Cognitive Reserve Proxies Relate to Gray Matter Loss in Cognitively Healthy Elderly with Abnormal Cerebrospinal Fluid Amyloid-β Levels

Eider M. Arenaza-Urquijo, José-Luis Molinuevo, Roser Sala-Llonch, Cristina Solé-Padullés, Mircea Balasa, Beatriz Bosch, Jaume Olives, Anna Antonell, Albert Lladó, Raquel Sánchez-Valle, Lorena Ramírez, and David Bartrés-Faz

Handling Associate Editor: Christine Bastin

Accepted 12 February 2013

Abstract. Cognitive reserve capacity may increase tolerance of neurodegenerative processes. However, its role regarding amyloid-β (Aβ42) deposition in cognitively normal subjects is not well understood. We aimed to investigate the association between areas showing Aβ42-related structural changes and cognitive reserve proxies in cognitively intact subjects showing normal or abnormal Aβ42 cerebrospinal fluid (CSF) concentrations. Thirty-three subjects (aged 55–85) underwent lumbar puncture and high resolution anatomical magnetic resonance imaging analyzed by voxel-based morphometry and cortical thickness procedures. Subjects with abnormal Aβ42 CSF levels showed significant left hippocampal atrophy and greater cortical thinning in parietal, temporal, and frontal regions (including the supramarginal and the anterior cingulate gyrus) compared to subjects with normal Aβ42 CSF levels. Using a multivariate general linear model, we investigated the relationship between these areas and cognitive reserve proxies. We found a significant relationship between decreased volume of the left hippocampus or decreased cortical thickness of the right supramarginal gyrus and higher cognitive reserve proxies only in the group with abnormal Aβ42 CSF levels. Thus, subjects with abnormal Aβ42 CSF levels (which may be at a higher risk of developing Alzheimer’s disease) and with high scores on cognitive reserve proxies may be tolerating a more advanced neurodegenerative process in critical cortical and subcortical regions. The present results emphasize the relevance of evaluating cognitive reserve proxies, as well as the importance of using neuroimaging techniques for early diagnosis in individuals with higher reserve.

Keywords: Aging, amyloid, cognitive reserve, hippocampus, structural MRI

INTRODUCTION

Recent research in cognitively healthy elderly individuals suggests that the pathophysiological process of Alzheimer’s disease (AD) begins decades before the manifestation of clinical symptoms, that is, decades before the diagnosis of clinical dementia. The most commonly accepted model of AD proposes amyloid-β (Aβ42) peptide accumulation as a key early event in the pathophysiological process of AD [1–3]. This means that older individuals may harbor pathological Aβ42 deposition without presenting any clinical symptoms. These asymptomatic individuals may in part represent...
the preclinical phase of AD. Interestingly, thanks to previous autopsy [4–8] and ‘in vivo’ Aβ42 imaging and cerebrospinal fluid (CSF) studies [9–14], we know that around one-third of these individuals with pathological Aβ42 deposition may not become symptomatic before death. Differences in the lag phase between Aβ42 deposition and the appearance of symptoms may be partially caused by interindividual differences in brain reserve [15] and/or cognitive reserve [16]. Brain reserve refers to interindividual differences in the neural substrate: for example, greater synaptic density or a larger number of neurons to support normal function despite pathological processes. Cognitive reserve is the capacity of the adult brain to cope with more advanced pathology by taking advantage of functional resources (for example, the capacity to use alternative networks or cognitive strategies to cope with the effects of the pathology). Common indexes reflecting brain reserve include increased intracranial or brain volumes while, as operationalized in the present article, high scores on proxy variables such as education, occupational status, and lifetime exposure to cognitively stimulating activities reflect cognitive reserve [17].

Recent Pittsburgh Compound B (PiB) and autopsy studies in healthy elderly suggested greater brain reserve in terms of larger temporal and hippocampal areas in cognitively spared individuals with high Aβ42 deposition [18, 19]. Furthermore, several amyloid imaging and CSF studies suggested that cognitive reserve may have a modulating role at different levels: i) influencing the relationship between Aβ42 accumulation and cognition [20–22]; ii) acting directly upon Aβ42 accumulation, that is, slowing Aβ42 deposition [23]; or iii) permitting longer tolerance of Aβ42-related neural death or whole brain atrophy [9]. This last point is of special interest since previous cognitive reserve studies in AD showed that higher cognitive reserve proxies allow individuals to cope with greater AD-related cortical thinning [24].

