Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer’s disease

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Abstract

Introduction: Cognitive reserve (CR) reflects the capacity of the brain to endure neuropathology in order to minimize clinical manifestations. Previous studies showed that CR modulates the patterns of brain activity in both healthy and clinical populations. In the present study we sought to determine whether reorganizations of functional brain resources linked to CR could already be observed in amnestic mild cognitive impairment (a-MCI) and mild Alzheimer’s disease (AD) patients when performing a task corresponding to an unaffected cognitive domain. We further investigated if activity in regions showing task-induced deactivations, usually identified as pertaining to the default-mode network (DMN), was also influenced by CR.

Methods: Fifteen healthy elders, 15 a-MCI and 15 AD patients underwent functional magnetic resonance imaging (fMRI) during a speech comprehension task. Differences in the regression of slopes between CR proxies and blood-oxygen-level dependent (BOLD) signals across clinical groups were investigated for activation and deactivation areas. Correlations between significant fMRI results and a language comprehension test were also computed.

Results: Among a-MCI and AD we observed positive correlations between CR measures and BOLD signals in task-induced activation areas directly processing speech, as well as greater deactivations in regions of the DMN. These relationships were inverted in healthy elders. We found no evidence that these results were mediated by gray matter volumes. Increased activity in left frontal areas and decreased activity in the anterior cingulate were related to better language comprehension in clinical evaluations.

Conclusions: The present findings provide evidence that the neurofunctional reorganizations related to CR among a-MCI and AD patients can be seen even when considering
a preserved cognitive domain, being independent of gray matter atrophy. Areas showing both task-induced activations and deactivations are modulated by CR in an opposite manner when considering healthy elders versus patients. Brain reorganizations facilitated by CR may reflect behavioral compensatory mechanisms.

1. Introduction

In aging and dementia, the concept of cerebral or cognitive reserve (CR) relates to the capacity of the brain to cope with neuropathology so as to minimize clinical manifestations (Stern, 2002). Evidence from prospective epidemiological studies indicates that higher indexes of CR variables such as education, occupation or leisure activities protect against the appearance of clinical symptoms of dementia (Scarmeas, 2007). Some experimental data further suggest that high CR is related to more preserved brain structure (Solé-Padullés et al., 2009; Bartrés-Faz et al., 2009) and to less brain atrophy at follow-up examinations (Valenzuela et al., 2008). In contrast, higher CR ratings in patients with a clinical diagnosis of Alzheimer’s disease (AD) are associated with faster progression of the disease (Stern et al., 1999; Wilson et al., 2000; Scarmeas et al., 2006; Helzner et al., 2007), increased neuropathology burden (Snowdon, 2003), lower rates of regional brain glucose metabolism (Perneckzky et al., 2006) and increased brain atrophy (Kidron et al., 1997; Solé-Padullés et al., 2009). These latter findings are interpreted as reflecting more advanced brain pathology but similar severity of clinical impairments in AD cases with greater CR, thus evidencing the protective effect of CR in clinical manifestations of the disease.

CR status is generally inferred from clinical evaluations that seek to capture the lifetime involvement of patients or healthy subjects in intellectual, social, physical and leisure activities (Valenzuela and Sachdev, 2005). Functional neuroimaging studies show that CR modulates brain activity in the face of cognitive demands. In this regard, previous reports have demonstrated that functional reorganizations associated with CR measures can already be detected in healthy populations. In particular, CR has been associated with the ability to recruit brain networks in a more effective way (Stern, 2002) in both young and elder subjects (Habeck et al., 2003; Scarmeas et al., 2003, 2004; Stern et al., 2003, 2005). Furthermore, Waiter et al. (2008) found that elders presenting sustained general cognitive function across their lifespan had similar patterns of brain activation/deactivation and functional connectivity to young subjects, whereas this was not the case for elders showing cognitive decline. As regards clinical samples, we recently reported that CR variables modulated differentially the pattern of brain activity in mild AD cases and healthy controls during a visual episodic memory task. Specifically, we observed positive correlations between CR ratings and functional magnetic resonance imaging (fMRI) signal in AD patients in the superior temporal gyrus (Brodmann area – BA 22) and superior parietal lobule (BA 7), whereas negative correlations appeared in healthy elders in these same areas. These findings most likely reflect compensatory mechanisms in response either to direct consequences of neuropathological abnormalities in particular regions, or to secondary changes resulting from damage in the earliest affected structures (i.e., entorhinal cortex; Solé-Padullés et al., 2009).

