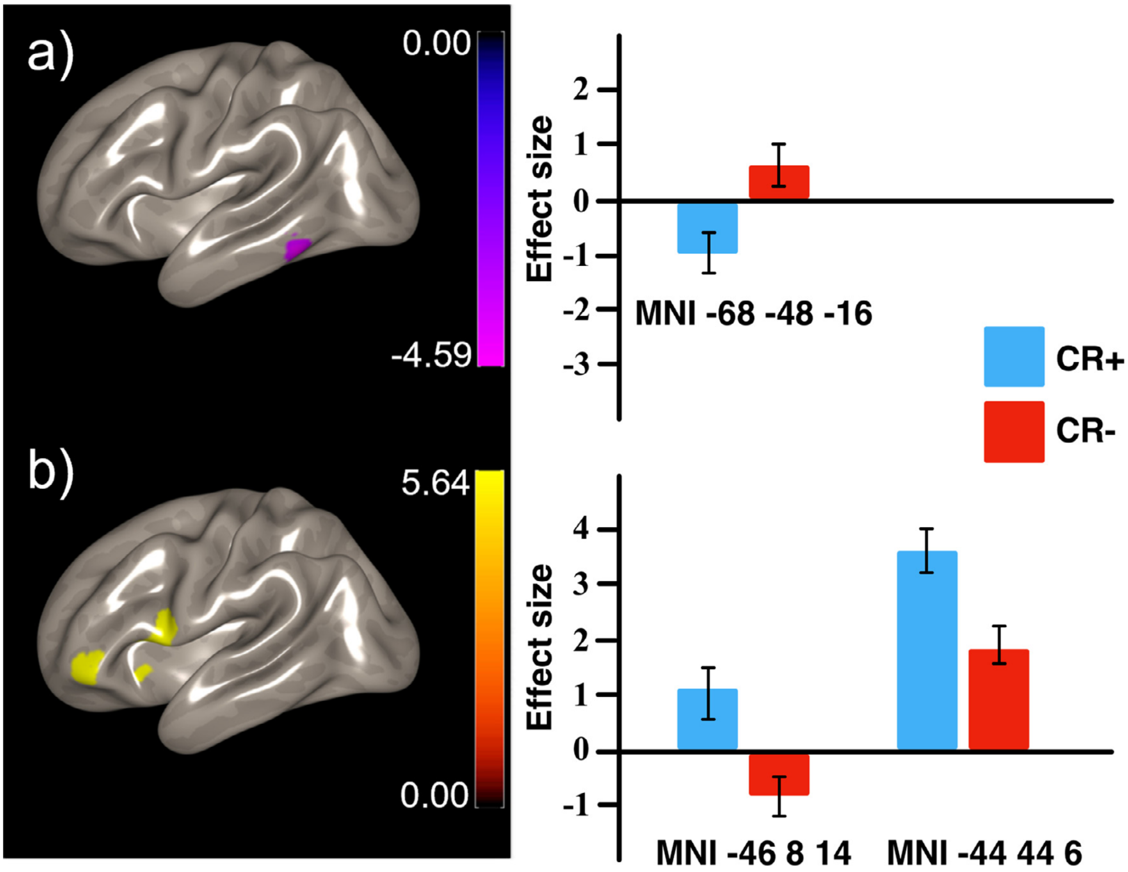


Fig. 2. Significant differences in brain connectivity obtained through ICA (left) and effect size based on mean Fisher's Z scores for the significant clusters (right). Top panel: decrease in connectivity of the inferior temporal gyrus within the DAN (CR+ < CR-). Bottom panel: increased connectivity in 2 clusters mainly located in the ventrolateral prefrontal cortex within the left FPCN (CR+ > CR-). Color scales correspond to t-scores, warm colors represent positive t values, cool colors indicate negative t values. "(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)"

mon rest effects and control for within-participant realignment and scrubbing covariates. No significant differences were observed between groups in terms of the movement parameters measured by CONN or between groups in relation to the number of scans after outlier regression.

Two modalities of resting state functional analysis were applied with the aim of studying the right and left dorsal attention (DAN) and the frontoparietal (FPCN) networks. First, Independent Component Analysis (ICA) satisfactorily identified the DAN and FPCN (right and left) networks. Since the ICA method only addresses within-network connectivity, seed-based analysis (SBA) was conducted to better understand the nature of the observed differences at network-level connectivity (i.e., whether the differences are constrained to within-network or without-network regions) (Smitha et al., 2017; Yang et al., 2020). A seed to voxel analysis was performed, with the regions that showed maximum significant differences in connectivity through group-ICA analysis (post-hoc analysis) used as seeds (for a similar approach see Soman et al., 2020). In addition, bivariate correlations (Pearson's r for variables adjusted to normal distribution, Spearman's rho for variables not adjusted to normal distribution) between neuropsychological and functional connectivity (ICA and seed-to-voxel analysis) measures were determined. The automated anatomical atlas 3 (AAL3) was used for anatomical reference (Rolls et al., 2020).

Both ICA & SBA 1-sample and 2-sample t-tests were assessed at $p < 0.05$, with FWE cluster-level corrected for multiple comparisons in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level.

2.4. Independent component analysis

Independent component analysis was performed using the Group ICA of the fMRI Toolbox (http://mialab.mrn.org/software/, GroupICATv4.0b), the CONN 19c, ICN_Atlas (Kozák et al., 2017) and SPM12 toolboxes implemented in Matlab R2019a.

First, GroupICATv4.0b was used to estimate the number of independent components in the sample, as the CONN toolbox does not provide this function. We used the minimum description length (MDL) criterion to reduce the dimension of the data and estimate the number of components, which increases the efficiency of ICA (Akhbari and Fatemizadeh, 2009). The MDL criterion reported a value of 34 Independent Components for the sample ($n = 77$).

The first level ICA analysis was then carried out using the CONN toolbox for 34 components (estimation by the MDL criterion). We completed the following steps, implemented in CONN and derived from the Calhoun's group-level ICA approach (Calhoun et al. 2001): variance normalization pre-conditioning, subject-level dimensionality reduction (64, CONN default value), subject/condition concatenation of BOLD signal data along the temporal dimension, group-level dimensionality reduction (to target the 34 components estimated by the MDL criterion), fastICA1 (Hyvarinen, 1999) for estimation of independent spatial components, and GICA3 back-projection for the individual subject-level spatial map estimation (see Calhoun et al. 2001, CONN's official website https://web.conn-toolbox.org/home and/or Whitfield-Gabrieli and Nieto-Castanon, (2012) for detailed information).

Three components of interest were identified by the combination of visual and mathematical criteria examined with the spatial involvement measure implemented in the ICN_Atlas toolbox (Kozák et al., 2017) and using the networks (including the main brain networks) described by Laird et al. (2011) as templates. The second level analysis included the individual maps of the components of interest (DAN, left FPCN and right FPCN).

2.5. Seed-based connectivity analysis

We also performed a weighted SBA to compare the functional connectivity of the regions showing differences in maximum connectivity in the group-ICA analysis, with the intention of shedding some light on the origin of the differences observed at the network level (ICA). We seeded the regions that showed the greatest significant differences using 10 mm spheres created through CONN toolbox. For the FPCN results, we created a seed around the left pars opercularis ([-46, 8, 14] cluster-derived coordinates) and another one around the left pars orbitalis ([-44, 44, -6] cluster-derived coordinates). For the DAN results, one seed was created in the left inferior temporal gyrus ([-54, -50, -18] cluster-derived coordinates).

Weighted Seed based connectivity maps are used to characterize task-specific or condition-specific functional connectivity strength (Whitfield-Gabrieli and Nieto-Castanon, 2012). We applied a GLM hemodynamic response function (HRF) weighted to the first level by using the standard bivariate correlation measure for functional connectivity analyses. Individual seed-to-voxel functional connectivity maps were created for each participant and seed (pars orbitalis, pars opercularis and inferior temporal gyrus). The mean BOLD time series was calculated across all voxels within each ROI, and Fisher Z transformation was applied to correlation values between each pair of sources. The second-level analysis was formed by the individual seed-to-voxel maps evoked for the seeds during the resting condition.

As the SBA method can assess both intra-network and inter-network connectivity, the atlas of 7 major networks constructed by Yeo et al. (2011) was used as reference for comparison of the SBA results.

3. Results

3.1. Independent component analysis

A total of 34 components were computed (according to the MDL criterion) using ICA. The respective spatial maps of the FPCN and DAN networks derived from the 1 sample analysis are shown in Fig. 1.