Inverse associations between cognitive reserve proxies and measures of brain integrity observed in AD, we hypothesized that the associations would be reversed in the two groups. In agreement with the robust inverse associations between cognitive reserve proxies and measures of brain integrity observed in AD, we hypothesized that the associations would be reversed in the two groups (i.e., positive in the group with normal Aβ42 CSF levels, negative in the group with abnormal Aβ42 CSF levels).

**MATERIALS AND METHODS**

**Participants**

Thirty-three volunteers were recruited from the Alzheimer’s disease and other Cognitive Disorders Unit, Neurology Service, at Hospital Clinic, Barcelona, Spain. The study was approved by the local ethics committee and all subjects gave informed written consent. None of the participants selected had a medical history of acute neurologic deficit compatible with transient ischemic attack or stroke, or radiologic evidence of stroke. Subjects did not meet criteria for dementia or mild cognitive impairment (MCI), and their cognitive performance was not less than −1.5 SD on any test included in the neuropsychological examination [32]. Mini-Mental State Examination (MMSE) scores were between 24 and 30. On the Global Deterioration Scale (GDS) rating [33], all subjects presented normal functional capacity (GDS ratings 1 or 2).

CSF analyses and group classification

Ten milliliters of CSF were obtained during the morning (9:00 to 12:00 a.m.) and samples were centrifuged and stored in polypropylene tubes at 80°C. The Aβ42 at threonine 181 in CSF was measured by enzyme-linked immunosorbent assay (Innogenetics, Ghent, Belgium). Patients were not fasted. As patients
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Normal Aβ42 CSF levels mean (SD)</th>
<th>Abnormal Aβ42 CSF levels mean (SD)</th>
<th>T-test/Chi square (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>16</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Male: Female</td>
<td>6:10</td>
<td>8:9</td>
<td>0.30 (0.57)</td>
</tr>
<tr>
<td>Age</td>
<td>68.06 (5.66)</td>
<td>72.41 (7.83)</td>
<td>−1.81 (0.07)</td>
</tr>
<tr>
<td>Cognitive reserve proxy</td>
<td>13.60 (5.08)</td>
<td>12.38 (4.81)</td>
<td>0.84 (0.40)</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.31 (4.95)</td>
<td>9.52 (4.72)</td>
<td>0.46 (0.64)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.31 (4.14)</td>
<td>28.05 (4.14)</td>
<td>0.55 (0.58)</td>
</tr>
<tr>
<td>APOE ε4 carriers (%)</td>
<td>3 (18.8 %)</td>
<td>6 (35.3 %)</td>
<td>1.13 (0.28)</td>
</tr>
<tr>
<td>CSF Aβ42 (pg/ml)</td>
<td>688.72 (129.93)</td>
<td>372.80 (101.60)</td>
<td>7.80 (0.001)</td>
</tr>
<tr>
<td>CSF p-tau (pg/ml)</td>
<td>57.81 (21.19)</td>
<td>73.01 (45.83)</td>
<td>13.21 (0.23)</td>
</tr>
</tbody>
</table>

were participants in a quality control program, determinations in our laboratory of Aβ42 at threonine 181 values were within mean 2 SD. A cutoff of 500 pg/mL [34] was used to dichotomize the sample into 16 subjects with abnormal Aβ42 CSF levels (<500 pg/mL) and 17 with normal Aβ42 CSF levels (>500 pg/mL) (see Table 1). The percentage of subjects showing abnormal Aβ42 CSF levels was higher than might be expected in the population [8, 11].

Individual cognitive reserve estimations

All but two subjects included in the study underwent cognitive reserve proxy assessment. Proxies of cognitive reserve were estimated using a customized questionnaire [35] focusing on years of education and lifespan cognitive activities. Information regarding years of education was quantified and ranged from “no formal education” to “university education”. In detail, they were coded as 0 = no formal education, 1 = self-taught reader and writer, 2 = primary school, 3 = secondary school, and 4 = higher or university education. Occupational information was coded as follows: 0 = unskilled, 1 = skilled manual, 2 = skilled non-manual or technician, 3 = professional (university degree), and 4 = manager or director (university degree). We also recorded information about musical studies, languages, and lifetime involvement in leisure activities such as reading and playing intellectual games and their frequency. The questionnaire has a maximum score of 25, with 25 representing the highest cognitive reserve.

