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Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease

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Abstract

Cognitive reserve (CR) is the brain's capacity to cope with cerebral damage to minimize clinical manifestations. The 'passive model' considers head or brain measures as anatomical substrates of CR, whereas the 'active model' emphasizes the use of brain networks effectively. Sixteen healthy subjects, 12 amnestic mild cognitive impairment (MCI) and 16 cases with mild Alzheimer's disease (AD) were included to investigate the relationships between proxies of CR and cerebral measures considered in the 'passive' and 'active' models. CR proxies were inferred premorbid IQ (WAIS Vocabulary test), 'education–occupation', a questionnaire of intellectual and social activities and a composite CR measure. MRI-derived whole-brain volumes and brain activity by functional MRI during a visual encoding task were obtained. Among healthy elders, higher CR was related to larger brains and reduced activity during cognitive processing, suggesting more effective use of cerebral networks. In contrast, higher CR was associated with reduced brain volumes in MCI and AD and increased brain function in the latter, indicating more advanced neuropathology but that active compensatory mechanisms are still at work in higher CR patients. The right superior temporal gyrus (BA 22) and the left superior parietal lobe (BA 7) showed greatest significant differences in direction of slope with CR and activation between controls and AD cases. Finally, a regression analysis revealed that fMRI patterns were more closely related to CR proxies than brain volumes. Overall, inverse relationships for healthy and pathological aging groups emerged between brain structure and function and CR variables.

Keywords: Cognitive reserve; Brain reserve; Brain volumes; Functional magnetic resonance imaging (fMRI); Cognitive aging; Mild cognitive impairment; Alzheimer's disease; Recognition memory; Compensation

1. Introduction

Cognitive reserve (CR) refers to the hypothesized capacity of an adult brain to cope with brain pathology in order to minimize symptomatology (Stern, 2002). CR construct was proposed after having observed no direct relationships between brain damage severity and the clinical manifestation of symptoms. For instance, higher rates of Alzheimer's disease (AD) neuropathology at post mortem examinations were seen in individuals who were not clinically demented but possessed heavier brains and higher counts of large neurons (Katzman et al., 1988). More recent data is available indicating that a number of participants presenting with extensive AD-related neuropathology (Braak and Braak stage VI) and/or vascular damage were able to perform at

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a considerably high level in clinical and neuropsychological examinations, thus showing 'resistance to the clinical expression of neuropathology' (Snowdon, 2003).

Two hypotheses based on reserve mechanisms have been proposed to account for the abovementioned findings, one from a structural point of view and the other of a more functional fashion (Stern, 2002). At an anatomical level, the 'brain reserve capacity' (BRC) model ascertains that certain factors, such as the number of synapses and brain volume, confer a particular capacity to endure neuropathological processes. When considering dementia and pre-dementia conditions, BRC would be able to prolong the preclinical stage until a critical moment would be reached. From the moment of exceeding that threshold on, vulnerability to brain damage would be unavoidable and eventually, clinical and functional deficits would be evident (Satz, 1993). On the other hand, a more active or functional model of CR has been suggested by Stern (2002). According to this view, CR would be related to the ability to recruit brain networks in an effective way. Once pathological processes begin to occur, subjects would use alternative networks in order to perform a particular task successfully or to maintain one's clinical status within the normality, a process defined as compensation. The most frequently used proxies reflecting CR comprise educational/occupational attainment, premorbid intelligence quotient, leisure, cognitive and mental stimulating activities (Valenzuela and Sachdev, 2005).

Direct measures of brain (Katzman et al., 1988; Kidron et al., 1997; Coffey et al., 1999; Edland et al., 2002), head, or intracranial size (Schofield et al., 1995; Jenkins et al., 2000; Tisserand et al., 2001; Mortimer et al., 2003; Wolf et al., 2004) have been studied in the aging literature as surrogates of brain reserve. For instance, although negative findings have been reported (Edland et al., 2002; Jenkins et al., 2000), reduced intracranial volume or smaller head size by its own or in combination with low education may confer an increased risk for cognitive decline and dementia (Schofield et al., 1995, 1997; Mortimer et al., 2003) including mild cognitive impairment (MCI) in old age (Wolf et al., 2004). Further, inconclusive reports have been published regarding the relationship between these variables and proxies of CR such as education in normal aging (Coffey et al., 1999; Edland et al., 2002; Tisserand et al., 2001) with inverse relationships between education and brain volumes in the case of established AD (Kidron et al., 1997).

Similarly, at a functional level, investigations mainly using positron emission tomography (PET) have been undertaken in the research of CR in healthy elders and AD. At rest studies in the latter condition found that education and intellectual and social life activities were inversely correlated with regional brain metabolic activity and/or cerebral blood flow mainly in temporal, parieto-temporal and parieto-occipital regions (Scarmeas et al., 2003a; Perneczky et al., 2006) also extending to other cortical and subcortical areas in other reports (Alexander et al., 1997). Further, reports of activation studies during cognitive tasks among demented and non-demented individuals found specific brain networks which were differentially activated depending on CR background (Scarmeas et al., 2003b, 2004; Stern et al., 2005).