Significant differences were observed in the DAN (see Table 2 and Fig. 2A). Specifically, relative to the CR- group, the CR+ group exhibited lower connectivity, for a cluster mainly located in the left inferior temporal gyrus (ITG). ITG connectivity values within the DAN were negatively correlated with years of formal education, the vocabulary subscale of the WAIS-III, immediate, short term and long-term free memory recall scores in a verbal learning test (CVLT), total score of the CAMCOG-R, and with its subscales of executive function, and memory (see Table 5).

Regarding the FPCN, greater functional connectivity was observed in the CR+ group than in the CR- group, for 2 clusters located in the left ventrolateral prefrontal cortex (see Table 2 and Fig. 2B). The largest cluster was composed by the posterior part of the left ventrolateral prefrontal cortex (pars opercularis, BA 6/44), the posterior left pars triangularis (IFGtriang), the left insular cortex and the left rolandic operculum. This cluster was positively correlated with years of formal education (see Table 5). The second cluster, located in the mid-ventrolateral prefrontal cortex, mainly involved the left pars orbitalis and triangularis in the IFG, extending to a small portion of the left middle frontal gyrus (MFG). The second cluster was also positively correlated with years of formal education (see Table 5).

3.2. Seed-based post-hoc analysis

A post-hoc seed-based analysis was carried out to determine the origin of the significant differences indicated at the network level. With this aim, significant clusters were seeded with spheres located around regions that showed the maximum significant differences in the ICAs, with the intention of performing a seed to voxel analysis.

One-sample t-tests results for each seed can be observed in Fig. 3. Compared to the network atlas reported by Yeo et al. (2011), the left ITG seed evoked a network consistent with the DAN, whereas the seed in the pars orbitalis elicited a network consistent with the FPCN. On the other hand, the seed in the pars opercularis reflected a more diffuse network, including regions of the dorsal attention network (DAN), fronto-parietal control network (FPCN), ventral attention network (VAN), somatomotor network (SMN), visual network (VN), as well as a negative connectivity pattern in regions belonging to the default mode network (DMN).

For the left ITG sphere (see Table 3 and Figs. 3A and 4A), relative to the CR- group, the CR+ group showed lower functional connectivity between the left ITG and two clusters: one comprising the right inferior temporal/inferior occipital gyri (ITG/IOG), showing overlaps of 148 voxels with the visual network and of 59 voxels with the DAN defined by the altas constructed by Yeo et al. (2011), and another cluster located in the left superior parietal/inferior parietal gyri (SPG/IPG) along the left intraparietal sulcus (IPS), in this case showing an overlap of 168 voxels with the DAN defined in the aforementioned atlas. The connectivity values between the left ITG and right ITG/IOG was negatively correlated with years of formal education (see Table 5). The connectivity between the left ITG and the left SPG/IPG was negatively correlated with years of formal education and with the memory CAMCOG-R subscale (see Table 5).

Regarding the left FPCN network (see Table 4), 2 spheres were created to seed the 2 significant clusters observed in the group-ICA (IFGoperc and IFGorb). For the IFGoperc sphere, the CR+ group showed greater functional connectivity than the CR- group, with a large cluster covering parietal and occipital regions, mainly with the superior parietal gyrus (SPG), inferior parietal gyrus (IPG), precuneus (PCUN), middle occipital gyrus (MOG), superior occipital gyrus (SOG) and angular gyrus (ANG). This large cluster overlaps with parieto-occipital regions belonging to the DAN (752 voxels) and parietal regions of the FPCN (232 voxels), according to the network atlas of Yeo et al (2011) (see Fig. 3B and 4B). The connectivity between these regions was positively correlated with years of formal education (see Table 5). The IFGorb sphere, corresponding to the left mid-ventrolateral prefrontal cortex (BA 45/47), showed higher connectivity for the CR+ group than for the CR- group, mainly at the posterior part of the pars triangularis (IFGtriang), with an overlap of 230 voxels with the FPCN network (Yeo et al., 2011) (see Fig. 3C and 4C). The connectivity was significantly correlated with years of formal education and with scores on the executive function CAMCOG-R subscale, the vocabulary subscale of the WAIS-III and with the global scores on the BDAE (see Table 5).

4. Discussion

The present study explored the resting state activity of two networks that were found to play an important role in modulating brain activity related to the level of cognitive reserve (CR),

Table 2
Significant ICA results obtained by the two groups comparison (CR+ > CR-)

Cluster size	L/R	Brain regions	# Voxels in specificregion (overlap %)	MNI Coordinates (x,y,z)			t-value
Significant results for the DAN extracted from ICA.							
324	L	ITG	248 (8)	-68	-48	-16	-4.59
Significant results for the left FPCN extracted from ICA.							
551	L	IFGoperc	281 (27)	-46	8	14	5.01
	L	IFGtriang	81 (3)				
	L	INS	80 (4)				
	L	ROL	75 (8)				
342[a]	L	IFGorb	114 (14)	-44	44	-6	5.64
	L	MFG	93 (2)				
	L	IFGtriang	84 (3)				
	L	OFClat	29 (15)				

Results are significant at $p < 0.05$ Family-Wise Error (FWE) cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level. Only brain regions with >1% cluster overlap were presented.

Key: Cluster size, numbers of voxels in each cluster; IFGoperc, pars opercularis; IFGorb, pars orbitalis; IFGtriang, pars triangularis; INS, insula; ITG, inferior temporal gyrus; L/R, Left or right hemisphere; MFG, middle frontal gyrus; MNI, Montreal neurological institute coordinates; OFClat, lateral orbital gyrus; ROL, rolandic operculum.

[a] Also significant at peak p-FWE level.

Table 3
Significant post-hoc SBA results obtained by the two groups comparison (CR+ > CR-) for the ITG seed [-54, -50, -18], extracted from the DAN ICA

Cluster size	L/R	Brain regions	# Voxels in specificregion (overlap %)	MNI Coordinates(x, y, z)			t-value
281	L	SPG	143 (7)	-20	-62	58	-3.97
	L	IPG	73 (3)				
209	R	ITG	159 (4)	46	-64	-12	-4.38
	R	IOG	32 (3)				

Results are significant at $p < 0.05$ Family-Wise Error (FWE) cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level. Only brain regions with >1% cluster overlap were presented.

Key: Cluster size, numbers of voxels in each cluster; IOG, inferior occipital gyrus; IPG, inferior parietal gyrus; ITG, inferior temporal gyrus; L/R, Left or right hemisphere; MNI, Montreal neurological institute coordinates; SPG, superior parietal gyrus.

Table 4
Significant post-hoc SBA results obtained by the two groups comparison (CR+ > CR-) for the FPCN seeds

Cluster size	L/R	Brain regions	# Voxels in specificregion (overlap %)	MNI Coordinates (x,y,z)			t-value
Significant results for the left IFGoperc sphere [-46, 8, 14], extracted from the FPCN ICA.							
1338	L	SPG	391 (19)	-12	-74	50	4.80
	L	IPG	251 (10)				
	L	PCUN	239 (7)				
	L	MOG	177 (5)				
	L	SOG	114 (8)				
	L	ANG	18 (2)				
Significant results for the left IFGorb sphere [-44, 44, -6], extracted from the left FPCN ICA.							
280	L	IFGtriang	258 (10)	-40	32	18	4.51

Results are significant at $p < 0.05$ Family-Wise Error (FWE) cluster-corrected in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level. Only brain regions with >1% cluster overlap were presented.

Key: ANG: angular gyrus; cluster size: numbers of voxels in each cluster; IFGtriang: pars triangularis; IPG: inferior parietal gyrus; L/R: Left or right hemisphere; MOG: middle occipital gyrus; MNI: Montreal neurological institute coordinates; PCUN: precuneus; SOG: superior occipital gyrus; SPG: superior parietal gyrus.

specifically the dorsal attention network (DAN) (Alexander et al., 1997; Bastin et al., 2012; Franzmeier, et al., 2017b) and frontoparietal control network (FPCN) (Cole et al., 2012, Cole et al., 2015; Franzmeier et al., 2017c; Franzmeier et al., 2017d; Jiang et al., 2020). Both groups were matched in a validated index of global brain atrophy, the BV/CSF index (Orellana et al., 2016), indicating that the effects are related to the CR proxy rather than to other mechanisms of preservation or deterioration in aging.