In summary, there is evidence of CR-related functional reorganizations in normal aging that can also be observed in mild AD. Importantly, it should be noted that our and similar previous findings in clinical populations (i.e., Scarmeas et al., 2004) were obtained when challenging patients with cognitive tasks that tap into clinically-affected cognitive domains, such as memory encoding. Nonetheless, from the abovementioned findings reported in the healthy elder literature it seems feasible to hypothesize that functional reorganizations linked to CR mechanisms in patients might also be observed earlier in the course of the cognitive progression of the disease, when considering spared cognitive domains. Thus, the first objective of the present study was to investigate the functional brain correlates of CR measures in brain activity using fMRI during the performance of a passive language comprehension task, one for which the skill required was judged to be clinically unaffected in our sample of patients. Specifically, and on the basis of our previous findings (Solé-Padullés et al., 2009), we hypothesized that the same directionality of results observed formerly during cognitive testing of impaired functions would be detected when investigating an unaffected cognitive domain (i.e., CR-blood-oxygen-level dependent – CR–BOLD negative correlations in healthy elders and CR–BOLD positive correlations in patients). However, in contrast to our previous approach the present strategy has two potential advantages: first, it may help to detect earlier ‘cognitive markers’ evidencing the impact of brain disease on functional brain reorganizations; and second, it facilitates fMRI to be used in AD patients, thus avoiding the common difficulties encountered when considering impaired cognitive functions such as ‘floor effects’ or, in general, the difficulty of comparing patients with healthy controls via cognitive fMRI studies.

A growing body of evidence indicates that brain areas included in the ‘default-mode network (DMN)’ show functional abnormalities in the early stages of AD (for review, see Buckner et al., 2008). The DMN includes functionally connected regions, mainly prefrontal dorsal and ventral medial regions, the postero medial cortex (the posterior cingulate, precuneus and retrosplenial cortex), inferior parietal areas and, less robustly, the hippocampal formation. Previous fMRI studies searching for task-induced deactivations showed that DMN areas are more active during passive task conditions (e.g., passive fixation, rest) than during goal-directed conditions; alternatively, they showed deactivations during targeted or experimental conditions (e.g., making semantic decisions of visually presented stimuli) (Buckner et al., 2008). With some particularities, the basic DMN anatomy is highly consistent across different cognitive tasks and methodological...
approaches (i.e., resting-state studies or task-induced deactivations) (McKiernan et al., 2003; Rombouts et al., 2005; Harrison et al., 2008). In the case of AD the main functional deficit revealed by fMRI in these areas is a decrease of deactivation or lack of deactivations, particularly in the posteromedial region (Lustig et al., 2003; Greicius et al., 2004; Rombouts et al., 2005). The patterns of dysfunctional brain deactivations in the DMN are already observed in mild cognitive impairment (MCI) patients (Rombouts et al., 2005; Celone et al., 2006; Petrella et al., 2007a) and may have clinical implications. In this regard, the most clinically-affected MCI patients exhibit a greater inability to deactivate these brain areas during memory tasks (Celone et al., 2006), and this deficit is particularly present in those cases that will have developed dementia at follow-up evaluations (Petrella et al., 2007b).

An interesting particularity of the DMN is that its activity shows negative correlations (anticorrelations) with brain areas involved in cognitive processing (McKiernan et al., 2003; Fox et al., 2005; Celone et al., 2006; Persson et al., 2007), as well as the fact that greater deactivations are observed as the demands of cognitive processing increase (McKiernan et al., 2003; Persson et al., 2007). To our knowledge, no previous investigation has sought to elucidate whether DMN activity is modulated by CR variables. However, and as reported above, previous findings from our group showed that AD patients with higher CR loads presented the highest BOLD signal in areas involved in the processing of a memory encoding task (Solé-Padullés et al., 2009). Consequently, it could be hypothesized that these patients should also evidence concomitantly greater deactivations in this network. On the other hand, the correlations were reversed in the healthy elder group, as high CR elders used more efficient networks manifested by reduced task-induced brain activations (Solé-Padullés et al., 2009; Bartrés-Faz et al., 2009), reduced deactivations should also be expected in their DMN. Based on these predictions the second aim of the present study was to test whether CR variables modulate brain activity in the default network in an independent sample of healthy elders, amnestic mild cognitive impairment (a-MCI) and mild AD cases.