Neuropsychological and functional assessment

Participants were administered a one-hour neuropsychological battery test by a trained neuropsychologist. The battery included memory, language, praxis, visual perception, and frontal functions assessment. All neuropsychological scores were adjusted for age and educational level. Normative neuropsychological data and the neuropsychological battery have been described in detail elsewhere [32].

MRI acquisition and processing

High resolution 3D structural dataset (T1-weighted MP-RAGE, TR = 2300 ms, TE = 2.98 ms, 240 slices, FOV = 256 mm, matrix size = 256 × 256; Slice thickness = 1 mm) were acquired on a 3T MRI scanner (Magnetom Trio, Tim, Siemens Medical Systems, Germany) for the 33 subjects.

Cortical reconstruction of the structural images was performed with the FreeSurfer image analysis suite, version 4.3.1. (http://surfer.nmr.mgh.harvard.edu/). The procedures carried out with FreeSurfer software include removal of non-brain data, intensity normalization [36], tessellation of the gray matter/white matter boundary, automated topology correction [37, 38], and accurate surface deformation to identify tissue border [39, 40]. Reconstructed and registered individual cortical thickness maps were smoothed using a Gaussian Kernel of 15 mm Full-Width Half Maximum (FWHM). Structural MRI data were also processed with FSL-VBM, a voxel-based morphometry style analysis included in FSL suite [41] (http://www.fmrib.ox.ac.uk/fsl). First, brain extraction on all T1 images was carried out [42]. All brain-extracted images were segmented into gray matter, white matter, and CSF [43]. Gray matter images were then registered to the gray matter ICBM-152 template. The registered gray matter images were concatenated into a 4D image and averaged to create the study-specific gray matter template based on a non-linear registration. All the gray matter images were non-linearly registered to the study-specific template and concatenated into a 4D image introducing a compensation or modulation for the non-linear component of the transformation (Jacobian of the warp field). Finally
Neuropsychological performance of the two groups included in the study. Between group statistical differences are reported. FCSRT: Free and cued selective reminding test; ROCF: Rey-Osterrieth Complex Figure; CERAD battery: Consortium to Establish a Registry of Alzheimer’s Disease; VOSP: Visual Object and Space Perception battery; WAIS: Wechsler Adult Intelligence Scale; TMT: Trail Making Test.