Independent components analysis and seed to voxel post-hoc analysis (seeding the significant clusters resulting from the ICA analyses) were carried out. The results revealed that CR+ participants showed reduced connectivity in the DAN, but increased connectivity in the FPCN, with both effects correlated with better performance in neuropsychological tests. The study findings therefore suggest that CR allows greater recruitment of anterior regions (FPCN results) in detriment to posterior regions (DAN results), as proposed in the Scaffolding Theory of Aging (Park et al., 2009; Reuter-Lorenz and Park, 2014). In fact, the results support the prediction of the theory that life experiences impact the function of the brain, in this case promoting efficient connectivity of neural networks, and therefore affect the cognitive performance by enhancing neural resources enrichment and developing compensatory mechanisms (scaffolding) to cope with life-span related changes (Reuter-Lorenz and Park, 2014).

Regarding the DAN, network-level results showed multiple significant (all negative) correlations between the connectivity in the DAN with overall scores of CAMCOG (global, memory, and executive function scores), CVLT memory subscales, the vocabulary subscale of the WAIS, and years of formal education. In addition, activation of the left ITG within the DAN was negatively

Table 5
Significant correlations between ICA/SBA results, years of formal education and neuropsychological variables

ICA/SBAresults	DAN	FPCN		ITG seed		IFGoperc seed	IFGorb seed
	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)	MNI Coordinate (x,y,z)
	-68 -48 -16	-46 8 14	-44 44 -6	-20 -62 58	46 -64 -12	-12 -74 50	-40 32 18
Years of formal education	rho = - 0.434[b]	rho = 0.473[b]	rho = 0.428[b]	rho = - 0.431[b]	rho = - 0.388[a]	rho = 0.430[b]	rho = 0.434[b]
MMSE	–	–	–	–	–	–	–
CAMCOG-R Total	rho = - 0.544[c]	–	–	–	–	–	–
CAMCOG-R Attention-Calculation	–	–	–	–	–	–	–
CAMCOG-R Memory	r = - 0.402[a]	–	–	r = - 0.419[a]	–	–	–
CAMCOG-R Executive functions	rho = - 0.404[a]	–	–	–	–	–	rho = 0.387[a]
CVLT Immediate Free Recall	r = - 0.433[b]	–	–	–	–	–	–
CVLT Short-Delayed Free Recall	rho = - 0.517[c]	–	–	–	–	–	–
CVLT Long-Delayed Free Recall	rho = - 0.458[b]	–	–	–	–	–	–
WAIS-III Vocabulary	rho = - 0.421[a]	–	–	–	–	–	rho = 0.380[a]
BDAE	–	–	–	–	–	–	rho = 0.419[a]

Key: BDAE, Boston diagnostic aphasia examination; CAMCOG-R, Cambridge cognitive examination-revised; CVLT, California verbal learning test; MMSE, mini-mental state examination; r, Pearson's (parametric) correlation; rho, Spearman's non-parametric correlation; WAIS-III= Wechsler adult intelligence scale.

All *p* corrected to Bonferroni:

[a] <0.05

[b] <0.01

[c] <0.001

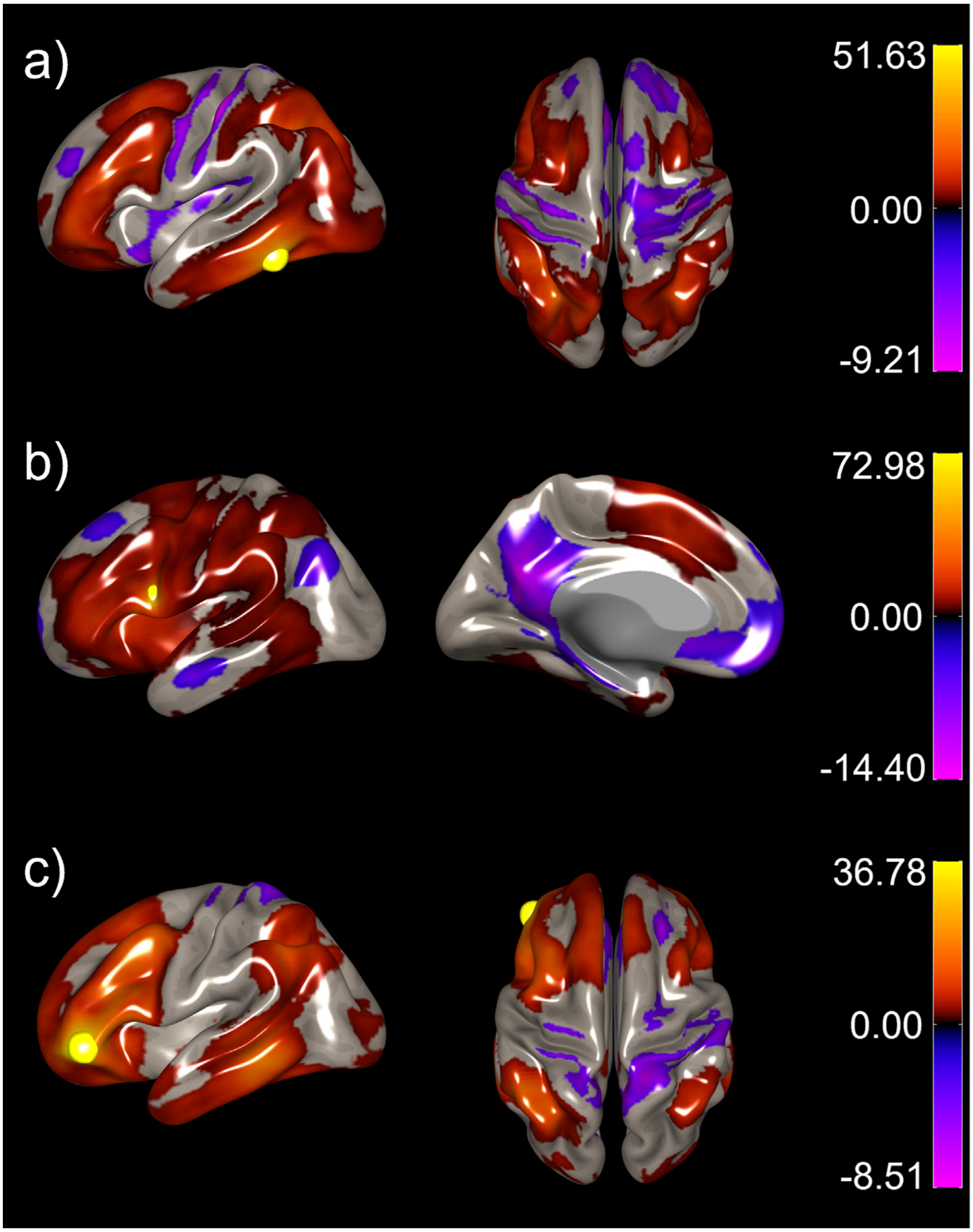


Fig. 3. One-sample t-tests results evoked by the regions used in seed-based analyses. (A) ITG seed. (B) Pars opercularis seed. (C) Pars orbitalis seed. "(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)"

correlated with memory outcomes. Considered together, and in line with the reserve hypothesis on neural activity (Cabeza et al., 2018), the present results indicate that CR leads to a greater efficiency/effectiveness within DAN, which is consistent with previously reported findings. Thus, Bastin et al. (2012) reported that high CR was related to lower metabolic activity in the left anterior intraparietal sulcus within the DAN in cognitively unimpaired older adults. Similarly, Karim et al. (2019) observed that educational level was negatively associated with left ITG activity. Furthermore, Strenziok et al. (2014) reported that cognitive training was associated with a reduction in the functional connectivity of the right superior parietal cortex and the left inferior temporal cortex within the DAN.