2. Method

2.1. Participants

Forty-five individuals older than 65 and who provided written informed consent (by their relatives in AD cases) were enrolled in the study, which was approved by the local ethics committee. The whole sample comprised 15 healthy elders, 15 patients with the amnestic variant of MCI (single-domain memory impaired) and 15 AD cases. All patients were prospectively and consecutively recruited from a unit for AD and other cognitive disorders, part of the Neurology Service of the Hospital Clinic in Barcelona. None of the patients or healthy elders had previously participated in studies by our group investigating brain correlates of CR variables (Solé-Padullés et al., 2009; Bartrés-Faz et al., 2009). All subjects underwent clinical and neuropsychological evaluations. The diagnostic procedures employed to classify individuals into the abovementioned groups have been described elsewhere (Rami et al., 2007). Briefly, healthy individuals did not meet criteria for dementia and presented no cognitive complaints. Further, they did not exhibit cognitive performance below −1.5 standard deviation (SD) on an episodic memory test or on any other test forming part of neuropsychological examinations of language, praxis, gnosis and abstract reasoning. Patients with a-MCI reported complaints of memory function and scores below −1.5 SD on an episodic memory test, while their remaining cognitive functions were within the normal limits for age- and education-adjusted values. None of the a-MCI had impaired activities of daily living according to scores on the Functional Activities Questionnaire (FAQ, Pfeffer et al., 1982). Probable AD diagnosis was established by an interdisciplinary clinical committee formed by two neurologists and one neuropsychologist. National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria were applied, taking into account clinical and objective functional and neuropsychological results. All AD patients included were in the mild stages of the disease (Global Deterioration Scale = 4). Atypical AD variants with non-significant episodic memory impairment were excluded from the study.

2.2. Proxies of CR

Three main proxies reflecting those commonly used in the CR literature and in our previous studies (Solé-Padullés et al., 2009; Bartrés-Faz et al., 2009) were defined. The first was the Vocabulary subtest of the Wechsler Adult Intelligence Scale 3rd version (WAIS-III), administered as a measure reflecting pre-morbid IQ (Lezak et al., 2004). A second CR variable was defined as “education–occupation” and included quantifications coded as in a previous report (Staff et al., 2004): 0 = no formal education, 1 = primary school, 2 = secondary education and 3 = superior or university education; and as regards occupation: 0 = non-qualified, 1 = qualified manual, 2 = qualified non-manual or technician, 3 = professional (university degree required), 4 = manager or director (university degree required). The final value was obtained by adding the education and occupation values (range 0–7). A third proxy was taken into account with the aim of considering other relevant variables related to CR (Scarmeas, 2007). This part included recording of lifetime occupations in leisure and cognitively-stimulating activities (reading, writing, music playing, painting), as well as physical (sports and daily walking) and social life (participation in social activities or groups, associations, voluntary work). These measures were gathered into a customized questionnaire with scores ranging from 0 to 19 (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. (2005). The single factor extracted (composite CR) accounted for 62.3% of the common variance of these three measures.

2.3. fMRI acquisition and task procedure

All 45 subjects underwent structural and functional MRI examinations on a 3 T MRI scanner (Magnetom Trio Tim,
Siemens Medical Systems, Germany) at the Centre for Image Diagnosis of the Hospital Clinic (CDIC). The MRI protocol included an fMRI dataset of 240 volumes of 36 axis slices each (using a gradient-echo echo-planar imaging – EPI sequence) and a high-resolution 3D structural dataset (T1-weighted Magnetization Prepared Rapid Gradient Echo – MP-RAGE image) for coregistering with the fMRI images. The acquisition parameters for the fMRI were: repetition time (TR) = 2000 msec; echo time (TE) = 29 msec; percentage phase field of view = 100; matrix size = 128 × 128; slice thickness = 3 mm; interslice gap = 3.75 mm; flip angle = 90°. The parameters for the structural images were: TR = 2300 msec, TE = 2.98 msec, inversion time (TI) = 900; FOV = 100 × 100 cm; matrix size = 256 × 256; flip angle = 9°; slice thickness = 1.

