Specific Anatomic Associations Between White Matter Integrity and Cognitive Reserve in Normal and Cognitively Impaired Elders

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Objectives: To investigate the associations between white matter (WM) integrity and cognitive reserve (CR) in healthy elders (HE), amnestic mild cognitive impairment (a-MCI), and Alzheimer’s disease (AD). The authors studied correlations between CR and WM integrity in regions showing WM age-related effects or pathologic changes and tested the differences of slopes between groups. Methods: Diffusion tensor images (DTIs) were obtained from 18 young individuals, 15 HE, 16 a-MCI cases, and 15 AD cases. Tract-based spatial statistics was used to process DTI data. Areas showing age-related fractional anisotropy (FA) shrinkages (HE < young) and pathology-related FA network (“AD < HE”) were defined. Correlations between CR and WM integrity were adjusted for age, gender, memory performance and brain volumes. Results: HE presented more negative correlations between CR and WM integrity than patients with a-MCI and AD in age-related areas, such as the genu of the corpus callosum. However, these results were mediated by normal variability in memory function and brain volumes. For patients with a-MCI, negative associations between CR and FA were found in several major tracts, being more robust than in AD group. Although longitudinal results need to be interpreted with caution because of the reduced sample of patients with MCI, after 2 years of follow-up, all patients who progressed to AD had high-CR scores, suggesting a putative link between reduced WM integrity (maximal in patients with high CR) and risk of progression to AD. Conclusions: CR correlates are implemented in different anatomic WM areas in HE and patients with a-MCI. Healthy elders with high CR may present better tolerance of typical age-related effects.
In ageing and dementia, cognitive reserve (CR) reflects the capacity of the brain to endure age-related changes and/or neuropathology, because it is predicted that those individuals with high-CR ratings, through more efficient cognitive processing capacities, will be able to tolerate advanced brain damage (or age-related changes) minimizing its impact on clinical and cognitive manifestations. CR is measured from clinical evaluations capturing lifetime exposure to intellectual, social/leisure, and physical activities. Increasing our knowledge of the neural implementation of CR is not only of scientific interest but also may be clinically relevant, because CR status is associated with a reduced risk of developing dementia and accelerated progression of the disease.

In previous neuroimaging studies including healthy elders (HE), mild cognitive impairment (MCI), and Alzheimer disease (AD) cases, we observed more direct correlations between the main proxies of CR and brain activity as measured by functional magnetic resonance imaging (fMRI), than for whole brain or gray matter (GM) atrophy. These correlations were mainly evidenced in areas that are early compromised in AD, such as the superior temporal lobe or the posterior cingulate cortex. These results provided support for the active model of CR, which posits that patients with high CR can compensate brain damage by using more efficiently neural networks underlying cognitive performance. However, the findings also suggested the need to study more sensitive anatomic substrates associated with this construct. One of these cerebral structural substrates could be white matter (WM) status, as indeed, recent evidence indicates that education and aerobic fitness, which are two of the variables commonly included in CR evaluations, are associated with WM volume in HE. In addition, reports from two independent studies including large samples of elders revealed that WM pathology, as reflected by MRI-based measures of white matter hyperintensities (WMHs), was related to reduced cognitive performance among elders with low educational level, whereas highly educated individuals performed better on cognitive evaluations and exhibited no negative modulation of WMH, implying increased tolerance of their brains in front of WM damage, minimizing cognitive manifestations.

Based on this previous evidence linking WM status with variables commonly included in CR evaluations, the objective of this report was to provide information on the relationship between comprehensive measures of CR and more refined evaluations of white matter integrity, using diffusion tensor imaging (DTI). For all DTI analyses, we focused on fractional anisotropy (FA), a parameter that provides quantitative measures of the integrity of WM fiber tracts. We used tract-based spatial statistics (TBSS), a method that allows exploratory whole-brain voxel-based analyses and circumvents some of the issues of misalignment and partial voluming associated with conventional voxel-based morphometry approaches. TBSS also provides increased reliability and more anatomical localization for group differences.