More specifically, reduced connectivity within the DAN was found in the group with high CR relative to the group with low CR of left ITG, an area that seems to play an important role in the top-down processing of visual information in the context of the visual working memory operations (Ranganath, 2006; Ranganath and D'Esposito, 2005; Hamamé et al., 2012; Postle et al., 2000) Left ITG presented a reduced connectivity with the left superior and inferior parietal gyri (SPG/IPG), a key region in the DAN, underlying the focus of attention and acting as working memory storage; Cowan, 2011), and with the right inferior temporal and occipital gyri (ITG/IOG), which forms part of the Visual Network. Previous studies have revealed that DAN regions modulate the activity of bilateral regions within the Visual Net-

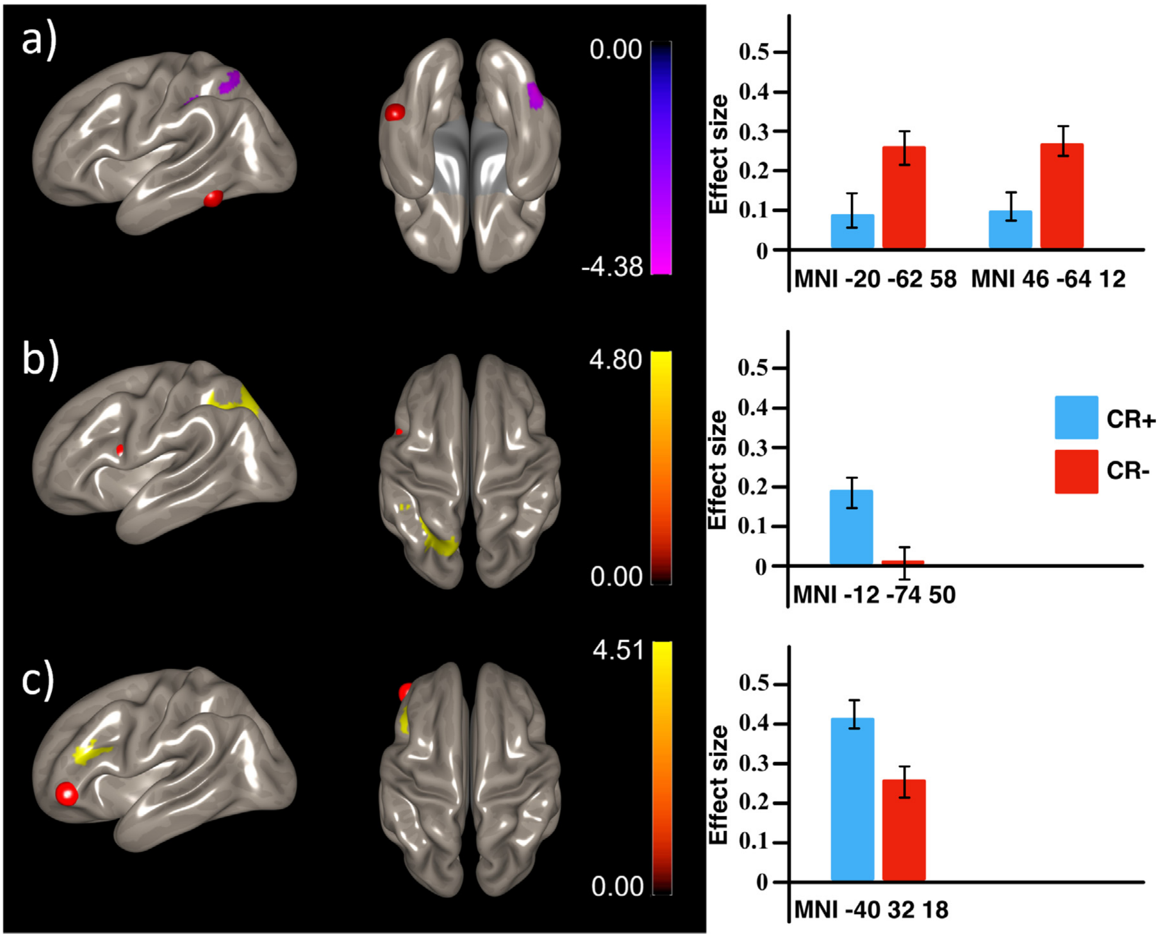


Fig. 4. Significant differences in brain connectivity obtained through the post-hoc SBA (left) and effect size based on mean Fisher's Z scores for the significant clusters (right). Top panel: decreased connectivity of the left ITG seed with the right ITG/IOG and left parietal regions. (CR+ < CR-). Middle panel: increased connectivity of the IFGoper seed with occipito-parietal regions (CR+ > C-). Bottom panel: increased connectivity of the IFGorb seed with the IFGtriang (CR+ > CR-). Color scales correspond to t-scores, warm colors represent positive t values, cool colors indicate negative t values. "(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)"

work in the context of the visual working memory operations (Spadone et al., 2015), which may explain the effect observed in the present study.

It is possible that participants with high cognitive reserve have lower attentional dependence in sensory regions (bilateral ITG) and greater resistance to distraction, although the lack of measures of distractibility does not allow us to confirm this interpretation. However, 2 studies reported reduced dependence of the DAN on sensory regions as a result of perceptive training, a reduction that was also correlated with higher task performance (Lewis et al., 2009; Strenziok et al., 2014). On the other hand, a study which evaluated selective attention in the context of aging found that higher resting-state DAN activity was related to increased distraction (Geerligs et al., 2014). In a study evaluating the relationship between off-task thoughts and memory related to a reading task in youth, greater resting connectivity between the left ITG and regions of the right hemisphere (ITG and lateral occipital cortex) within the DAN was found to be associated with worse recall of the task text, and the increased resting connectivity was interpreted as a greater tendency to disengage attention during the task (Zhang et al., 2019).

Another interpretation of our results is possible considering previous interpretations regarding cerebral hypometabolism in the context of Alzheimer's dementia and mild cognitive impairment (Alexander et al., 1997; Hanyu et al., 2008; Kemppainen et al., 2008; Morbelli et al., 2013; Perneczky et al., 2006; Scarmeas et al., 2003). Thus, the decreased activity observed in DAN regions could be considered to reflect greater brain pathology/impairment in participants with high cognitive reserve. However, this interpretation seems unlikely for our sample as none of the participants showed any signs of cognitive impairment; furthermore, the activity observed in regions of the DAN was negatively correlated with general cognitive status and with performance in memory and executive function measures.

The results for the FPCN showed differences between groups only in the left component (left FPCN), specifically greater activation in volunteers with high CR relative to those with low CR in 2 regions: the first, the mid-ventrolateral prefrontal cortex (BA 45/47) extending to the MFG (BA 46), presented greater functional connectivity with the pars triangularis in the high CR group than in the low CR group and was correlated with better executive performance and language. This finding suggests, as previously considered, that this region underlies a domain-general cognitive control mechanism and is particularly important in the attentional control of memory (Badre and Wagner, 2007; Badre et al., 2005; Moss et al., 2005; Petrides, 2002).

The second region comprised the posterior ventrolateral prefrontal cortex (BA 44/6) extending to the insula and the posterior part of the pars triangularis. Previous studies have reported this region as playing a key role in the effects of CR: in young populations, an association between the across-network connectivity of the left lateral prefrontal cortex (BA6/44) and individual differences in fluid intelligence were observed (Cole et al., 2012, 2015). Franzmeier et al., (2017b) reported that higher global activity of the FPCN and, in particular, of LFC, was associated with more years of formal education in patients with MCI, as observed in the present study in cognitively unimpaired individuals. In addition, activation of the same left frontal region was associated with success in a memory task and with greater CR in the memory domain in normal controls and MCI patients (Franzmeier, et al., 2017d), as well as in individuals with the presence of B-amyloid (Lin et al., 2017). In another study comparing task-related activation and deactivation in normal older adults and patients with AD dementia and amnestic MCI (aMCI), the positive relationship between the activation in this region and language comprehension was interpreted as a compensatory mechanism associated with CR in individuals with aMCI (Bosch et al., 2010). Furthermore, the left frontal cortex (LFC; BA 6/44) has been proposed as a hub of the FPCN where communication with other networks is regulated, including a strong positive connectivity mainly with the DAN and anti-correlation with the default mode network (Franzmeier, et al., 2017c). The results of the present study corroborate this hypothesis, given the diffuse network elicited by the one-sample t-test results and as participants with high CR showed greater functional connectivity between the LFC and parieto-occipital regions belonging to the DAN and parietal regions of the FPCN than in participants with low CR.

Thus, the ventrolateral prefrontal cortex, as part of the FPCN (Androulakis et al., 2018; Chen et al., 2016; Laird et al., 2011; Metzler-Baddeley et al., 2016), has been associated with multiple functions such as language production, decision making, action programming and cognitive control of memory (Badre et al., 2005; Badre and Wagner, 2007; Petrides, 2002; Sakagami and Pan, 2007; Tremblay and Dick, 2016). It is considered a supramodal integration region in which information from the ventral visual pathway and the orbitofrontal cortex and subcortical areas (motivational/emotional information) converge (Badre et al., 2005; Badre and Wagner, 2007; Petrides, 2002; Sakagami and Pan, 2007). It is possible that the greater activation in these areas in older adults with high CR reflects a compensatory mechanism, which acts as a protective factor against the adverse effects of the aging process, in line with the Scaffolding Theory of Aging (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2014), in which CR is associated with a greater capacity for compensation in aging, allowing greater recruitment of anterior regions. Furthermore, in line with this hypothesis, the role of the inferior frontal gyrus as an important structure in maintaining performance (compensation) has previously been described in aging and during transient pharmacological induction of a suboptimal state of noradrenergic signalling in young adults (Angel et al., 2016; Becker et al., 2013).