We used an fMRI task previously employed by our group in studies of younger samples (Fernández-Espejo et al., 2008) and adapted from the one proposed by Dehaene-Lambertz et al. (2002). This task consists of the passive listening to eight spoken narratives (20 sec each) played forwards, backwards and alternated with periods of silence of the same length in a three-condition block-design whose total length was 480 sec. Narratives included everyday events with neutral emotional content and without personally meaningful content. They were read by a female Spanish speaker with vivid intonation and recorded using the freeware software Audacity 1.3.4 (http://audacity.sourceforge.net). Reversed narratives (narratives played backwards) matched the originals in terms of physical complexity and acoustic characteristics such as amplitude and power of spectrum, but they violated several segmental and suprasegmental phonological properties of human speech (Binder et al., 2000; Dehaene-Lambertz et al., 2002). These characteristics make reversed speech an ideal control condition for the non-linguistic aspects of speech. The stimuli were presented using the Presentation software (Presentation v.10.1 Neurobehavioural Systems) running on a Windows XP PC and an MRI-compatible high-quality digital sound system incorporating noise-attenuated headphones (VisuaStim Digital, Resonance Technology, Inc.).

While inside the fMRI scanner, healthy elders and patients were instructed just to listen to the narrative presentations and simply try to understand them (which was only possible for forward narratives); they were told to rest during the silent periods. Although we did not record responses inside the scanner all patients had demonstrated preserved language comprehension on the Auditory Comprehension subtest of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass and Kaplan, 1972) and showed that they could understand the meaning of the sentences in pilot trials before fMRI acquisitions.

2.4. Data analysis

The Statistical Package for Social Sciences (SPSS v.14.0) was used to investigate group differences in demographic, clinical and CR measures, employing adequate tests (analysis of variance – ANOVA, χ²) when appropriate. Pearson coefficient correlations were used to test for relationships between significant regions of brain activity (fMRI value at the most significant voxel) and performance on the BDAE Auditory Comprehension subtest. Differences in the regression slopes between CR and fMRI signals between clinical groups were calculated using t-Student statistics. All analyses performed in SPSS were considered significant for values of p < .05.

To analyze fMRI data we used SPM5 running in Matlab 6.5. Original magnetic resonance images registered were organized into three-dimensional files (240 volumes per subject) by means of MRICro software (University of Nottingham, UK) and saved in a format compatible with SPM5. Following alignment along the anterior commissure/posterior commissure line and realignment of the scans to remove the effects of head movement, images were transferred into a standardized coordinate system. Normalized images were smoothed with an isotropic Gaussian kernel (full width half maximum) of 8 mm. The analysis was based on the general linear model. Three regressors (one corresponding to each condition) were modeled per subject and each scan was coded to belong to one of these conditions. After modeling, individual t-contrasts were performed to reveal linguistic processing or task-induced activations. This was achieved by creating the following contrast: 'language played forwards > language played backwards'. A second individual contrast was created to reveal task-induced deactivations (contrast: 'silent periods > language forward'), revealing decreased MRI signal during language processing (or relatively greater MR signal during the low-level rest baseline). Recent studies in elder populations including AD patients evidence that this approach is useful to identify brain areas of the DMN (e.g., Lustig et al., 2003; Celone et al., 2006; Person et al., 2008). Second level (group) analyses were performed to search for brain areas showing group differences in the slopes of the relationship between CR variables and regions of task-increased and task-decreased brain activations. To this end we used the ‘full factorial’ design implemented in SPM5. For the analyses involving the ‘silent periods > language forward’ contrast, group analyses were restricted to brain areas constituting the DMN, as summarized by Buckner et al. (2008). These include the ventral medial prefrontal cortex (BA 24, 31, 10), the posterior cingulate/retrosplenial cortex (BA 29, 30, 23/31), the inferior parietal lobe (BA 39, 40), the lateral temporal cortex (BA 21), the dorsal medial prefrontal cortex (BA, 24, 32, 10, 9) and the hippocampal formation. All fMRI results were interpreted only if they attained both a voxelwise threshold of p < .001 (uncorrected) and a p < .05 (corrected) threshold on the extent of clusters. Only significant clusters containing more than 20 contiguous voxels were considered.