Despite its lower invasiveness, higher spatial and temporal resolution and the knowledge that increases and decreases of BOLD signal from functional magnetic resonance imaging (fMRI) studies reflect increases and decreases in neural activity, respectively (Logothetis et al., 2001; Shmuel et al., 2006); this technique has been less frequently applied to investigate CR. A number of reports have been published using this methodology to indicate that measures such as general fluid intelligence are related to variations in BOLD activity (reviewed in Jung and Haier, 2007). Further, studies in distinct pathological conditions (Chang et al., 2006; Cader et al., 2006; Ernst et al., 2002; Bartres-Faz et al., 2006) have corroborated the capacity of this technique to reveal the usage of cerebral reserve mechanisms during cognitive tasks. However, only few investigations were specifically designed and interpreted in terms of the cognitive reserve theory. In this regard, Habeck et al. (2003) and Stern et al. (2003) found that the pattern of activation during a nonverbal recognition task in healthy young subjects was related to individual differences in CR variables. Yet, very scarce data is available in healthy elders or among AD patients.

Even when considering previous findings, there is still little or inexistent data of how functional and structural brain measures are distinctly related to CR measures in the same samples of individuals. Since previous reports have found positive evidences for a relationship between accounts of education, occupation, or premorbid IQ variables and both morphologic brain measurements and patterns of brain activity, an issue of interest would be to determine the effects of these relationships in the same sample of individuals that differ according to their clinical status. Specifically, very scarce data (Wolf et al., 2004) addressed these questions in patients presenting high-risk conditions for AD such as MCI. Thus, the aim of the present report was to investigate the correlations between the main proxies for CR, brain activity (by means of fMRI) and cerebral structural characteristics among healthy elders, patients diagnosed as having MCI and mild AD patients.

2. Method

2.1. Subjects

Forty-four subjects older than 65, who provided written informed consent (or their relatives in AD cases) were enrolled in the study. The whole sample comprised 16 healthy elders, 12 amnestic MCI (MCI) cases and 16 mild AD patients. Participants were selected from Alzheimer's disease and other cognitive disorders unit, at the Neurology Service, Hospital Clinic of Barcelona, and from a primary care health centre in the area of Barcelona (CAP Castellar del Vallès). All subjects underwent clinical and

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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 did not present cognitive complaints. Further, they did not exhibit cognitive performance below 1.5S.D. in a secondary memory test or in any other test comprised in neuropsychological examinations of language, praxis, gnosis and abstract reasoning (Rami et al., 2007). Amnestic MCI was diagnosed according to the modified Petersen et al. criteria (2001) and two additional criteria, similar to Lopez et al. (2003): (1) memory decline according to clinical judgment and preferably corroborated by an informant, (2) impaired memory function for age and education, (3) preserved general cognitive function, (4) intact activities of daily living and (5) non-demented; (6) the memory impairment had to be of the episodic memory type defined by 1.5S.D. below the control group mean, taking into account age and educational level, and (7) absence of psychiatric or medical causes accounting for these memory problems. A previously validated normative Spanish test: the Delayed Text Memory Test (Pena-Casanova et al., 1997) was used as an episodic memory test for determining a 1.5S.D. cut-off below the mean, taking into account age and educational level. Probable AD diagnosis was established by an interdisciplinary clinical committee formed by two neurologists and one neuropsychologist. DSM-IV and NINCDS-ADRDA criteria were applied taking into account clinical and objective functional and neuropsychological results. All AD patients included were mild AD (Global Deterioration Scale-4 stage). Atypical AD variants with non-significant episodic memory impairment were excluded from the study.

2.2. Proxies of cognitive reserve

Three main proxies reflecting those commonly used in the CR literature were defined. The first one was the Wechsler Adult Intelligence Scale 3rd version (WAIS-III) Vocabulary subtest, administered as a measure reflecting premorbid IQ (Lezak et al., 2004). A second CR variable was defined as 'education–occupation' and included quantifications of both educational and occupational attainment. This measure was coded as in a previous study (Staff et al., 2004) using ordinal values as follows: 0 = no formal education, 1 = primary school, 2 = secondary education and 3 = superior or university education and as regards occupation; 0 = non-qualified manual, 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 taken into account as an aim to consider other relevant variables related to CR (Scarmeas, 2007) including recordings 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 greater the score indicating increased CR. The questionnaire was administered directly to the subject participating in the study with the presence of their relatives in the case of patients 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 using factorial analyses (principal component methods) following the procedure described by Stern et al. (2005). The single factor extracted (composite CR) accounted for 79.6% of the common variance of these three measures.