The cross-sectional nature of the experimental design represents a limitation of the present work. This leads us to be cautious when interpreting the observed increases/decreases in the functional connectivity of the attentional networks under study. The ratio of males and females in the sample is also a limitation, as males were underrepresented. Future studies should also consider different biomarkers, such as the amyloid deposits or presence of APOE4, because of their possible interaction with CR in neural changes.

5. Conclusions

Reduced connectivity in the DAN (Dorsal Attention Network), increased activation of frontal regions of the left FPCN (Fronto-Parietal Control Network) and increased LFC-DAN connectivity were associated with higher levels of CR, as measured by a validated standardized questionnaire including demographic, educational, occupation and leisure time data. The activation pattern (increased FPCN/LFC-DAN and decreased DAN) was correlated with better cognitive executive function, memory and language performance, thus supporting the role of CR as protecting against cognitive impairment, increasing neural capacity and efficiency, and with potential implications for the research on brain stimulation targets in the context of aging.

Author contributions

Varela-López, Benxamín: Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing; Cruz-Gómez, Álvaro Javier: Methodology, Writing - review & editing; Lojo-Seoane, Cristina: Data curation, Writing - review & editing; Díaz, Fernando: Conceptualization, Funding acquisition, Project administration, Writing - review & editing; Pereiro, A.X.: Data curation, Writing - review & editing; Zurrón, Montserrat: Conceptualization, Funding acquisition, Project administration, Writing - review & editing; Lindín, Mónica: Conceptualization, Investigation, Writing - review & editing; Galdo-Álvarez, Santiago: Conceptualization, Investigation, Supervision, Visualization, Writing - review & editing.

Disclosure statement

The authors declare that the work submitted has not been published previously it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Acknowledgements

This study was supported by grants from the Spanish Government, Ministerio de Ciencia e Innovación (PSI2017-89389-C2-R; PID2020-114521RB-C21/C22); the Galician Government (Xunta de Galicia), Axudas para a Consolidación e Estruturación de Unidades de Investigación Competitivas do Sistema Universitario de Galicia*:* GRC (GI-1807-USC); Ref: ED431-2017/27; ED431C-2021/04; all with ERDF/FEDER funds.

References

Akhbari, M., Fatemizadeh, E., 2009. Application of independent component analysis for activation detection in functional magnetic resonance imaging (FMRI) data. 2009 IEEE/SP 15th Workshop on Statistical Signal Processing, 129-132. doi:10.1109/SSP.2009.5278621

Alexander, G.E., Furey, M.L., Grady, C.L., Pietrini, P., Brady, D.R., Mentis, M.J., Schapiro, M.B., 1997. Association of premorbid intellectual function with cerebral metabolism in Alzheimer's disease: implications for the cognitive reserve hypothesis. Am J Psychiatry 154 (2), 165–172. doi:10.1176/ajp.154.2.165.

Androulakis, X.M., Krebs, K.A., Jenkins, C., Maleki, N., Finkel, A.G., Rorden, C., Newman, R., 2018. Central executive and default mode network intranet work functional connectivity patterns in chronic migraine. J Neurol Dis 6 (5), 393. doi:10.4172/2329-6895.1000393.

Angel, L., Bastin, C., Genon, S., Salmon, E., Fay, S., Balteau, E., Maquet, P., Luxen, A., Isingrini, M., Collette, F., 2016. Neural correlates of successful memory retrieval in aging: do executive functioning and task difficulty matter? Brain Res 1631, 53–71. doi:10.1016/j.brainres.2015.10.009.

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. doi:10.1093/arclin/acx125.

Badre, D., Poldrack, R.A., Paré-Blagoev, E.J., Insler, R.Z., Wagner, A.D., 2005. Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron 47 (6), 907–918. doi:10.1016/j.neuron.2005.07.023.

Badre, D., Wagner, A.D., 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia 45 (13), 2883–2901. doi:10.1016/j.neuropsychologia.2007.06.015.

Barulli, D., Stern, Y., 2013. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci 17 (10), 502–509. doi:10.1016/j.tics.2013.08.012.

Bastin, C., Yakushev, I., Bahri, M.A., Fellgiebel, A., Eustache, F., Landeau, B., Scheurich, A., Feyers, D., Collette, F., Chételat, G., Salmon, E., 2012. Cognitive reserve impacts on inter-individual variability in resting-state cerebral metabolism in normal aging. NeuroImage 63 (2), 713–722. doi:10.1016/j.neuroimage.2012.06.074.

Becker, B., Androsch, L., Jahn, R.T., Alich, T., Striepens, N., Markett, S., Maier, W., Hurlemann, R., 2013. Inferior frontal gyrus preserves working memory and emotional learning under conditions of impaired noradrenergic signaling. Front Behav Neurosci 7. doi:10.3389/fnbeh.2013.00197.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. NeuroImage 37 (1), 90–101. doi:10.1016/j.neuroimage.2007.04.042.

Benedet, M.J., Alejandre, M.A., 1998. TAVEC: test de aprendizaje verbal de España–Complutense. TEA ediciones, Madrid.

Bennett, D.A., Schneider, J.A., Arvanitakis, Z., Kelly, J.F., Aggarwal, N.T., Shah, R.C., Wilson, R.S., 2006. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 66 (12), 1837–1844. doi:10.1212/01.wnl.0000219668.47116.e6.

Bennett, D.A., Wilson, R.S., Boyle, P.A., Buchman, A.S., Schneider, J.A., 2012. Relation of neuropathology to cognition in persons without cognitive impairment. Ann Neurol 72 (4), 599–609. doi:10.1002/ana.23654.

Betzel, R.F., Byrge, L., He, Y., Goñi, J., Zuo, X.N., Sporns, O., 2014. Changes in structural and functional connectivity among resting-state networks across the human lifespan. NeuroImage 102, 345–357. doi:10.1016/j.neuroimage.2014.07.067.

Bosch, B., Bartrés-Faz, D., Rami, L., Arenaza-Urquijo, E.M., Fernández-Espejo, D., Junqué, C., Solé-Padullés, C., Sánchez-Valle, R., Bargalló, N., Falcón, C., Molinuevo, J.L., 2010. Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease. Cortex 46 (4), 451–461. doi:10.1016/j.cortex.2009.05.006.

Bozzali, M., Dowling, C., Serra, L., Spanò, B., Torso, M., Marra, C., Castelli, D., Dowell, N.G., Koch, G., Caltagirone, C., Cercignani, M., 2015. The impact of cognitive reserve on brain functional connectivity in Alzheimer's disease. J Alzheimer's Dis 44 (1), 243–250. doi:10.3233/JAD-141824.

Buchman, A.S., Bennett, D.A., 2012. Amyloid pathology in persons with "normal" cognition. Neurology 78 (4), 228–229. doi:10.1212/WNL.0b013e31824367c2.

Cabeza, R., Albert, M., Belleville, S., Craik, F.I., 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. Nat Rev Neurosci 19 (11), 701–710. doi:10.1038/s41583-018-0068-2.

Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 14 (3), 140–151.

Chai, X.J., Castañón, A.N., Öngür, D., Whitfield-Gabrieli, S., 2012. Anticorrelations in resting state networks without global signal regression. NeuroImage 59 (2), 1420–1428. doi:10.1016/j.neuroimage.2011.08.048.

Chen, Y., Meng, X., Hu, Q., Cui, H., Ding, Y., Kang, L., Juhás, M., Greenshaw, A.J., Zhao, A., Wang, Y., Cui, G., Li, P., 2016. Altered resting-state functional organization within the central executive network in obsessive–compulsive disorder. Psychiatry Clin Neurosci 70 (10), 448–456. doi:10.1111/pcn.12419.

Chiu, Y.C., Jiang, J., Egner, T., 2017. The caudate nucleus mediates learning of stimulus–control state associations. J Neurosci 37 (4), 1028–1038. doi:10.1523/JNEUROSCI.0778-16.2016.