3. Results

Demographic data, MMSE scores and values for the CR composite score and its components are all given in Table 1. As expected, mild AD cases had reduced global cognitive performance when compared to controls and a-MCI patients. The differences between the two patient groups also reached statistical significance. Based on these differences MMSE scores were included as a covariate in subsequent analyses testing for group differences between CR and fMRI results. Age, gender and CR ratings were equally distributed across groups. However, since we could not rule out the possibility that these variables may differentially influence the
relationships between CR and brain activity within the selected groups, they were also included as covariates in further analyses.

The pattern of brain activity for the whole group of subjects obtained from the individual ‘activation contrasts’ (forward vs backward narratives) revealed significantly increased brain activity in a large cluster [centered at BA 46, (x: −54, 21, 24) t: 6.49, cluster: 515 voxels] that extended laterally in the left hemisphere, including areas of the left inferior frontal and precentral gyri (BA 44/6) and temporal regions of the middle and superior temporal gyri (BA 21/22). These results showing peaks of activity in frontal and temporal areas are in accordance with previous results obtained by our group using the same task in healthy young individuals (Fernández-Espejo et al., 2008).

In the present study we focused our analyses on identifying brain regions showing differences in the direction of slopes between CR and fMRI signal in healthy elders and patients. In this regard, a clear dissociation emerged for the activation and deactivation contrasts. First, both a-MCI and AD cases presented positive correlations between CR composite scores and BOLD for the contrast reflecting task-induced activations. These correlations were negative in the control group, with the differences of the regression slopes between CR and BOLD showing significant functional reorganization. The opposite effect was observed in both groups and task-induced activations and deactivations. AD patients presented more positive correlations in the left inferior frontal gyrus as compared to both controls and a-MCI patients.

Conversely, both clinical groups showed increased deactivations in the DMN that were related to higher CR ratings, as compared to healthy elders where higher CR was associated with increased activity in DMN regions. The regions showing significant differences in the regression slopes between groups were the right anterior cingulate and supramarginal areas for the comparison between a-MCI and controls and the posteromedial region (precuneus/posterior cingulate) for both groups of patients as compared to the reference group. As in our recent study (Bartrés-Faz et al., 2009), we further examined whether these results were influenced by the underlying brain atrophy, as would be predicted by CR theory. To this end we reanalyzed the data after adjusting in a voxel-based manner by gray matter volumes derived from processing 3D-MRI acquisitions and using the Biological Parametric Mapping (BPM). This toolbox implemented in SPM allows a direct comparison to be made between different MR modalities (Casanova et al., 2007). Unexpectedly, the results of these new analyses revealed that GM had little or no influence on the results described above. The precise areas showing significant differences in the regression slopes between CR and BOLD activity across groups in the final model are detailed in Table 2 and represented graphically in the figures (see Figs. 1 and 2).

Finally, we investigated whether the brain areas of activation and deactivation showing significant functional reorganizations on the basis of CR were related to language comprehension performance in controls and patients. To this end we correlated BOLD activity in each identified area with performance on the BDAE Auditory Comprehension task. These analyses were performed separately for each group and also after combining the two patient groups. The only significant results were a positive correlation between fMRI signal in the left inferior frontal/precentral gyri (BA 44/6) and temporal regions of the middle and superior temporal gyri (BA 21/22). These results showing peaks of activity in frontal and temporal areas are in accordance with previous results obtained by our group using the same task in healthy young individuals (Fernández-Espejo et al., 2008).

### 4. Discussion

In the present study we observed a double dissociation in the relationship between CR and fMRI activity across clinical groups and task-induced activations and deactivations. Among healthy elders, highest CR was associated with reduced activity in brain areas processing speech comprehension, whereas increased activity was observed in regions of the DMN. The opposite effect was observed in both groups of patients, whose brain activity patterns were increased in areas directly processing language, showing more marked deactivations in the DMN for higher CR cases. These findings reveal that cognitive or brain reserve is associated with early functional brain reorganization in patients even when considering a clinically-affected cognitive domain.

When investigating how CR variables are differentially related to cerebral activity during task-induced activations across clinical groups we observed negative correlations for the healthy elder sample, as compared to patients. The most
direct interpretation of this finding is that healthy elders with higher CR exhibit increased neural efficiency (Stern, 2007), since diminished recruitment of linguistic areas was required in these cases. These results fit well with our recent observations in independent samples and with more complex cognitive tasks (Solé-Padullés et al., 2009; Bartre’s-Faz et al., 2009), and they evidence that neurofunctional implementation of CR is already at work in low-demanding cognitive processes.