To our knowledge, only one study has considered the associations between measures of CR (education and occupation) and WM integrity using DTI in HE and patients with AD. This report focused on three groups of subjects: HE, patients with MCI, and patients with AD. Following our previous studies, the reason for focusing on these groups was to explore how CR allows individuals to cope with WM damage, as we move from normal elder brains to patients showing MCI or initial stages of dementia. In this investigation conducting whole-brain analyses, we were particularly interested in testing specific interactions between CR and WM microstructure in areas identified as showing age-related compromises and in regions exhibiting pathologic WM changes. We used this approach in view of our earlier findings in which functional brain correlates of CR were more likely to be identified in regions showing early pathologic
damage among patients with AD\textsuperscript{4} and in areas reflecting typical age-related changes in HE.\textsuperscript{12}

\section*{METHODS}

\textbf{Subjects}

Sixty-four subjects were recruited, including 18 young volunteers (mean age: 22.5 years, SD: 1.6, 10 women), 15 HE (age: 74.1 years, SD: 6.1, 10 women; Mini–Mental State Examination [MMSE]: 27.7 SD: 1.5), 16 patients with the amnestic variant of MCI (a-MCI, age: 74.6 years, SD: 6.9, 10 women; MMSE: 25.5, SD: 2.0), and 15 patients with AD (age: 75.27 years; 8 women; MMSE: 21.4, SD: 3.1). All participants were recruited from patients and their spouses at the AD and related cognitive disorders unit of the Neurology Service at the Hospital Clinic, Barcelona, Spain. None of the participants selected had a medical history of acute neurological deficit compatible with TIA or stroke, or radiological evidence of stroke. All elderly participants underwent clinical and neuropsychological evaluations. The diagnostic procedures used to classify individuals into the abovementioned groups have been described elsewhere.\textsuperscript{13} Briefly, healthy individuals did not meet criteria for dementia, presented no cognitive complaints, and their cognitive performance was not less than \(-1.5\) SD on an episodic memory test or on any other test included in the neuropsychological examinations of language, praxis, gnosia, and abstract reasoning. Patients with a-MCI were prospectively selected only if they presented the amnestic form of the disorder. They reported complaints of memory function and scores less than \(-1.5\) SD on an episodic memory test, whereas their remaining cognitive functions and activities of daily living were within the normal range. After a mean period of 2 years after inclusion, all patients with a-MCI were revaluated clinically and cognitively to determine whether they had progressed to dementia or remained stable. An interdisciplinary clinical committee formed by two neurologists and one neuropsychologist using the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer disease and Related Disorders Association criteria established probable AD diagnosis. All patients with AD were in the mild stages of the disease (Global Deterioration Scale Score = 4).

The sample of young individuals was included in this investigation only to isolate areas with age-related FA changes (see below). All elderly groups underwent clinical and neuropsychological assessments with the procedures used previously in our group.\textsuperscript{4} Groups did not differ in terms of age \((F = 1.1; df = 2.45; p = 0.4)\) or gender distributions \((\chi^2 = 0.3; df = 2, p = 0.4)\), but MMSE scores were lower in both patient groups than in the HE group \((F = 29.1; df = 2.45; p < 0.001)\); post-hoc T3 Dunnett (mean differences and \(p\) values) based on heterogeneous variances \((\text{Levene test } = 6.40, p = 0.004): \text{HE versus a-MCI: } 2.17, p < 0.02; \text{HE versus patients with AD: } 6.27, p < 0.001)\) and in patients with AD compared to patients with a-MCI \((4.10, p < 0.001)\).

Proxies of CR were estimated using three main variables reflecting the ones commonly used in the CR literature\textsuperscript{14} and in our previous studies.\textsuperscript{4,12} The first was the Vocabulary Subtest of the WAIS 3rd version (WAIS-III), administered as a measure of premorbid IQ.\textsuperscript{15} A second CR variable was defined as “education-occupation” and included quantifications coded as in a previous report.\textsuperscript{16} 0 = no formal education, 1 = primary school, 2 = secondary education, and 3 = superior or university education; and as regards occupation: 0 = nonqualified, 1 = qualified manual, 2 = qualified nonmanual or technician, 3 = professional (university degree required), 4 = manager or director (university degree required). The final score was obtained by adding the education and occupation values (range: 0–7). A third proxy recorded lifetime occupations in leisure and cognitively stimulating activities, such as reading, writing, music playing, as well as sports and walking (physical activities), and participation in social activities or groups, associations, and voluntary work (social life activities).\textsuperscript{17} These measures were compiled in a customized questionnaire (the higher the score, the greater the CR). The questionnaire was administered directly to each subject; in the case of patients, this was done in the presence of their relatives to ensure the validity of the data provided. Finally, to summarize the information relating the three CR variables, a composite CR score was obtained for each subject by using factor analyses (principal component methods) and following the procedure described by Stern.
et al. The single factor extracted (composite CR) accounted for 62.3% of the common variance of these three measures.