<table>
<thead>
<tr>
<th></th>
<th>Normal Ap42 CSF levels mean (SD)</th>
<th>Abnormal Ap42 CSF levels mean (SD)</th>
<th>T-test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCSRT: Learning</td>
<td>25.38 (9.23)</td>
<td>22.06 (7.53)</td>
<td>1.86 (0.07)</td>
</tr>
<tr>
<td>FCSRT: Total learning</td>
<td>41.00 (7.27)</td>
<td>39.94 (6.67)</td>
<td>0.43 (0.67)</td>
</tr>
<tr>
<td>FCSRT: Recall</td>
<td>10.00 (1.51)</td>
<td>8.19 (3.56)</td>
<td>1.87 (0.07)</td>
</tr>
<tr>
<td>FCSRT: Total recall</td>
<td>14.25 (2.23)</td>
<td>13.63 (2.50)</td>
<td>0.89 (0.38)</td>
</tr>
<tr>
<td>ROCF: Immediate recall</td>
<td>17.87 (4.12)</td>
<td>14.97 (9.97)</td>
<td>1.56 (0.13)</td>
</tr>
<tr>
<td>ROCF: Delayed recall</td>
<td>18.25 (4.05)</td>
<td>14.88 (6.45)</td>
<td>1.73 (0.09)</td>
</tr>
<tr>
<td>Boston naming test</td>
<td>54.62 (4.54)</td>
<td>53.50 (4.54)</td>
<td>0.55 (0.59)</td>
</tr>
<tr>
<td>Semantic memory (Animals)</td>
<td>18.06 (4.84)</td>
<td>18.18 (4.38)</td>
<td>0.07 (0.94)</td>
</tr>
<tr>
<td>Phonologic memory (F AS)</td>
<td>32.13 (15.33)</td>
<td>29.06 (14.44)</td>
<td>0.65 (0.52)</td>
</tr>
<tr>
<td>CERAD: Praxia</td>
<td>10.25 (1.34)</td>
<td>10.41 (0.87)</td>
<td>0.41 (0.68)</td>
</tr>
<tr>
<td>VOSP: Number location</td>
<td>9.06 (1.12)</td>
<td>8.69 (1.74)</td>
<td>0.72 (0.48)</td>
</tr>
<tr>
<td>VOSP: Incomplete letters</td>
<td>19.44 (9.63)</td>
<td>19.19 (1.76)</td>
<td>0.49 (0.62)</td>
</tr>
<tr>
<td>Digit (WAIS III): Direct</td>
<td>8.08 (1.66)</td>
<td>8.21 (1.97)</td>
<td>0.19 (0.85)</td>
</tr>
<tr>
<td>Digit (WAIS III): Reverse</td>
<td>5.08 (1.55)</td>
<td>5.21 (1.63)</td>
<td>0.22 (0.82)</td>
</tr>
<tr>
<td>Digit (WAIS III): Total</td>
<td>13 (2.97)</td>
<td>13.13 (2.72)</td>
<td>0.12 (0.90)</td>
</tr>
<tr>
<td>TMT A</td>
<td>56.67 (17.21)</td>
<td>50.82 (7.05)</td>
<td>0.39 (0.69)</td>
</tr>
<tr>
<td>TMT B</td>
<td>160.25 (82.01)</td>
<td>154.35 (76.54)</td>
<td>0.21 (0.83)</td>
</tr>
</tbody>
</table>

RESULTS

Demographical and neuropsychological assessment

The two groups did not differ in any of the demographical variables studied (see Table 1 for details) or cognitive function (see Table 2). However, the between-group comparison showed a trend toward significance (p = 0.07) for learning and delayed recall memory performances.
Differences in cortical thickness and gray matter volumes (Elderly with Abnormal < Normal $A_{42}$ CSF Levels)

Statistically significant cortical thickness reductions were observed in subjects with abnormal $A_{42}$ CSF levels than in those with normal $A_{42}$ CSF levels at $p<0.05$ FWE corrected. The anatomical pattern included superior and middle temporal areas, frontal areas (lateral orbitofrontal, parsopercularis, parstriangularis, rostral middle frontal, caudal middle frontal, superior frontal, and caudal cingulate) in the left hemisphere, and parietal regions including the supramarginal gyrus in the right hemisphere (see Fig. 1A, Table 3). Moreover, the voxel-based statistical analyses for the group comparison revealed gray matter differences in the left hippocampus. Elderly with abnormal $A_{42}$ CSF levels showed lower hippocampal volume than those with normal $A_{42}$ CSF levels (see Fig. 1B, Table 3). When a less strict correction was used for the VBM analysis (uncorrected $p<0.001$), the pattern of atrophy was extended to temporal and frontal areas (data not shown). No results were found when the opposite contrast (subjects with abnormal $>$ subjects with normal $A_{42}$ CSF levels) was tested.

Relationships between cognitive reserve proxies, volume, and cortical thickness

We observed a statistically significant group-by-cognitive reserve proxy interaction in the left hippocampal volume ($F = 6.19; p = 0.02$) and the right supramarginal gyrus ($F = 7.17; p = 0.01$) (Fig. 2). Correlation coefficients showed a significant negative association between left hippocampal volume and cognitive reserve proxies (see Fig. 2, in red, $r = -0.554$; $p = 0.03$) and between the cortical thickness of the right supramarginal gyrus and cognitive reserve proxies (see Fig. 2, in red, $r = 0.516$; $p = 0.04$) in elderly with abnormal $A_{42}$ CSF levels. This association was not significant (hippocampal volume: $r = 0.17$, $p = 0.52$; supramarginal cortical thickness: $r = 0.38$, $p = 0.16$), in elderly with normal $A_{42}$ CSF levels.