In the case of a-MCI and mild AD patients, several cortical regions (and the cerebellum in a-MCI patients) reflected a positive covariance with CR when compared to healthy elders. As stated above, the CR hypothesis predicts that for a given level of neuropathology among AD cases, those patients with higher CR will present mild clinical manifestations; or alternatively, considering patients with a similar degree of clinical impairment, those with greater CR should present a more advanced stage of the disease (Snowdon, 2003). In this regard, it should be noted that, in clinical terms, our AD and a-MCI patients constituted homogeneous groups. With these conceptions in mind it may be speculated that our high CR elders exhibited less sufficient to disrupt the DMN in healthy subjects. Based on this, the fact that our high CR elders exhibited less regions identified here with aspects related to language or speech comprehension, including the right middle frontal gyrus (Mashal et al., 2008), the anterior cingulate cortex (Tyler et al., 2005) and the right cerebellum (Uchiyama et al., 2008). However, it should be noted that in subsequent analyses correlating fMRI signal with language comprehension, only increased activity in the left inferior frontal (BA 44)/precentral gyrus (BA 6) (a region that emerged in the whole group pattern of brain activity for the ‘forward vs backward narratives’ contrast) in the a-MCI group had a significant behavioral impact. These data further reinforce the idea that non-demented, memory-impaired patients can use compensation mechanisms linked to CR in a more effective way than can AD cases when considering task-induced activity areas.

In the present report we provide the first evidence that CR status differentially modulates the magnitude of deactivation in the DMN in healthy elders and patients suffering from MCI and AD. For all groups the relationships between CR and brain activity were the opposite for areas of the DMN as compared to those obtained in the main linguistic regions. It is interesting to note that previous findings evidenced inverse relationships between activity in regions of the default network and brain areas routinely exhibiting task-induced activations during cognitive demands (McKiernan et al., 2003; Fox et al., 2005; Celone et al., 2006; Persson et al., 2007). Our results for both healthy elders and patients complement previous observations and suggest that the interaction between this dichotomy is modulated by CR variables.

When compared to patients, healthy elders exhibited reduced deactivations in areas of the DMN. Greicius et al. (2003, 2004) demonstrated that in a complex cognitive process such as working memory, the reallocation of neural resources from default-mode brain regions to lateral prefrontal areas could be clearly evidenced. In contrast, a passive sensory task was insufficient to disrupt the DMN in healthy subjects. Based on these findings, the fact that our high CR elders exhibited less

<p>| Table 2 – Brain regions showing differences in the direction of the slopes for the correlations between CR variables and fMRI BOLD signal across clinical groups. |
|-----------------------------------------------|-------------------------------|---------------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Main contrast</th>
<th>t-Value</th>
<th>MNI coordinates</th>
<th>Region (BA)</th>
<th>Number of voxels</th>
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<tbody>
<tr>
<td>Activation</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>a-MCI more positive than CTR</td>
<td>5.10</td>
<td>[24, –60, 60]</td>
<td>R middle/superior frontal gyrus (BA 6)</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>4.83</td>
<td>[24, –60, 21]</td>
<td>R cerebellum</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>4.21</td>
<td>[–30, –9, 33]</td>
<td>L inferior frontal gyrus gyrus precentralis (BA 44/46)</td>
<td>48</td>
</tr>
<tr>
<td>AD more positive than CTR</td>
<td>5.43</td>
<td>[–42, 12, 12]</td>
<td>L inferior frontal gyrus (BA 46)</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>4.65</td>
<td>[–6, 33, –6]</td>
<td>L anterior cingulate (BA 24)</td>
<td>58</td>
</tr>
<tr>
<td>AD more positive than a-MCI</td>
<td>4.49</td>
<td>[–45, 45, 12]</td>
<td>L inferior frontal gyrus (BA 46)</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>4.38</td>
<td>[–27, 36, 6]</td>
<td>L insula</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>3.75</td>
<td>[–6, 33, –3]</td>
<td>L anterior cingulate (BA 32)</td>
<td>64</td>
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<tr>
<td>Deactivation</td>
<td></td>
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<tr>
<td>a-MCI more negative than CTR</td>
<td>5.79</td>
<td>[12, 12, 51]</td>
<td>R anterior cingulate (BA 24/32)</td>
<td>210</td>
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<tr>
<td></td>
<td>4.75</td>
<td>[60, –33, 24]</td>
<td>R supramarginal (BA 40)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>4.25</td>
<td>[0, –45, 39]</td>
<td>L posterior cingulate/precentral (BA 31)</td>
<td>37</td>
</tr>
<tr>
<td>AD more negative than CTR</td>
<td>6.31</td>
<td>[–12, –39, 33]</td>
<td>L posterior cingulate/precentral (BA 31)</td>
<td>71</td>
</tr>
</tbody>
</table>