Cole, M.W., Ito, T., Braver, T.S., 2015. Lateral prefrontal cortex contributes to fluid intelligence through multinetwork connectivity. Brain Connect 5 (8), 497–504. doi:10.1089/brain.2015.0357.

Cole, M.W., Yarkoni, T., Repovš, G., Anticevic, A., Braver, T.S., 2012. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. J Neurosci 32 (26), 8988–8999. doi:10.1523/JNEUROSCI.0536-12.2012.

Cowan, N., 2011. The focus of attention as observed in visual working memory tasks: making sense of competing claims. Neuropsychologia 49 (6), 1401–1406. doi:10.1016/j.neuropsychologia.2011.01.035.

Delis, D.C., Kramer, J.H., Kaplan, E., Ober, B.A., 1987. California Verbal Learning Test. Psychological Corporation, San Antonio, TX.

Dennis, E.L., Thompson, P.M., 2014. Functional brain connectivity using fmri in aging and alzheimer's disease. Neuropsychol Rev 24 (1), 49–62. doi:10.1007/s11065-014-9249-6.

Dosenbach, N.U.F., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E., 2006. A core system for the implementation of task sets. Neuron 50 (5), 799–812. doi:10.1016/j.neuron.2006.04.031.

Dukelow, S.P., DeSouza, J.F.X., Culham, J.C., van den Berg, A.V., Menon, R.S., Vilis, T., 2001. Distinguishing subregions of the human MT+ complex using visual fields and pursuit eye movements. J Neurophysiol 86 (4), 1991–2000. doi:10.1152/jn.2001.86.4.1991.

Elman, J.A., Oh, H., Madison, C.M., Baker, S.L., Vogel, J.W., Marks, S.M., Crowley, S., O'Neil, J.P., Jagust, W.J, 2014. Neural compensation in older people with brain amyloid-β deposition. Nat Neurosci 17 (10), 1316–1318. doi:10.1038/nn.3806.

Facal, D., Valladares-Rodriguez, S., Lojo-Seoane, C., Pereiro, A.X., Anido-Rifon, L., Juncos-Rabadán, O., 2019. Machine learning approaches to studying the role of cognitive reserve in conversion from mild cognitive impairment to dementia. Int J Geriatr Psychiatry 34, 941–949. doi:10.1002/gps.5090.

Ferreira, L.K., Busatto, G.F., 2013. Resting-state functional connectivity in normal brain aging. Neurosci Biobehav Rev 37 (3), 384–400. doi:10.1016/j.neubiorev.2013.01.017.

Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., 2017. Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. Neurobiol Aging 50, 152–162. doi:10.1016/j.neurobiolaging.2016.11.013.

Franzmeier, N., Caballero, M.Á.A., Taylor, A.N.W., Simon-Vermot, L., Buerger, K., Ertl-Wagner, B., Mueller, C., Catak, C., Janowitz, D., Baykara, E., Gesierich, B., Duering, M., Ewers, M., 2017. Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. Brain Imaging Behav 11 (2), 368–382. doi:10.1007/s11682-016-9599-1.

Franzmeier, N., Göttler, J., Grimmer, T., Drzezga, A., Áraque-Caballero, M.A., Simon-Vermot, L., Taylor, A.N.W., Bürger, K., Catak, C., Janowitz, D., Müller, C., Duering, M., Sorg, C., Ewers, M., 2017. Resting-state connectivity of the left frontal cortex to the default mode and dorsal attention network supports reserve in mild cognitive impairment. Front Aging Neurosci 9, 264. doi:10.3389/fnagi.2017.00264.

Franzmeier, N., Hartmann, J.C., Taylor, A.N.W., Araque Caballero, M.Á., Simon-Vermot, L., Buerger, K., Kambeitz-Ilankovic, L.M., Ertl-Wagner, B., Mueller, C., Catak, C., Janowitz, D., Stahl, R., Dichgans, M., Duering, M., Ewers, M, 2017. Left frontal hub connectivity during memory performance supports reserve in aging and mild cognitive impairment. J Alzheimer's Dis 59 (4), 1381–1392. doi:10.3233/JAD-170360.

Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J., Turner, R., 1996. Movement-related effects in fMRI time-series: movement artifacts in fMRI. Magn Reson Med 35 (3), 346–355. doi:10.1002/mrm.1910350312.

Fritsch, T., McClendon, M.J., Smyth, K.A., Lerner, A.J., Friedland, R.P., Larsen, J.D., 2007. Cognitive functioning in healthy aging: the role of reserve and lifestyle factors early in life. Gerontologist 47 (3), 307–322. doi:10.1093/geront/47.3.307.

Galvin, J.E., Price, J.L., Yan, Z., Morris, J.C., Sheline, Y.I., 2011. Resting bold fMRI differentiates dementia with Lewy bodies vs Alzheimer disease. Neurology 76 (21), 1797–1803. doi:10.1212/WNL.0b013e31821ccc83.

Geerligs, L., Saliasi, E., Maurits, N.M., Renken, R.J., Lorist, M.M., 2014. Brain mechanisms underlying the effects of aging on different aspects of selective attention. NeuroImage 91, 52–62. doi:10.1016/j.neuroimage.2014.01.029.

Giogkaraki, E., Michaelides, M.P., Constantinidou, F., 2013. The role of cognitive reserve in cognitive aging: results from the neurocognitive study on aging. J Clin Exper Neuropsychol 35 (10), 1024–1035. doi:10.1080/13803395.2013.847906.

Goodglass, H., Kaplan, E., 1996. Evaluación de la afasia y de trastornos relacionados. Madrid: Editorial Médica Panamericana.

Griffis, J.C., Elkhetali, A.S., Burge, W.K., Chen, R.H., Visscher, K.M., 2015. Retinotopic patterns of background connectivity between V1 and fronto-parietal cortex are modulated by task demands. Front Hum Neurosci 9. doi:10.3389/fnhum.2015.00338.

Hafkemeijer, A., van der Grond, J., Rombouts, S.A.R.B., 2012. Imaging the default mode network in aging and dementia. Biochim Biophys Acta 1822 (3), 431–441. doi:10.1016/j.bbadis.2011.07.008.

Hamamé, C.M., Vidal, J.R., Ossandón, T., Jerbi, K., Dalal, S.S., Minotti, L., Bertrand, O., Kahane, P., Lachaux, J.P., 2012. Reading the mind's eye: online detection of visuo-spatial working memory and visual imagery in the inferior temporal lobe. NeuroImage 59 (1), 872–879. doi:10.1016/j.neuroimage.2011.07.087.

Hanyu, H., Sato, T., Shimizu, S., Kanetaka, H., Iwamoto, T., Koizumi, K., 2008. The effect of education on rCBF changes in Alzheimer's disease: a longitudinal SPECT study. Eur J Nuclear Med Mol Imaging 35 (12), 2182. doi:10.1007/s00259-008-0848-4.

Hoffman, P., Morcom, A.M., 2018. Age-related changes in the neural networks supporting semantic cognition: a meta-analysis of 47 functional neuroimaging studies. Neurosci Biobehav Rev 84, 134–150. doi:10.1016/j.neubiorev.2017.11.010.

Hojjati, S.H., Ebrahimzadeh, A., Khazaee, A., Babajani-Feremi, A.Alzheimer's Disease Neuroimaging Initiative, 2017. Predicting conversion from MCI to AD using resting-state fMRI, graph theoretical approach and SVM. J Neurosci Methods 282, 69–80. doi:10.1016/j.jneumeth.2017.03.006.

Huk, A.C., Dougherty, R.F., Heeger, D.J., 2002. Retinotopy and functional subdivision of human areas MT and MST. J Neurosci 22 (16), 7195–7205. doi:10.1523/JNEUROSCI.22-16-07195.2002.

Hyvarinen, A., 1999. Fast and robust fixed-point algorithms for independent component analysis. IEEE Trans Neural Netwk 10 (3), 626–634. doi:10.1109/72.761722.

Jiang, J., Liu, T., Crawford, J.D., Kochan, N.A., Brodaty, H., Sachdev, P.S., Wen, W., 2020. Stronger bilateral functional connectivity of the frontoparietal control network in near-centenarians and centenarians without dementia. NeuroImage 215, 116855. doi:10.1016/j.neuroimage.2020.116855.