DISCUSSION

In the present study, we aimed to investigate the differences in the relationship between areas showing $A_{42}$-related structural changes and cognitive reserve proxies in healthy elderly subjects showing biomarker positivity for CSF $A_{42}$ levels (at higher risk of developing AD) compared to elderly with normal $A_{42}$ levels. We first identified regions showing differences in regional cortical thinning and gray matter atrophy between groups. Elderly with abnormal $A_{42}$ CSF levels showed greater cortical thinning in temporal, parietal, and frontal regions and greater left hippocampal atrophy than elderly with normal $A_{42}$ CSF levels. Higher cognitive reserve proxies were related to greater hippocampal atrophy and cortical thinning of the supramarginal gyrus only among subjects with abnormal $A_{42}$ CSF levels, suggesting that among these individuals those with higher cognitive reserve proxies are tolerating greater $A_{42}$-related atrophy and cortical thinning.

Our results showing greater cortical thinning and regional atrophy in elderly with abnormal $A_{42}$ CSF levels corroborate previous studies demonstrating structural changes in these individuals. The pattern of thinning that we found (i.e., superior temporal, supramarginal gyrus, anterior cingulate, and inferior frontal) shows differences as well as similarities with regard to previous studies investigating gray matter atrophy related to $A_{42}$ deposition as measured by PET imaging or CSF levels. Dickerson et al. [27] demonstrated a signature of AD in cortical anatomy by comparing healthy elderly individuals to mild AD subjects. This cortical signature of mild AD included the temporal and parietal cortex (including angular and supramarginal gyrus and precuneus) and the inferior frontal gyrus. In the same study, these areas were defined as regions of interest (ROI) and investigated in a small sample of cognitively healthy elderly with high brain amyloid binding (as detected by PiB-PET imaging). Only the temporal pole and, as we reported in the present study, the inferior frontal cortex showed significant cortical thinning compared to subjects with low brain amyloid binding. However, Dickerson et al. [27] found a pattern of subtle thinning in all the regions, including areas described in the present study such as the supramarginal gyrus. Anterior cingulate and superior temporal lobe were not regions described in Dickerson et al.’s proposed AD signature; however, cortical thinning of these areas has been reported in previous studies comparing cognitively normal individuals with high and low $A_{42}$ deposition [46–48]. The discrepancies in the $A_{42}$-related cortical thinning in cognitively healthy elderly described in the different studies are most likely the result of methodological differences. Unlike in the present study, ROI-based approaches [27, 46, 48] are mainly used, although a combination of ROI-based and whole brain approaches has also been applied [47] to study elderly with abnormal $A_{42}$ CSF levels. Measures of amyloid...
Fig. 1. Results of cortical thickness (A) and voxel-based morphometry analyses (B) showing differences between healthy elderly subjects with normal versus abnormal Aβ42 CSF levels (abnormal < normal Aβ42 CSF levels). All results are FWE-corrected.

Table 3

Cortical thickness and voxel-based morphometry (VBM) results for between-group comparison. Reported clusters are corrected for multiple comparisons (FWE). The coordinates x, y and z refer to the anatomical location, indicating T1-talairach standard stereotactic space. L: left, R: right

<table>
<thead>
<tr>
<th>Cortical area/ Brain region</th>
<th>Cluster size (mm2)</th>
<th>Coordinates x, y, z</th>
<th>Normal Aβ42 CSF levels mean (SD)</th>
<th>Abnormal Aβ42 CSF levels mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical thickness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Superior temporal</td>
<td>2580.30</td>
<td>−51.9 −15.6 −6.7</td>
<td>2.72 (0.12)</td>
<td>2.50 (0.10)</td>
<td>0.009</td>
</tr>
<tr>
<td>L Frontal parietal</td>
<td>4480.98</td>
<td>−47.4 25.2 10.1</td>
<td>2.60 (0.16)</td>
<td>2.41 (0.10)</td>
<td>0.008</td>
</tr>
<tr>
<td>L Caudal cingulate</td>
<td>2661.77</td>
<td>−1 18.3 17.7</td>
<td>2.84 (0.19)</td>
<td>2.65 (0.16)</td>
<td>0.008</td>
</tr>
<tr>
<td>R Supramarginal</td>
<td>2943.54</td>
<td>−43.5 −32.7 24.7</td>
<td>2.56 (0.11)</td>
<td>2.34 (0.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>VBM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Hippocampus</td>
<td>73</td>
<td>−22 −14 −18</td>
<td>0.63 (0.04)</td>
<td>0.53 (0.05)</td>
<td>0.035</td>
</tr>
</tbody>
</table>
Fig. 2. Scatter plots showing interactions between cognitive reserve proxies and Aβ42-related areas of cortical thinning or atrophy in elderly with normal versus abnormal Aβ42 CSF levels. In red, statistically significant correlation coefficients (see Results for statistical details). Cth: cortical thickness; CR: cognitive reserve; R: right; L: left.