2.3. Magnetic resonance imaging acquisition

All 44 subjects underwent structural and functional MRI examinations. Scans were obtained on a GE Signa 1.5T (General Electric, Milwaukee, WI). High-resolution T1-weighted images were acquired for anatomical identification with a Fast Spoiled Gradient-Recalled Echo three-dimensional sequence (Digital Imaging and Communications in Medicine) format: repetition time [TR]/echo time [TE] = 12/5.2, inversion time = 300, number of exitations = 1, FOV = 24 3 24 cm, 256 3 256 matrix. Whole-brain volumes were acquired in an axial plane yielding contiguous slices with slice thickness of 1.5 mm. Functional images were acquired using a T2*-weighted gradient echo planar imaging (TR = 2000 ms, TE = 40 ms, FOV = 24 3 24 cm, flip angle of 90). Twenty axial slices were obtained for each brain volume with a slice thickness of 5 mm and a gap of 1.5 mm.

2.4. Structural MRI

Statistical Parametric Mapping (SPM2) running in Matlab 6.5 was used to analyze structural brain images. A single investigator performed the prior manual steps in image preparation (anterior–posterior commissure line determination and image reorienting). Following segmentation (which was performed against the T1 template (MNI) implemented in SPM) of the three tissue compartments, a measure of whole-brain volume was obtained in mm^3 by adding the gray and white matter volumes. This measure was then corrected for whole intracranial volume ([gray + white]/[gray + white + CSF]). We used brain volumes in our study instead of head size or intracranial volumes previously employed to reflect premorbid brain status (Schofield et al., 1995, 1997; Mortimer et al., 2003; Wolf et al., 2004; Edland et al., 2002; Jenkins et al., 2000) because we did not aim to determine a risk for AD or MCI associated with these variables but instead we were interested in directly investigating the correlations between CR proxies and brain integrity (or otherwise atrophy) for each subject relative to their overall head size.

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2.5. fMRI procedure and memory recognition assessment

Original magnetic resonance images registered in format GE-advanced (1 two-dimensional file per slice) were organized into three-dimensional files (150 volumes per subject) by means of MRICro software (University of Nottingham, UK) and saved in ANALYZE 7.5 format compatible with SPM2. 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. As a cognitive experiment, we used a 15-block design task with alternating "repeated", "rest" and "experimental" conditions (5 blocks each) presented in an alternating way until the total duration of the experiment (15 blocks, 30 s per block, 450 s) was reached. The presentation time was 2 s and the interstimuli period 1 s. The task started with a repeated block, which consisted of the projection of one single photograph. The same picture was used for all the 'repeated' blocks. Following this condition and before the "experimental" block, a 'blank' block (presentations of a bare cross hair) was inserted. As regards the experimental task *per se*, subjects had to focus on 50 non-emotional photographs for a later recall test, as they were told before the scanning. Pictures were outdoor images showing a person or a group of people doing or performing different activities or landscape images. For each 'experimental' block, 10 novel pictures were presented. Following the scanning, subjects underwent a 2 forced-choice task where they were given two photographs each time and they had to decide which one had been previously displayed in the fMRI session. The maximum score for recognition memory was 50.

2.6. Data analysis

The Statistical Package for Social Sciences (SPSS v.14.0) was used to investigate group differences in demographic, clinical and CR measures by means of ANOVA, and χ^2 tests when appropriate. Partial correlations (adjusting for age, gender and MMSE score) of whole-brain volumes and CR measures were performed separately for each clinical group. Further, Student's *t*-tests were employed to formally test whether the regression slopes between CR and brain volumes differed between groups. All analyses performed in SPSS were considered significant for values of $p \leq 0.05$. To analyze fMRI data we used SPM2. First, individual analyses for each subject were undertaken to compare brain activity observed during the 'experimental' condition compared with that seen during the 'repeated' condition (contrast: experimental > repeated). For group analyses we performed within-group as well as between-group comparisons (in a similar manner to the analyses between brain volumes and CR). Within-group analyses included a series of regression

Table 1
Demographic global cognitive and CR variables across the three studied groups

	Controls ($n = 16$)	MCI ($n = 12$)	Mild AD ($n = 16$)	F/χ^2	Post hoc (Scheffe)
Age	73.31 (4.90) [CI 70.7–75.9]	74.25 (6.18) [CI 70.3–78.2]	76.50 (5.80) [CI 73.7–76.4]	1.36	n.s.
Gender (M/F)[a]	5/11	2/10	5/11	0.94	n.s.
MMSE	27.75 (0.86) [CI 27.29–28.21]	25.83 (2.18) [CI 24.45–27.22]	21.69 (4.03) [CI 19.54–23.83]	20.38	C > AD***; MCI > AD***
Recognition memory (fMRI)	43.37 (5.21) [CI 40.6–46.2]	36.25 (6.88) [CI 31.9–38.1]	26.31 (5.35) [CI 32.4–38.1]	35.43	C > MCI**; C > AD***; MCI > AD***
Cognitive reserve (CR)					
Composite CR	0.66 (0.80) [CI 0.23–1.09]	−0.40 (0.77) [CI −0.89 to 0.09]	−0.36 (1.03) [CI −0.91 to 0.19]	6.91	C > MCI*; C > AD**
Vocabulary WAIS-III	43.56 (9.06) [CI 38.7–48.4]	30.08 (7.99) [CI 25.0–35.2]	29.75 (14.54) [22.0–37.5]	7.64	C > MCI*; C > AD**
Education–occupation	4.56 (1.86) [CI 3.1–5.6]	2.42 (2.02) [CI 1.6–3.7]	2.75 (2.21) [CI 1.6–3.9]	4.79	C > MCI*
CR questionnaire	9.00 (4.24) [CI 6.7–11.3]	5.67 (3.82) [CI 3.2–8.1]	5.56 (3.93) [CI 3.5–7.7]	3.63	n.s.