All results displayed are adjusted for age, gender, MMSE and regional gray matter volumes. t-Value: statistical value for the most significant voxel within each cluster; R = right; L = left. For interpretation of clusters, MNI coordinates were corrected to Talairach using the WFU Pickatlas software (version 2.3). a-MCI: amnestic mild cognitive impairment.
suspension of the DMN may reflect that for this group with more efficient functional resources, our linguistic task was processed as being more automatic or effortless. In summary, the present findings demonstrate that for healthy elders, the increased neural efficiency associated with CR, as revealed by fMRI, seems to include both reduced recruitment of task-induced activation areas and reduced suppression of the DMN.

As discussed above, two lines of evidence suggest that: 1) diverting activity from processes occurring at rest is especially evident during highly cognitively-demanding conditions (McKiernan et al., 2003); and 2) according to the CR hypothesis, greater brain pathology for high CR patients should be expected given a similar degree of clinical manifestations (Snowdon, 2003). Based on these premises, it may be hypothesized that greater reallocation of processing resources from the DMN to brain areas directly processing the linguistic task in our patients could be reflecting increased demands of functional compensatory mechanisms in the context of a more advanced stage of neuropathology. However, it should be noted that in the present study we failed to confirm this assumption when considering reduced GM volumes as a measure of brain damage, thus suggesting that other morphological correlates should be considered in further studies to account for this interpretation (see discussion below).

Although our findings suggest that functional brain reorganizations related to CR can be observed in mild stages of cognitive decline, it is possible that these differences are pre-existing. Using functional neuroimaging techniques both Stern et al. (2005) and Springer et al. (2005) reported alternative usage of neural networks as a function of CR – and in the face of increasing cognitive demands – in healthy elders as compared to young subjects. These results were interpreted as providing evidence of neural compensation for the inability to recruit the healthy (young) brain’s response to increased task difficulty. More recently, Waiter et al. (2008) used a task of information processing speed called inspection time to compare the BOLD activation and connectivity in elders with successful and unsuccessful cognitive aging on the basis of non-verbal reasoning ability evaluations. The authors observed that successful elders showed similar regions of brain activation, deactivation and connectivity to those of young subjects (previously studied by the group). In contrast, the elders exhibiting cognitive decline deviated clearly from these patterns. These findings are of relevance because they
indicate that using a simple psychophysical task it is possible to evidence functional reorganizations within the aged population without clinically-relevant cognitive impairment. The present results indicate that these reorganizations are associated with our CR evaluation and can also be evidenced when considering clinical populations and unaffected cognitive domains. However, it should be noted that the study by Waiter et al. (2008) is methodologically unique since they employed a longitudinal design, where the two groups of elders were defined as ‘sustainers’ (successful aging) or ‘decliners’ (unsuccessful) in comparison with their own IQ scores at age 11. In contrast, our report is a cross-sectional study that cannot provide definitive evidence as regards when brain reorganization took place in our patients. Furthermore, our patients were recruited from an AD unit and, therefore, while they are representative of amnesic and AD patients referred to a memory clinic, they may not represent primary care patients as a whole. These aspects are acknowledged as limitations of the present study.

Previous findings in healthy subjects (Daselaar et al., 2004; Rombouts et al., 2005; Persson et al., 2007; Andrews-Hanna et al., 2007), as well as in MCI and AD patients (Celone et al., 2006), have evidenced that greater deactivations in areas of the DMN were related to increased cognitive performance. In this context, a further limitation of the present report is that we did not collect behavioral measures inside the scanner, thus precluding the direct investigation of relationships between fMRI signal and performance on the particular cognitive task used. In a complementary manner, we observed positive correlations between the degree of deactivation in the right anterior cingulate region and improved comprehension ratings in the whole group of patients. Thus, while replication with direct analyses is required, increased capacity to suppress regions of the DMN, which can be more easily accommodated in high CR patients, may have a behavioral impact. This finding may explain part of the compensatory functional mechanisms that allow patients, including mild AD cases, to minimize cognitive manifestations.