deposition (PiB-PET imaging or CSF levels), differences in the criteria used to dichotomize the sample, and the differential treatment of potential nuisance variables vary across studies and may lead to differences. For example, in the present study we were specifically interested in the relationships between Aβ42 and cognitive reserve proxies (see Introduction), and so we introduced APOE status and p-tau levels as covariates in order to isolate Aβ42-related brain changes. Finally, the mean age of our subjects with abnormal Aβ42 levels was lower than in the rest of the studies. This may partially explain why we did not find differences in the areas that have been described as having an important role in the preclinical phase of AD [49] and showing Aβ42-related cortical thinning in cognitively healthy elderly [46, 48] such as the posterior cingulate or precuneus. Along these lines, a previous study [46] found that
these regions showed age-related cortical thickness reductions. When the between-group comparison was carried out without controlling for age, gender, p-tau levels, and APOE status, precuneus and parahippocampal regions also showed Aβ42-related cortical thinning (data not shown). Overall, our cortical thickness results lend support to earlier PiB and CSF studies suggesting that Aβ42 deposition in normal elderly may represent the preclinical or asymptomatic AD phase.

When VBM analyses were carried out in a whole brain manner, we found a significant difference in the subjects with abnormal Aβ42 CSF levels compared to those with normal Aβ42 CSF levels circumscribed to the left hippocampus. The finding of Aβ42-related hippocampal atrophy in this study is in agreement with previous studies in cognitively healthy elderly harboring high Aβ42 deposition [10, 48, 50], although conflicting results have also been reported [51]. Mormino et al. [50] studied the relationship between hippocampal volume, episodic memory, and Aβ42 deposition (as measured by PiB imaging) in three independent samples of cognitively healthy elderly. They found that higher Aβ42 deposition was associated with smaller hippocampal volume across the three samples. Storand et al. [48] observed smaller hippocampal volumes in 29 participants with high Aβ42 deposition (measured by PiB-PET imaging). Finally comparing high and low PiB retention in cognitively normal subjects, Jack et al. [10] found that the hippocampus on average was more atrophic (though not significantly so) in the high PiB subgroup. With regard to the asymmetry shown in the present study (only the left hippocampus was more atrophic (though not significantly so) in the high PiB subgroup). With regard to the asymmetry shown in the present study (only the left hippocampus showed Aβ42-related atrophy), previous investigations have consistently reported an asymmetry (left less than right) between the left and the right hippocampal volumes in healthy subjects, MCI, and AD [52]; the left hippocampus thus showed greater atrophy.

The differences in the results using VBM versus cortical thickness methods may appear surprising. However, previous studies also presented discrepancies [53, 54] due, perhaps, to differences in the sensitivity of the two measures. Cortical thickness is thought to be a more sensitive measure, because gray matter volume (measured by VBM) is dependent on the local cortical surface (and hence cortical folding) as well as on the local cortical thickness [55]. Based on previous evidence of neurodegenerative and psychiatric diseases using the same combination of methods [56, 57], we concluded that the combination of the two methods may provide complementary information. It is important to note that when a less strict statistical threshold was used for the VBM analyses (uncorrected p<0.001, data not shown) more extended regions of the temporal lobe and the frontal lobe showed greater atrophy in subjects with abnormal Aβ42 CSF levels.