Values are given in means (standard deviations); n.s., non-significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.005$. MMSE: Mini-Mental State Examination; WAIS-III: Wechsler Adult Intelligence Scale 3rd version. Vocabulary rates are given in direct scores. CI: confidence interval for the mean (confidence level CL = 95%).
[a] M, male; F, female.

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analyses (adjusted for age, gender, MMSE score and post-fMRI recognition memory performance) where CR proxies were entered as independent variables and brain activity during cognitive performance was the dependent variable. Between-group analyses were performed to investigate the interaction between group and CR on brain activity to test for differences between groups in the slopes of the relationship between CR and brain activity (Scarmeas et al., 2003b, 2004). Except when specified, all fMRI results were interpreted if they attained both voxelwise threshold of $p < 0.001$ (uncorrected) and at $p < 0.05$ (corrected) threshold on the extent of clusters. Only significant clusters containing more than 20 contiguous voxels were considered. This study was approved by the local ethics committee.

3. Results

Demographic variables, MMSE scores, recognition memory and values for CR proxies are given in Table 1. Groups were statistically comparable for age but controls and MCI cases outperformed AD for the MMSE performance. For recognition memory following fMRI, controls outperformed both MCI participants and AD cases. As regards CR proxies, the composite CR factor value and the Vocabulary WAIS-III subtest performance were higher for controls as compared to the clinical groups and the measure for 'education–occupation' was higher for controls than for MCI. Our CR questionnaire correlated positively with Vocabulary and 'education–occupation' in the whole sample ($r = 0.62$, $p < 0.0001$; $r = 0.64$, $p < 0.0001$, respectively).

3.1. CR and brain structure

Results for partial correlations for each clinical group indicated that there were negative correlations between CR proxies and brain volumes both for MCI and AD groups. In contrast, positive relationships were observed in the case of control subjects (Table 2 and Fig. 1).

We further tested the differences of the regression slopes between CR proxies and brain volumes between groups. As expected from the visual inspection of the results displayed in Table 2 and Fig. 1, the slope for controls differed significantly (more positive) from the one observed for MCI and/or AD in most measures, whereas for these two groups they were comparable in all cases (Table 2).

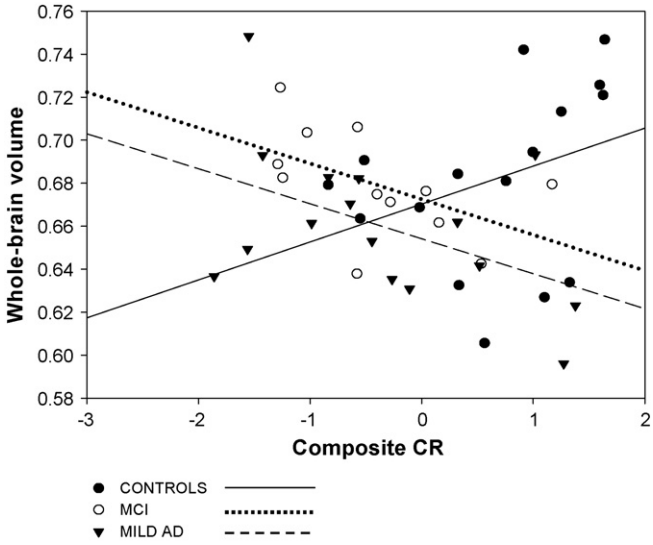

Fig. 1. Scatterplot displaying partial correlations (adjusted for age, gender and MMSE scores) between whole-brain measures and the composite CR score for healthy elders (controls), MCI and AD cases. *r* values and significant differences between CR measures and brain volumes for each clinical group are given in Table 2.

3.2. CR and brain function

For clinically normal and demented participants, opposite brain activation patterns during fMRI were observed as a function of CR. On the one hand, among healthy subjects, higher values in the composite CR measure were related to decreased activations in several cortical and subcortical regions including the frontal lobe and the cerebellum bilaterally, the right temporal cortex and the left thalamus. When CR proxies were considered separately, the variable of literacy rates and occupational attainment was the one variable emerging significant from this analysis (Table 3). No positive correlations between CR and brain activity were observed for healthy elders.