Jockwitz, C., Caspers, S., Lux, S., Eickhoff, S.B., Jütten, K., Lenzen, S., Moebus, S., Pundt, N., Reid, A., Hoffstaedter, F., Jöckel, K.H., Erbel, R., Cichon, S., Nöthen, M.M., Shah, N.J., Zilles, K., Amunts, K., 2017. Influence of age and cognitive performance on resting-state brain networks of older adults in a population-based cohort. Cortex 89, 28–44. doi:10.1016/j.cortex.2017.01.008.

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. J Int Neuropsychol Soc 17 (4), 593–601. doi:10.1017/S1355617710001748.

Juncos-Rabadán, O., Pereiro, A.X., Facal, D., Rodríguez, N., Lojo, C., Caamaño, J.A., Eiroa, P., 2012. Prevalence and correlates of cognitive impairment in adults with subjective cognitive complaints in primary care centres. Dement Geriatr Cogn Disord 33 (4), 226–232. doi:10.1159/000338607.

Karim, H.T., Tudorascu, D.L., Cohen, A., Price, J.C., Lopresti, B., Mathis, C., Klunk, W., Snitz, B.E., Aizenstein, H.J., 2019. Relationships between executive control circuit activity, amyloid burden, and education in cognitively healthy older adults. Am J Geriatr Psychiatry 27 (12), 1360–1371. doi:10.1016/j.jagp.2019.07.008.

Kemppainen, N.M., Aalto, S., Karrasch, M., Någren, K., Savisto, N., Oikonen, V., Viitanen, M., Parkkola, R., Rinne, J.O., 2008. Cognitive reserve hypothesis: Pittsburgh compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. Ann Neurol 63 (1), 112–118. doi:10.1002/ana.21212.

Kim, H., 2015. Encoding and retrieval along the long axis of the hippocampus and their relationships with dorsal attention and default mode networks: the HERNET model: encoding and retrieval along the long axis. Hippocampus 25 (4), 500–510. doi:10.1002/hipo.22387.

Kim, H., 2019. Neural activity during working memory encoding, maintenance, and retrieval: a network-based model and meta-analysis. Hum Brain Mapp 40 (17), 4912–4933. doi:10.1002/hbm.24747.

Kozák, L.R., van Graan, L.A., Chaudhary, U.J., Szabó, Á.G., Lemieux, L., 2017. ICN_Atlas: automated description and quantification of functional MRI activation patterns in the framework of intrinsic connectivity networks. NeuroImage 163, 319–341. doi:10.1016/j.neuroimage.2017.09.014.

Koziol, L.F., Barker, L.A., Jansons, L., 2016. Chapter 10 - conceptualizing developmental language disorders: a theoretical framework including the role of the cerebellum in language-related functioning. In: Mariën, En P., Manto, M. (Eds.), The Linguistic Cerebellum. Academic Press, pp. 223–256. doi:10.1016/B978-0-12-801608-4.00010-4.

Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., McKay, D.R., Glahn, D.C., Beckmann, C.F., Smith, S.M., Fox, P.T., 2011. Behavioral interpretations of intrinsic connectivity networks. J Cogn Neurosci 23 (12), 4022–4037. doi:10.1162/jocn_a_00077.

Lee, M.H., Smyser, C.D., Shimony, J.S., 2013. Resting state fMRI: a review of methods and clinical applications. Am J Neuroradiol 34 (10), 1866–1872. doi:10.3174/ajnr.A3263.

Lewis, C.M., Baldassarre, A., Committeri, G., Romani, G.L., Corbetta, M., 2009. Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci 106 (41), 17558–17563. doi:10.1073/pnas.0902455106.

Lobo, A., Saz, P., Marcos, G., Día, J.L., de la Cámara, C., Ventura, T., 1999. Revalidación y normalización del mini-examen cognoscitivo (primera versión en castellano del mini-mental status examination) en la población general geriátrica. Med Clín 112 (20), 767–774.

Lin, F., Ren, P., Lo, R.Y., Chapman, B.P., Jacobs, A., Baran, T.M., Porsteinsson, A.P., Foxe, J.J., Initiative, for the A.D.N, 2017. Insula and inferior frontal gyrus' activities protect memory performance against Alzheimer's disease pathology in old age. J Alzheimer's Dis 55 (2), 669–678. doi:10.3233/JAD-160715.

Lojo-Seoane, C., Facal, D., Guàrdia-Olmos, J., Juncos-Rabadán, O., 2014. Structural model for estimating the influence of cognitive reserve on cognitive performance in adults with subjective memory complaints. Arch Clin Neuropsychol 29 (3), 245–255. doi:10.1093/arclin/acu007.

Lojo-Seoane, C., Facal, D., Guàrdia-Olmos, J., Pereiro, A.X., Juncos-Rabadán, O., 2018. Effects of cognitive reserve on cognitive performance in a follow-up study in older adults with subjective cognitive complaints. the role of working memory. Front Aging Neurosci 10, 189. doi:10.3389/fnagi.2018.00189.

Mak, L.E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S.H., Milev, R., 2017. The default mode network in healthy individuals: a systematic review and meta-analysis. Brain Connectivity 7 (1), 25–33. doi:10.1089/brain.2016.0438.

Malagurski, B., Liem, F., Oschwald, J., Mérillat, S., Jäncke, L., 2020. Functional dedifferentiation of associative resting state networks in older adults—a longitudinal study. NeuroImage 214, 116680. doi:10.1016/j.neuroimage.2020.116680.

Marek, S., Dosenbach, N.U.F., 2018. The frontoparietal network: function, electrophysiology, and importance of individual precision mapping. Dialogues Clin Neurosci 20 (2), 133. doi:10.31887/DCNS.2018.20.2/smarek.

Metzler-Baddeley, C., Caeyenberghs, K., Foley, S., Jones, D.K., 2016. Task complexity and location specific changes of cortical thickness in executive and salience networks after working memory training. NeuroImage 130, 48–62. doi:10.1016/j.neuroimage.2016.01.007.

Morbelli, S., Perneczky, R., Drzezga, A., Frisoni, G.B., Caroli, A., van Berckel, B.N.M., Ossenkoppele, R., Guedj, E., Didic, M., Brugnolo, A., Naseri, M., Sambuceti, G., Pagani, M., Nobili, F., 2013. Metabolic networks underlying cognitive reserve in prodromal Alzheimer disease: a European Alzheimer disease consortium project. J Nuclear Med 54 (6), 894–902. doi:10.2967/jnumed.112.113928.

Moss, H.E., Abdallah, S., Fletcher, P., Bright, P., Pilgrim, L., Acres, K., Tyler, L.K., 2005. Selecting among competing alternatives: selection and retrieval in the left inferior frontal gyrus. Cereb Cortex 15 (11), 1723–1735. doi:10.1093/cercor/bhi049.

Mitchell, M.B., Shaughnessy, L.W., Shirk, S.D., Yang, F.M., Atri, A., 2012. Neuropsychological test performance and cognitive reserve in healthy aging and the Alzheimer's disease spectrum: a theoretically driven factor analysis. J Int Neuropsychol Soc 18 (6), 1071–1080. doi:10.1017/S1355617712000859.

Murman, D., 2015. The impact of age on cognition. Semin Hear 36 (03), 111–121. doi:10.1055/s-0035-1555115.

Nashiro, K., Sakaki, M., Braskie, M.N., Mather, M., 2017. Resting-state networks associated with cognitive processing show more age-related decline than those associated with emotional processing. Neurobiol Aging 54, 152–162. doi:10.1016/j.neurobiolaging.2017.03.003.

Nucci, M., Mapelli, D., Mondini, S., 2012. Cognitive reserve index questionnaire (CRIq): a new instrument for measuring cognitive reserve. Aging Clin Exper Res 24 (3), 218–226. doi:10.3275/7800.

Oh, H., Steffener, J., Razlighi, Q.R., Habeck, C., Liu, D., Gazes, Y., Janicki, S., Stern, Y., 2015. Aβ-related hyperactivation in frontoparietal control regions in cognitively normal elderly. Neurobiol Aging 36 (12), 3247–3254. doi:10.1016/j.neurobiolaging.2015.08.016.

Orellana, C., Ferreira, D., Muehlboeck, J.-S., Mecocci, P., Vellas, B., Tsolaki, M., Kłoszewska, I., Soininen, H., Lovestone, S., Simmons, A., Wahlund, L.-O., Westman, E.Initiative, for the A. consortium and for the A. D. N., 2016. Measuring global brain atrophy with the brain volume/cerebrospinal fluid index: normative values, cut-offs and clinical associations. Neurodegener Dis 16 (1-2), 77–86. doi:10.1159/000442443.