It is worthy of mention that compared to controls, patients with higher CR indexes exhibited larger deactivations in the posteromedial region (precuneus and posterior cingulate gyrus). Previous metabolic studies and morphological MRI
data indicate that this brain area is among the first to be affected in the early stages of AD (Minoshima et al., 1997; Scahill et al., 2002). Furthermore, lower regional glucose metabolism and anatomical abnormalities within this region increase the risk of conversion to dementia among a-MCI patients (Chételat et al., 2003; Anchisi et al., 2005; Bozzali et al., 2006). In the same vein, it was reported that reduced capacity to deactivate the posteromedial region during cognitive processing was characteristic of a-MCI patients who developed dementia at follow-up (Petrella et al., 2007b). Our study evidences that deactivation of this critical area is facilitated by higher CR loads in both MCI and early AD. While the interpretation of this observation as regards the clinical progression of patients is beyond the scope of the present cross-sectional study, its relevance should probably be investigated in further longitudinal reports.

The present study found no evidence that gray matter atrophy, adjusted in a voxel-based manner, mediates the relationship between CR and brain activations and deactivations. These findings are unexpected and counterintuitive as regards the CR hypothesis, which predicts that functional compensations in AD are a result of increased brain damage. In our previous study (Solé-Padullés et al., 2009) we observed that AD patients with higher CR exhibited increased brain activity during an episodic memory task, together with more advanced whole brain atrophy rates. However, when we used a multiple regression analysis it was evidenced that fMRI changes are more closely related to CR proxies than to brain atrophy, thus providing further support for the active models of CR (Stern, 2002). The present findings, obtained using a more refined voxel-by-voxel coregistration between fMRI and GM values, reinforce the idea that functional reorganizations linked to CR are implemented beyond structural brain differences, even at the early stages of cognitive impairment and AD. It should be clearly noted, however, that one plausible explanation for the lack of evidence produced by our study is limited statistical power due to a small sample size. Alternatively, it is possible that the low-demand cognitive task employed here and/or the fact that it tapped into an unaffected cognitive domain precluded the identification of functional/structure associations. Furthermore, gray matter atrophy may not be the most sensitive structural brain correlate associated with the observed functional reorganizations. Recent findings using both resting-state fMRI (Andrews-Hanna et al., 2007) and task-induced activations (Greicius et al., 2009) demonstrated that disruptions of the DMN are associated with white matter integrity, as revealed by diffusion tensor imaging. Further, accounting measures of gray matter volume (Damoiseaux et al., 2008) or typical AD pathology such as Pittsburgh Compound B (PIB) – positron emission tomography (PET) (Andrews-Hanna et al., 2007) did not modify the differences between young and older subjects in resting-state networks. Taken together, previous and the present findings indicate that further studies are required to investigate the precise role of white matter track integrity as a more sensitive morphological correlate of CR and its relationships with functional changes in healthy elders and patients.

In conclusion, the main results of the present study can be summarized as follows. First, CR variables modulate inversely the activation and deactivation of neural networks, both in healthy elders and patients with a-MCI and mild AD. Among healthy elders, high CR is related to more efficient usage of brain networks involved in the cognitive process tested and to fewer deactivations of the DMN. These findings confirm previous studies reporting competitive activations or inverse correlations between task-induced activations and task-induced deactivation networks. In the case of patients, greater CR was related to increased BOLD signal in linguistic processing areas, with concomitantly more deactivations in the DMN. Despite being indirect, these associations between changes in brain activity related to CR and language comprehension performance could be reported among a-MCI cases, thus indicating probable increased reorganization of functional compensatory resources in patients with high CR. It should be noted, however, that we failed to show that this functional reorganization is related to increased brain atrophy (measured by GM volumes), as would be predicted by the CR hypothesis. Finally, the present fMRI findings were obtained when studying an unaffected cognitive domain in our patients. Thus, they indicate that CR effects, as modulators of functional brain reorganizations, can be observed early in the course of the cognitive dysfunction in AD and even in a-MCI.

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