On the other hand, results from AD patients reflected a direct relationship between brain activity and CR. In these patients, we found positive slopes for the multiple regression analyses between the CR composite variable and brain function in the right cerebellum and left lingual gyrus. Further,

Table 2
Partial correlations (adjusted for age, gender and MMSE score) between brain volumes and CR measures for each clinical group

	Controls ($n = 16$)	MCI ($n = 12$)	Mild AD ($n = 16$)	Correlation slope differences (t values)		
				Controls vs. MCI	Controls vs. AD	MCI vs. AD
Composite CR	0.44	−0.47	−0.51	2.21*	2.23*	0.08
Vocabulary WAIS-III	0.26	−0.73*	−0.58*	2.12*	1.41	−0.71
Education–occupation	0.59*	−0.28	−0.30	2.08*	1.94	−0.18
CR questionnaire	0.25	−0.28	−0.44	1.19	1.66	0.7

* $p < 0.05$.

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Table 3
Brain regions showing significant relationships between CR proxies and brain activity in healthy elders and mild AD cases

CR proxies	Correlation	*t*-Value	Talairach coordinates [*x*, *y*, *z*]	Region (BA)	Number of voxels
Controls					
Composite CR	Negative	9.62	[−36, −9, 24]	L precentral gyrus (BA 4–6)	250
		9.30	[−7, −38, −37]	L cerebellum	582
		8.13	[−18, −25, 5]	L thalamus	134
		8.04	[43, −48, −4]	R middle temporal gyrus (BA 21)	98
		7.76	[8, −40, −36]	R cerebellum	120
		7.09	[8, −15, 48]	R medial frontal gyrus (BA 6)	118
		5.90	[−4, −17, 38]	L anterior cingulate (BA 24)	241
		5.74	[24, −17, 15]	R claustrum	180
Education–occupational attainment	Negative	7.74	[33, −7, 26]	R precentral gyrus (BA 4–6)	105
		7.09	[−2, −46, −28]	L cerebellum	82
Mild AD					
Composite CR	Positive	8.09	[8, −40, −16]	R cerebellum	147
		7.42	[−15, −67, 2]	L lingual gyrus	80
CR questionnaire	Positive	6.80	[11, 8, 28]	Anterior cingulate gyrus	123
		6.59	[15, −61, 2]	R lingual gyrus	110

All results are displayed after regressions were adjusted for age, gender, MMSE and memory recognition performance following fMRI. R = right; L = left; *t*-value: statistical value for the most significant voxel within each cluster.

higher scores in the CR questionnaire score were related to increased brain activity in the right anterior cingulate and lingual gyri (Table 3 and Fig. 2). In contrast to what was observed among control subjects, no negative correlations were found in this analysis. No significant correlations (either positive or negative) were seen between CR variability and brain activity in the MCI group.

As described in Section 2, further analyses were undertaken to test for differences in direction of slope in the relationship between cognitive reserve and activation between controls and mild AD cases (MCI cases were not included since no significant data for the correlation of brain activity × CR was available). These results revealed brain regions where the regression slope between CR and brain activity was more negative for controls than for AD; specifically the right superior temporal gyrus (Talairach coordinates: [40, −34, 12], BA 22, $t = 5.02$, $p = 0.05$ uncorrected for cluster level) and the left superior parietal lobule (precuneus; Talairach: [−13, −32, 46], BA 7, $t = 4.93$, $p = 0.02$ uncorrected for cluster level). No regions emerged where the slope was more positive for controls than for AD (Fig. 3).

3.3. CR, brain volume and brain function

As an attempt to integrate the relationships between cognitive reserve, volume, and activation we conducted stepwise