**MRI Acquisition and DTI Processing**

All subjects were examined on a 3T MRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany). Diffusion–weighted images were acquired using an echo-planar imaging sequence (30 directions, TR = 5600 msec, TE = 89 msec, 49 slices; slice thickness = 2 mm, distance factor = 30%, FOV = 100 mm, and matrix size = 122 × 122). This sequence also provides a T2-weighted volume (B0), which was used to rate WMHs. Specifically, a board-certified neuroradiologist (N.B.) rated all images using the Fazekas scale. Thus, cases with above normal age-related WM damage or with ratings of three on the abovementioned scale were excluded. Because of this, some WM abnormalities were observed in our sample, probably age-related (all 46 cases with Fazekas score range 1–2 (mean: 1.13, SD: 0.63). A high-resolution 3D structural dataset (T1-weighted MPRAGE, TR = 2300 msec, TE = 2.98 msec; FOV = 100 × 100 cm; matrix size = 256 × 256; Flip angle = 9°; and Slice thickness = 1) was also acquired to coregister with the DTI data.

DTI processing and voxel-wise statistical analysis were performed with FSL v4.0 software. We calculated an FA image from each subject using FDT FSL toolbox and Brain Extraction Tool of applied FSL. Nonlinear transforms were applied to obtain FA images aligned to standard space, the resulting images being merged into single 4D images. Mean FA image was fed into skeletonization program obtaining the mean FA skeleton, which was thinned (threshold 0.25) to identify all the fiber pathways consistent across subjects. Finally, FA data were projected onto the thresholded mean FA skeleton and a 4D a image was created.

**Data Analysis**

Detailed descriptions of DTI differences across groups and correlations with neuropsychological performance were not the primary objective of this report, which focused on DTI × CR associations. We proceeded as follows: first, we conducted whole-brain correlations between CR and FA for each clinical group separately and studied the areas of interaction (i.e. regions at which the slope of the regression between CR and FA differed between groups). We then isolated WM areas showing age-related FA shrinkages (HE < young controls) and regions exhibiting loss of WM integrity associated with dementia (AD < HE). Finally, direct correlations between CR and FA and group interactions were computed within these two regions using a voxel-based approach comprising the whole mask by means of TBSS. These results were corrected for multiple comparisons across voxels (FWE corrected).

For clinical, demographic, and cognitive variables analysis of variances with Scheffe’s post-hoc comparisons (or T3 Dunnet test for samples with non-homogeneous variables) and χ² were used using SPSS (v.14.0), considering p < 0.05 to be statistically significant. Because of the low sample sizes, for the demographic and clinical comparisons between the a-MCI converter and a-MCI stable subgroups (see Results section), the Mann-Whitney U test and the Fisher’s exact test were used when appropriate. Probability values for the DTI-based voxelwise correlations between CR and FA and for the interaction were estimated using a simple permutation program (randomize) with a standard GLM design (permutations = 5000, threshold p < 0.05 corrected for multiple comparisons). These latter analyses were adjusted for age, gender, whole-brain volumes, and cognitive performance. Corrected whole-brain volume for each individual was obtained with the following formulae: (GM + WM)/(GM + WM + CSF). Cognitive performance was used to adjust the analyses and was estimated by calculating a composite memory score per individual, which included the mean standardized individual scores of the Consortium to Establish a Registry for Alzheimer Disease, recognition visual memory test as well as the Grober and Buschke Free and Cued Selective Reminding test (total free recall and delayed free recall subtests).

**RESULTS**

The regions evidencing age-related FA decreases (HE < young subjects contrast) were mainly located in the anterior parts of the brain and in the right
hemisphere including the genu of the corpus callosum, parts of the cingulate bundle, and the superior and inferior longitudinal fasciculi. The pathological areas (AD < HE) mainly comprised the posterior left hemisphere involving the uncinate fasciculus and inferior fronto-occipital and cingulate bundles (Fig. 1). Both analyses were corrected for multiple comparisons across voxels (FWE corrected). The mean FA values within this latter network for the a-MCI group were also lower than HE (HE mean FA: 0.42, SD: 0.02; MCI mean FA: 0.38, SD: 0.03; t = 3.59, p < 0.001, df = 29) evidencing incipient WM damage.