The main finding of our study was that there was a group-by-cognitive reserve proxy interactional effect on the left hippocampus and right supramarginal gyrus. Follow-up analyses showed that cognitive reserve proxies were significantly and negatively associated with hippocampal volumes and supramarginal cortical thinning in subjects with abnormal Aβ42 CSF levels but not in those with normal Aβ42 CSF levels. As groups did not differ on cognitive tests, the most straightforward interpretation within the theoretical framework of the reserve hypothesis is that elderly subjects with abnormal Aβ42 CSF levels and with higher cognitive reserve proxies exhibit more advanced gray matter atrophy while remaining cognitively normal. Although there were no significant between-group differences in task performance, memory performance showed a trend toward significance (p = 0.07). Some studies [13, 18, 50], but not all [10], found Aβ42 deposition to be related to episodic memory performance. We therefore repeated the GLM (see Methods), controlling for memory performance. The interactional effect (group-by-cognitive reserve proxy) remained significant (data not shown). This suggests that the interactional effect is independent of interindividual differences in memory performance. Therefore, in accordance with the cognitive reserve theory, and taking Aβ42 CSF levels as a surrogate for pathology, our results suggest that at a comparable level of cognitive performance, the underlying neuropathological process is more advanced in patients with higher cognitive reserve proxies [51].

Inverse relationships between cognitive reserve proxies and brain measures have been consistently found in AD studies [25]. This is corroborated by the results of the present study if we consider that our subjects with abnormal Aβ42 CSF levels may in part represent the preclinical phase of AD. Nevertheless, previous studies in healthy elderly found that mental activity across the lifespan correlated with a reduced rate of hippocampal atrophy [58] or that healthy elderly subjects with higher education presented reduced mean diffusivity (indicating higher integrity) in the bilateral hippocampus [59]. Following these investigations, we might have expected to find a positive correlation reflecting more preserved hippocampal structure as a function of cognitive reserve in elderly with normal Aβ42 CSF levels. However, we did not record this observation, possibly due to a lack of statistical...
with abnormal Aβ42. Furthermore, we found greater cortical MCI to AD has been stressed by several investigations of hippocampal volume to the conversion from predictors of conversion. On the other hand, the relevance of hippocampal volume to the conversion from non-converters; both education and CSF levels were years of education (a proxy of cognitive reserve) than those converting to dementia had significantly fewer patients either converting to dementia or remaining healthy subjects without memory complaints but only in subjects with memory complaints, thus the inclusion of subjects with memory complaints may have influenced our results. This issue needs to be studied in future investigations.

In summary, we provide evidence that in elderly people with abnormal Aβ42 CSF levels, those with greater cognitive reserve proxies can tolerate more atrophy while remaining cognitively normal. Based on our findings, we hypothesize that elderly with abnormal Aβ42 CSF levels with higher cognitive reserve proxies are expressing higher neural compensation (i.e., tolerating greater hippocampal atrophy) than elderly with abnormal Aβ42 CSF levels with lower cognitive reserve proxies. These observations imply that cognitive reserve is significant even in cognitively preserved elderly adults that may represent in part the preclinical phase of AD, that is, prior to clinical symptoms. At the clinical level, these results emphasize the relevance of evaluating cognitive reserve proxies in combination with neuroimaging techniques for early diagnosis. Finally, we demonstrate that Aβ42 status could have been a confounding factor in earlier studies combining cognitive reserve with neuroimaging measures in samples of healthy elderly defined using clinical and neuropsychological information.
ACKNOWLEDGMENTS

Elder M. Arenaza-Urquijo is supported by a Catalán Government predoctoral research fellowship. Dr. Bartrés-Faz is supported by a Spanish Ministerio de Ciencia e Innovación (SAF2009-07489) and by the Ministerio de Sanidad, Política Social e Igualdad (IMSERSO 2009-0371) research grants. Dr. Molinuevo has provided scientific advice and has been an investigator or data monitoring board member receiving consultancy fees from Pfizer-Eisai, Janssen-Cilag, Novartis, Lundbeck, Roche, Bayer, Bristol-Myers Squibb, GE Health Care, GlaxoSmithKline, Merz, MSD and Innogenetics. Dr. Lorena Rami is supported by Servet grant as a senior investigator from the Spanish Ministry of Science (CP08/00147), FIS PI11/01071, Fondo europeo de desarrollo regional, una manera de hacer Europa, grant from IMSERSO 1979/2011.


REFERENCES