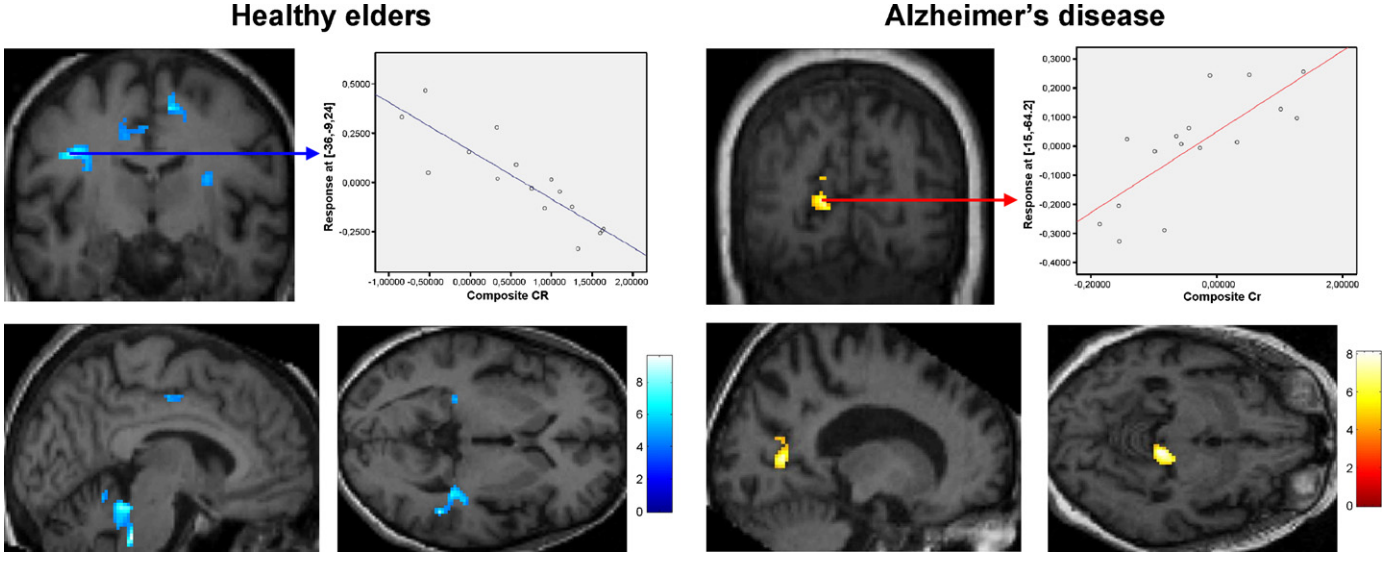

Fig. 2. Brain areas showing positive (in hot colours) and negative (in winter colours) correlations with the CR composite score in healthy controls and Alzheimer's disease patients. Scatterplots for the left precentral gyrus in the case of controls and the left lingual gyrus in AD patients are also depicted. For a precise localization of the cerebral regions, see Table 3.

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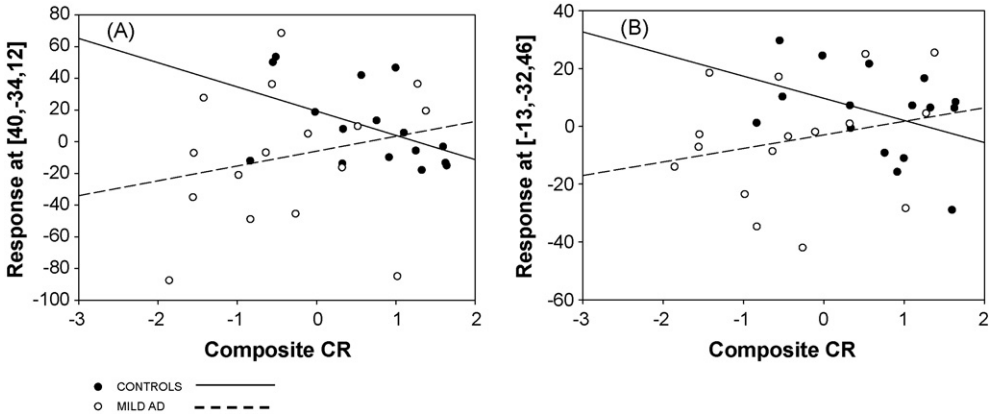

Fig. 3. Scatterplots showing brain areas where the direction of slope in the relationship between cognitive reserve and activation was more negative for controls than for AD. The regions represented are: A: superior temporal gyrus (BA 22); B: superior parietal lobule (BA 7).

regression analyses separately for controls and mild AD cases. In these analyses, the predicted dependent variable was the composite CR score and the independent predictor variables were brain volume, the extracted value of the most significant voxel for each cluster observed in the previous within-group analyses (correlations between CR composite score and brain activity for each group) and the previously used covariates (MMSE, age and gender). Thus, this analysis attempted to test which variables (brain volume, brain activity or covariates) best predicted CR status for controls and AD. The regression analyses results showed that in both groups, fMRI patterns were more closely related to the CR composite score than brain volumes. In this regard, for control subjects brain activity in left precentral gyrus ($B = -1.73$; $t = -2.35$, $p = 0.035$) and left cerebellum ($B = -1.25$; $t = -2.27$, $p = 0.041$) explained 83% of the variability of CR composite measures. For AD patients, the variables entered in the model explaining 93% of the variance were brain activity in the right cerebellum ($B = 1.88$; $t = 2.77$, $p = 0.017$) and the left lingual gyrus ($B = 2.03$; $t = 2.24$, $p = 0.044$), despite for this group the MMSE also entered in the equation ($B = 0.14$; $t = 7.25$, $p < 0.001$).

4. Discussion

In the present study we gathered a number of CR indicators as an attempt to examine their relationships with brain structure and function in three aging conditions: normal aging, MCI and mild AD. Overall and as it is discussed below, results from healthy elders compared to clinical samples reflect an inverse effect of CR measures both on brain function and structure. Specifically, among healthy elders, higher CR was associated with larger brains and increased efficiency (as reflected by reduced brain activity) during cognitive performance, whereas among cognitively impaired elders the opposite pattern was observed. Present results thus, suggest reverted relationships between the passive (brain structure) and active (brain activity) correlates of cognitive reserve measures between normal aging as compared to conditions where a threshold implying clinical manifestations has been exceeded.