When contrasting the whole model (i.e., adjusted for age, gender, the composite memory score, and corrected whole-brain volumes) no significant interactions between CR and FA were found for HE. However, when removing the composite memory score and brain volumes from the equation (both with and without the MMSE as a further covariate), we observed a negative correlation between FA values and CR only when analyses were restricted to regions showing age-related FA shrinkages, which included the genu and the anterior parts of the body of the corpus callosum (Fig. 2). Within this region, correlation slopes between CR and FA were more negative for control subjects than for patients with MCI (Wald test between two correlation estimates against a chi-square distribution W = 14.12, df = 1, p = 0.052) and AD (W = 9.77, df = 1, p = 0.019; see Fig. 2). To further clarify the impact of the composite memory and whole-brain volume variables when testing CR × FA associations in the HE group, complementary analyses were performed, which showed positive correlations between CR ratings and the composite memory score, after adjusting for age, gender, and mean FA values (r = 0.68, p < 0.02, df = 10) or whole-brain volumes (r = 0.62, p < 0.03, df = 10). These latter results suggest that some structural brain correlates other than FA or global brain volumes may be mediating the better memory performance in high-CR elders.

For a-MCI, significant negative correlations were seen between FA values and CR in whole-brain analyses, adjusting for age, gender, composite memory scores, and corrected brain volumes (r = −0.48, p = 0.001). These included regions in the genu and callosal body, the cingulate bundle bilaterally, the inferior and superior longitudinal fasciculi, and the inferior fronto-occipital bundle. In general, right hemisphere FA measures sustained more negative correlations with CR than the left hemisphere including the genu of the corpus callosum, parts of the cingulate bundle, and the superior and inferior longitudinal fasciculi. The pathological areas (AD < HE) mainly comprised the posterior left hemisphere involving the uncinate fasciculus and inferior fronto-occipital and cingulate bundles (Fig. 1). Both analyses were corrected for multiple comparisons across voxels (FWE corrected). The mean FA values within this latter network for the a-MCI group were also lower than HE (HE mean FA: 0.42, SD: 0.02; MCI mean FA: 0.38, SD: 0.03; t = 3.59, p < 0.001, df = 29) evidencing incipient WM damage.
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FIGURE 2. Tract-based spatial statistics results and scatter plots exhibiting negative correlation between cognitive reserve (CR) measures and WM integrity in normal aging (FWE corrected \( p < 0.05 \)). Interactions depict WM regions showing age-related fractional anisotropy (FA) decreases in which the correlation was more negative in HE than in patients. To represent single correlations, \( r \) values were directly converted from \( t \) values of the TBSS output. The \( t \) and \( r \) values correspond to the most statistically significant voxel for each cluster. The scatter plots have been represented using the mean FA value of the age-related area.

When focusing on age-related and pathology-associated FA networks, it was confirmed that loci in both regions showed negative correlations with CR for this group, although more extended regions were involved in the pathology-related network. Thus, for areas showing age-related FA shrinkages, negative associations were found within the genu of the corpus callosum, whereas for pathology-related areas, an extended network was identified, involving the left superior longitudinal fasciculus, the uncinate bundle, the internal capsule, and the splenium of the corpus callosum. As regards the interactions, more negative associations between CR and FA emerged for MCI than for the AD group (\( W = 7.21, df = 1, p = 0.021 \)) in the cingulate bundle, the genu of the CC, and the inferior fronto-occipital fasciculus (see Fig. 3A).

Regarding the results of the 2-year follow-up evaluation, we found that 5 of the 16 patients with a-MCI fulfilled criteria for AD (converter MCI), whereas the remaining cases (\( N = 11 \)) could still be classified as a-MCI (stable MCI). To investigate whether distinct levels of CR were related to the clinical progression, patients with MCI patients were categorized into two groups, high and low CR, with the 50th percentile scores as cutoff point. Comparing the proportion of cases progressing to AD in relation to this new variable, we found that 100% of
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FIGURE 3. [A] Tract-based spatial statistics results (FWE corrected p < 0.05) showing axial and coronal views and scatter plots of areas exhibiting negative correlations between cognitive reserve (CR) measures and WM integrity in a-MCI, in regions showing age-related (green) and pathology-related (red) fractional anisotropy (FA) decreases. Interactions depict WM regions at which the correlation was more negative in a-MCI than in AD (see a more precise description of the anatomic WM areas in the “Results” section of the article). To represent single correlations, r values were directly converted from t values of the tract-based spatial statistics output. The t and r values correspond to the voxel of maximum significance for each cluster. The scatter plots have been represented using the mean FA value of the age-related and pathology-related areas. [B] Comparison of CR composite values between patients with a-MCI that progressed to AD during a 2-year follow-up (c-MCI) and patients who remained clinically stable (s-MCI, see main text for statistical analyses).