Oschmann, M., Gawryluk, J.R.for the Alzheimer's Disease Neuroimaging Initiative, 2020. A longitudinal study of changes in resting-state functional magnetic resonance imaging functional connectivity networks during healthy aging. Brain Connect 10 (7), 377–384. doi:10.1089/brain.2019.0724.

Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K., 2002. Models of visuospatial and verbal memory across the adult life span. Psychol Aging 17 (2), 299–320.

Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Ann Rev Psychol 60 (1), 173–196. doi:10.1146/annurev.psych.59.103006.093656.

Patriat, R., Molloy, E.K., Meier, T.B., Kirk, G.R., Nair, V.A., Meyerand, M.E., Prabhakaran, V., Birn, R.M., 2013. The effect of resting condition on resting-state fMRI reliability and consistency: a comparison between resting with eyes open, closed, and fixated. NeuroImage 78, 463–473. doi:10.1016/j.neuroimage.2013.04.013.

Perneczky, R., Drzezga, A., Diehl-Schmid, J., Schmid, G., Wohlschläger, A., Kars, S., Grimmer, T., Wagenpfeil, S., Monsch, A., Kurz, A., 2006. Schooling mediates brain reserve in Alzheimer's disease: findings of fluoro-deoxy-glucose-positron emission tomography. J Neurol Neurosurg Psychiatry 77 (9), 1060–1063. doi:10.1136/jnnp.2006.094714.

Petrides, M., 2002. The mid-ventrolateral prefrontal cortex and active mnemonic retrieval. Neurobiol Learn Mem 78 (3), 528–538. doi:10.1006/nlme.2002.4107.

Pereiro, A.X., Ramos-Lema, S., Juncos-Rabadán, O., Facal, D., Lojo-Seoane, C., 2015. Cambridge cognitive examination-revised: a normative study in a healthy spanish sample. Psicothema 27, 32–39. doi:10.7334/psicothema2014.169.

Postle, B.R., Stern, C.E., Rosen, B.R., Corkin, S., 2000. An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. NeuroImage 11 (5), 409–423. doi:10.1006/nimg.2000.0570.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341. doi:10.1016/j.neuroimage.2013.08.048.

Ranganath, C., 2006. Working memory for visual objects: complementary roles of inferior temporal, medial temporal, and prefrontal cortex. Neuroscience 139 (1), 277–289. doi:10.1016/j.neuroscience.2005.06.092.

Ranganath, C., D'Esposito, M, 2005. Directing the mind's eye: prefrontal, inferior and medial temporal mechanisms for visual working memory. Curr Opin Neurobiol 15 (2), 175–182. doi:10.1016/j.conb.2005.03.017.

Reuter-Lorenz, P.A., Park, D.C., 2014. How does it STAC up? revisiting the scaffolding theory of aging and cognition. Neuropsychol Rev 24 (3), 355–370. doi:10.1007/s11065-014-9270-9.

Rolls, E.T., Huang, C.-C., Lin, C.-P., Feng, J., Joliot, M., 2020. Automated anatomical labelling atlas 3. NeuroImage 206, 116189. doi:10.1016/j.neuroimage.2019.116189.

Roth, M., Huppert, F.A., Mountjoy, C.Q., Tym, E., 1999. CAMDEX-R: The Cambridge Examination for Mental Disorders of the Elderly (Revised). Cambridge University Press, Cambridge, UK [Spanish version: Roth M, Huppert FA, Mountjoy CQ, Tym E, López-Pousa S (2003) CAMDEX-R: prueba de exploración cambridge revisada para la valoración de los trastornos mentales en la vejez. Adaptación española. Madrid: TEA Ediciones].

Sakagami, M., Pan, X., 2007. Functional role of the ventrolateral prefrontal cortex in decision making. Curr Opin Neurobiol 17 (2), 228–233. doi:10.1016/j.conb.2007.02.008.

Salthouse, T.A., 2019. Trajectories of normal cognitive aging. Psychol Aging 34 (1), 17–24. doi:10.1037/pag0000288.

Scarmeas, N., Zarahn, E., Anderson, K.E., Habeck, C.G., Hilton, J., Flynn, J., Marder, K.S., Bell, K.L., Sackeim, H.A., Van Heertum, R.L., Moeller, J.R., Stern, Y., 2003. Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis. Arch Neurol 60 (3), 359. doi:10.1001/archneur.60.3.359.

Shirer, W.R., Jiang, H., Price, C.M., Ng, B., Greicius, M.D., 2015. Optimization of rs-fmri pre-processing for enhanced signal-noise separation, test-retest reliability, and group discrimination. NeuroImage 117, 67–79. doi:10.1016/j.neuroimage.2015.05.015.

Siedlecki, K.L., Stern, Y., Reuben, A., Sacco, R.L., Elkind, M.S.V., Wright, C.B., 2009. Construct validity of cognitive reserve in a multiethnic cohort: the Northern Manhattan study. J Int Neuropsychol Soc 15 (4), 558–569. doi:10.1017/S1355617709090857.

Smitha, K., Akhil Raja, K., Arun, K., Rajesh, P., Thomas, B., Kapilamoorthy, T., Kesavadas, C, 2017. Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. Neuroradiol J 30 (4), 305–317. doi:10.1177/197140091769734.

Soman, S.M., Raghavan, S., Rajesh, P.G., Mohanan, N., Thomas, B., Kesavadas, C., Menon, R.N., 2020. Does resting state functional connectivity differ between mild cognitive impairment and early Alzheimer's dementia? J Neurol Sci 418, 117093. doi:10.1016/j.jns.2020.117093.

Spadone, S., Della Penna, S., Sestieri, C., Betti, V., Tosoni, A., Perrucci, M.G., Romani, G.L., Corbetta, M., 2015. Dynamic reorganization of human resting-state networks during visuospatial attention. Proc Natal Aad Sci 112 (26), 8112–8117. doi:10.1073/pnas.1415439112.

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

Strenziok, M., Parasuraman, R., Clarke, E., Cisler, D.S., Thompson, J.C., Greenwood, P.M., 2014. Neurocognitive enhancement in older adults: comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity. NeuroImage 85, 1027–1039. doi:10.1016/j.neuroimage.2013.07.069.

Tomasi, D., Volkow, N.D., 2012. Aging and functional brain networks. Mol Psychiatry 17 (5), 549–558. doi:10.1038/mp.2011.81.

Tremblay, P., Dick, A.S., 2016. Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain Lang 162, 60–71. doi:10.1016/j.bandl.2016.08.004.

Varangis, E., Habeck, C.G., Razlighi, Q.R., Stern, Y., 2019. The effect of aging on resting state connectivity of predefined networks in the brain. Front Aging Neurosci 11, 234. doi:10.3389/fnagi.2019.00234.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 100 (6), 3328–3342. doi:10.1152/jn.90355.2008.

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

Vossel, S., Geng, J.J., Fink, G.R., 2014. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 20 (2), 150–159. doi:10.1177/1073858413494269.

Weiler, M., Casseb, R.F., de Campos, B.M., de Ligo Teixeira, C.V., Carletti-Cassani, A.F.M.K., Vicentini, J.E., Magalhães, T.N.C., de Almeira, D.Q., Talib, L.L., Forlenza, O.V., Balthazar, M.L.F., Castellano, G., 2018. Cognitive reserve relates to functional network efficiency in Alzheimer's disease. Front Aging Neurosci doi:10.3389/fnagi.2018.00255.

Wechsler, D., 2002. WAIS - III. Escala de inteligencia para adultos de Wechsler- Tercera edición. Paidós, Buenos Aires.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. *Conn*: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2 (3), 125–141. doi:10.1089/brain.2012.0073.

Yang, J., Gohel, S., Vachha, B., 2020. Current methods and new directions in resting state fMRI. Clin Imaging 65, 47–53. doi:10.1016/j.clinimag.2020.04.004.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106 (3), 1125–1165. doi:10.1152/jn.00338.2011.

Zhang, M., Savill, N., Margulies, D.S., Smallwood, J., Jefferies, E., 2019. Distinct individual differences in default mode network connectivity relate to off-task thought and text memory during reading. Sci Rep 9 (1), 16220. doi:10.1038/s41598-019-52674-9.

Zhu, D., Chang, J., Freeman, S., Tan, Z., Xiao, J., Gao, Y., Kong, J., 2014. Changes of functional connectivity in the left frontoparietal network following aphasic stroke. Front Behav Neurosci 8. doi:10.3389/fnbeh.2014.00167.