In our sample of healthy elders, we found a positive significant correlation between 'educational–occupational' attainment and whole-brain volume. At first glance, these results may appear counterintuitive as regards to the cerebral reserve hypothesis. In this sense, a study by Coffey et al. (1999) investigating the association between education and brain measures in a large sample of non-demented elders (MMSE > 24) found results in the opposite direction (more brain atrophy for those more educated) suggesting that the more educated individuals possessed larger reserve (in that they were able to remain clinically healthy despite a more advanced age-related brain atrophy). Discrepancies between present and previous findings could be related to the heterogeneity of the samples (i.e. individual differences) according to conditions with a proved effect on brain structure. A number of variables could be considered including alcohol intake (Taki et al., 2006) a different distribution of genetic variations (i.e. Apolipoprotein E ε4 allele; Serra-Grabulosa et al., 2003), individual differences in global cognitive, or even personality measures (Wright et al., 2007), among others. Thus a limitation of the present report is that although we adjusted our results for a measure of global cognitive function (MMSE) other potential variables could have influenced our results.

In the line of our results, an increasing body of literature has been published evidencing positive associations between behavioral measures similar to the CR proxies used here and cerebral volumes. For example, highly qualified/skilled occupation such as being a professional musician is related to increased gray matter volumes in particular brain areas (Gaser and Schlaug, 2003). Further, Haier et al. (2004) found a direct relationship between gray matter volumes and full-scale IQ WAIS scores among healthy older adults (mean age = 59), and Colom et al. (2006) evidenced positive correlations between measures of the general intelligence factor (including the Vocabulary subtest of the WAIS) and increased gray matter volume throughout the brain. Finally, higher education

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has also been associated with enlarged brain or head size in normal elders (Edland et al., 2002; Tisserand et al., 2001). Altogether previous and present findings may suggest that when subtle putative cases of clinical impairment (such as MCI) are ruled out, higher rates of CR in normal elders are related to increased levels of cerebral reserve as reflected by MRI volumetric measurements. Thus, according to our results, aging *per se* would not revert the association between CR and structural brain integrity observed in former studies of younger individuals until a critical clinical threshold has been overcame (see discussion below for MCI and mild AD groups).

Regarding the fMRI results among healthy elders, a negative association emerged between CR and brain activity during a memory-encoding task. In our study, healthy elders with reduced CR recruited additional regions to perform a visual memory task. These regions included mainly fronto-temporal regions, subcortical nuclei and the cerebellum. These brain regions have been previously found to show activity during memory tasks among healthy elders and were associated with compensatory responses. In this regard, the cerebellum and the anterior cingulate cortex were identified as a region within a network showing enhanced response to increased memory demands (Gould et al., 2003). Further, mounting evidence indicates that the frontal lobes have an important compensatory role during aging in a variety of cognitive tasks (reviewed in Grady, 2007). Only few previous studies using functional neuroimaging procedures have included samples of elder participants and interpreted their findings in the terms of CR hypotheses. Scarmeas et al. (2003b) used PET to demonstrate CR-related differential success in coping with age-associated changes in cognition. In their study, the authors found positive correlations between brain activity and CR variables during a visual memory-encoding task in young individuals whereas more brain regions including parietal, frontal and medial and lateral temporal lobe areas were negatively correlated among the elders. Similarly, using PET and a nonverbal recognition memory task, Stern et al. (2005), identified an 'age-related' topography whose change in expression varied from a low to a titrated demand as a function of CR variables within each group. These findings reflecting the differential usage by the elders of a network normally used by the younger partners were interpreted as providing evidence of neural compensation, as the altered network is used to compensate for the inability to recruit the healthy (young) brain's responses to increased task difficulty.

Finally, Springer et al. (2005) used fMRI to identify brain networks recruited during encoding and recognition episodic memory tasks whose activity was correlated with years of education in elder and young participants. Among the elder, they found that bilateral frontal activity was associated with more education whereas posterior medial temporal lobe showed the opposite pattern. On the whole all these studies reflect that CR relates to individual differences in how tasks are processed and that the reorganization of brain function in old participants is associated with maintained cognitive function into old age. In contrast to previous reports, we only observed negative correlations between brain activity and CR proxies (CR composite score and 'educational–occupational' attainment) among our healthy elder subjects. These differences may be related to methodological approaches (i.e. comparing young vs. old and comparing distinct levels of task difficulty) and the methods used to analyze data (i.e. univariate in ours vs. multivariate in Stern et al. (2005) and Springer et al. (2005)). However, as previous reports, our findings are in accordance with the CR in the sense that while they cannot prove that CR is related to greater capacity (since there were no correlations between increased CR and enhanced cognitive performance) they suggest the use of more efficient brain networks among healthy elders with high CR (less activation for the same performance) (Stern, 2007).