CONCLUSIONS

Our study provides the first evidence of associations between WM tract integrity and comprehensive measures of CR (including educational-occupational, social, leisure, and physical ratings) in samples of healthy and pathological elders. In HE, earlier studies of the structural brain correlates of CR proxies found inconsistent associations, demonstrating both positive and negative associations. For example, direct correlations between CR and whole-brain or

c-MCI were classified in the high CR–group whereas 63.6% of stable patients with a-MCI were in the low CR group (Fig. 3B). Direct comparisons between these two groups revealed nonsignificant differences for the CR variable (U = 12, p < 0.079), age (U = 20.5, p < 0.42), MMSE (U = 23.5, p < 0.65), the memory composite score (U = 25.5, p < 0.82) and gender distribution (Fisher’s exact test: 0.95, p < 0.58). However, the increased proportion of converter cases among the high-CR group was significantly greater than in the low-CR group (Fisher’s exact test: 5.65, p < 0.03, df: 1).
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regional GM or WM volumes have been reported.4,6,7,12 Similarly, a recent investigation examining WM microstructure that higher education was associated with greater WM integrity in medial temporal lobe and fiber tracts in HE.11 Similarly, Valenzuela et al21 reported the first evidence of a diminished rate of hippocampal atrophy in high-CR HE during a 3-year follow-up study, but another study including large samples of normal elders and patients with MCI and AD found a relation between higher levels of education and thinner cerebral cortices in all groups.22 Finally, a study of 141 high-functioning older adults concluded that individuals with a high educational level were able to tolerate higher rates of WMHs without any negative impact on cognitive performance.9 Hence, this findings corroborate these latter reports, showing inverse associations between CR and MRI-derived structural parameters, specifically the WM microstructure.

In terms of the brain reserve theory, the divergent results provided by previous correlational studies may in fact reveal nonmutually exclusive and complementary conceptualizations, namely, the “moderation or compensation” and the “neuroprotection” models. The latter is supported by evidence from experimental manipulations of cognitive and/or physical training training not only in animals but also in humans,23 suggesting that lifetime variables linked to high CR do not moderate the relationship between brain burden and cognitive functioning, but act directly on brain health.24 Hence, earlier cross-sectional and particularly longitudinal findings revealing positive associations between CR and morphometric MRI measurements could reflect in vivo evidence for a structurally neuroprotective effect, which may be mediated by several neurorestorative mechanisms at the molecular and cellular levels.21 In contrast, the negative associations observed in some studies (such as ours) probably reflect that high-CR individuals can tolerate a higher degree of age-related brain burden in specific brain areas while at the same time maintaining optimal cognitive or functional abilities. Our observation (after accounting for mean FA values or whole-brain volumes) of positive associations between CR and memory performance in the healthy aged group but not in the a-MCI groups and AD groups suggests that other brain mechanisms (theoretically conceptualized under the “neuroprotection” model) must account for this association and thus explain the variance in neuropsychological performance among HE.

In this connection, it is interesting to note that in our previous study of a sample of healthy older individuals with similar characteristics, CR ratings were positively correlated with regional GM volumes in heteromodal prefrontal and parietal cortices. Moreover, individuals with higher CR exhibited facilitation as regards the implementation of “neural efficiency” mechanisms revealed by fMRI by decreased brain activity in the brain network engaged during a working memory task in the context of equivalent performance compared with subjects with lower CR.12 Therefore, although direct investigation within the same sample of individuals is required, it is conceivable that higher CR may protect against advanced biological effects of brain ageing in specific WM areas in the context of preserved regional GM volumes, resulting in more effective functional networks. These two latter aspects probably account for the cognitive advantage observed among HE with high CR.

Regarding the anatomical localizations of the CR x FA associations, this report suggests the existence of regional specificity. First, HE presented more negative correlations than patients in only areas showing physiological FA decreases, such as the callosal genu, a brain area affected by the ageing process in this study and in previous reports.25 In the patient with a-MCI, higher rates of CR were related to reduced WM microstructure in more widespread WM regions, although a larger network of tracts was involved for the associations located in pathology-related FA shrinkages. In general, late myelinating fibers that are early compromised in AD26 including corticocortical associative fasciculi and commissural fibers were implicated in this association. Hence, in terms of regional specificity, our results corroborate those of earlier functional and morphometric neuroimaging-based studies. For example, the longitudinal investigation of Valenzuela et al.21 stressed that maintenance of brain structure related to greater lifespan history of complex mental activities was observed in the hippocampus, but not when considering whole-brain volume measures or whole-brain ratings of WMHs. Similarly, Pernecky et al.27 demonstrated that the attenuation of the impact of brain damage on everyday functioning by education was
only observed in BA 19, a region known to be primarily affected by neuropathology in their patients. Finally, as previously stated, our earlier fMRI findings revealed a correspondence for the neural implementation of CR in brain regions that typically undergo age-related changes in the HE and in areas that may subserve incipient Alzheimer pathology in the case of cognitively impaired patients.

In this study, associations between CR and FA in MCI patients with MCI were also observed in the age-related network. Although not invalidating previous conclusions referring to regional specificity, these findings may reflect a progressive (i.e., accumulative) reorganization of WM as a function of CR, as microstructural damage increases from normal ageing to early pathologic stages. As several DTI studies have established that WM is compromised in prodromal stages of dementia, these results may show that patients with high CR a-MCI have more resistance to incipient neuropathological processes in these areas. This interpretation is supported by the fact that all patients in this group were clinically comparable (all single domain amnestic patients with MCI), and results were adjusted for memory function. These observations also corroborate those of Teipel et al. who reported regions of reduced FA with higher education among patients with AD, and in fact expand on these observations by using more comprehensive evaluations of CR in the prodromal stages of dementia. Interestingly, although our follow-up study provides information only on a small number of individuals, its observation of higher rates of conversion to dementia among a-MCI cases with high CR supports the idea of a link between reduced WM integrity, which was maximal in patients with high CR, and the risk of progression to AD. Conceptually, these observations recall the notion of a critical threshold of brain vulnerability, which would be able to prolong the preclinical stage in patients with high CR until a critical moment is reached. When this threshold is passed, vulnerability to brain damage seems to be unavoidable and clinical, and functional deficits will eventually appear, accounting for the faster progression observed in patients with dementia in other follow-up investigations. So, although it is clearly acknowledged that our results regarding the incident dementia cases among patient with MCI must be considered as preliminary and thus need to be interpreted with caution due to the small sample, they may suggest that faster progression related to high CR may also be found when considering preclinical phases of dementia and may somehow be related to a higher capacity to tolerate damage in particular WM areas.

Several particularities and limitations of our study should be considered and resolved in future research. First, we did not observe associations between CR and FA for the AD group. Possible explanations are the lack of statistical power associated with reduced samples and the small amount of variation in the variables investigated in this group. Second, although our longitudinal findings suggest that the loss of WM integrity among patients with high reserve MCI patients may modulate the risk of conversion to dementia, we did not consider the importance of this measure in comparison with other well-known risk variables such as the apolipoprotein E genotype or measures of hippocampal atrophy. Furthermore, the procedure used here to define CR is only one of the alternatives available in the literature. Our approach is similar to that used by Stern et al., including measures of premorbid IQ (the Vocabulary-WAIS in our case, because NART is not standardized in the Spanish population) and education. The inclusion of social and leisure activities is also equivalent to the “life activities” considered in other neuroimaging studies of CR from the same group. This procedure differs from the one used by Valenzuela and Sachdev in that their LEQ questionnaire also separates scores for distinct age phases (0-30 years, 30-65 years and older than 65 years). Finally, other research groups mainly focus on educational level, having recently shown that it attenuates the impact of brain damage on everyday functioning in dementia with Lewy bodies. In summary, we are aware that the present results may have differed if these or other approaches had been used to estimate CR. To our knowledge, no investigation has analyzed the common and unique contributions of each of these approaches to associations between CR and brain parameters.

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