In MCI and mild AD significant negative correlations were observed between whole-brain volume and CR, specifically with the WAIS Vocabulary test. According to the reserve capacity hypothesis, the findings would suggest that at particular level of clinical severity (all MCI of the amnestic type and all AD GDS = 4, and using MMSE as covariate in the analyses), those patients with increased background in terms of intellectual attainment do in fact, exhibit a more advanced neuropathological process as reflected by increased atrophy of their brains relative to their intracranial volume sizes. Similar findings were previously reported in AD samples (Kidron et al., 1997). Our results provide first evidence that a similar relationship can be evidenced in very early stages of the disease (MCI). Previous research in AD considering CR variables such as reading, education and occupation have demonstrated faster decline after dementia onset (reflecting more advanced brain pathology) for patients with higher CR (Wilson et al., 2000; Stern et al., 1999; Scarmeas et al., 2006). Since present findings reflect the same directionality between CR and brain atrophy measurements for AD and MCI and since this latter condition has been demonstrated to correspond to high risk (Petersen et al., 2001) or very incipient AD (Morris et al., 2001), it would be of interest to determine in further longitudinal studies whether among these patients higher rates of CR is also related to faster declines and/or higher rates of conversion to dementia.

Considering the fMRI findings, a positive correlation between CR and activity in the cerebellum and lingual gyrus (CR composite) and anterior cingulate and lingual gyrus (CR questionnaire) emerged in mild AD cases, an opposite pattern to that observed among healthy elders (all negative correlations). When we analyzed the impact of CR background on recognition memory performance, no particular variable was related to higher memory scores, indicating that despite increased brain damage (as reflected by reduced cerebral volumes), mild AD patients with higher CR were able to perform the task at an equivalent level to those with lower CR scores. In this regard, overactivation among these patients may reflect more efficient use of brain networks resulting in a behavioral compensation (i.e. maintenance of behavioral performance

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as compared to less atrophied patients with low CR). Despite less frequently studied as compared to healthy subjects, there is evidence that AD patients can also recruit brain regions to support performance both in memory and non-memory tasks (Grady, 2007). For example, additional recruitment of the anterior cingulate region was found among early AD patients as compared to controls during an episodic working memory task, a region usually recruited during semantic memory tasks. The authors suggested these increased activations as reflecting a residual capacity of their premorbid cerebral reserve (Starr et al., 2005).

As in a previous report, we identified brain regions where activity represents situations where the increasing level of CR is associated with opposite direction of activation in healthy elders and AD groups (Scarmeas et al., 2004). In particular, we found regions where correlation slopes were more positive in AD as compared to healthy adults as a function of CR in neocortical temporo–parietal areas. As discussed above, increased CR-related engagements (as compared to controls) in these brain areas may represent loci showing particular reorganizations or compensatory mechanisms in the early course of the disease. Neuropathological studies indicate that brain lesions are already present in the middle and superior temporal gyrus and the superior parietal lobule in incipient AD (including MCI and CDR = 0.5) although they are less frequent as compared to the ones observed in medial temporal areas (Berg et al., 1998; Markesbery et al., 2006; Haroutunian et al., 2007). Thus, CR-related slopes changes could represent either direct consequence of neuropathological abnormalities in these particular regions or secondary changes in response to damage in the earliest affected structures (i.e. entorhinal cortex). Finally, results deriving from the multiple regression analysis showed that both for controls and AD cases brain activity in significant clusters entered into the model to predict CR, whereas brain volume was excluded from the equation as a significant variable. Although active and passive models of CR should be regarded as complementary rather than mutually exclusive, findings in our sample of healthy elders and AD indicate that measures reflecting recruitment of brain networks more closely represent the neural implementation of CR than brain size, thus providing more support for active models (Stern, 2002). Future research using more refined anatomical measures such as voxel-based morphometry techniques or diffusion tensor-based imaging not considered here should be useful to further determine the relationship between CR and specific anatomical areas.

Several limitations should be considered in our study. An issue to bear in mind is the small sample sizes. Although our samples are comparable to many fMRI studies, a larger sample would have been desirable, especially in the MCI subgroup. The reduced number of subjects studied might explain the lack of significant results for the fMRI experiment in this group. As regards the fMRI task used, it was based on a paradigm which elicits the encoding of complex visual information (Stern et al., 1996). A previous version of this task has been used in a report restricted to medial temporal lobe activations which included healthy elders, MCI and AD patients (Dickerson et al., 2004). In another study where whole-brain activations were considered using a similar paradigm based on the presentation of novel vs. repeated scenes, a comparable pattern of brain activity as the one reported in our study for control subjects (including frontal, temporal, cingulate and cerebellar regions), as well as for AD (including the left lingual gyrus) was reported (Golby et al., 2005). Thus, despite the fMRI results are not directly comparable (patterns of brain activity for novel vs. repeated in the previous report and correlations with CR in our study), both studies suggest the involvement of similar brain areas during encoding of complex visual information. However, it should be noted that in the present investigation the fMRI memory task did not entail the same level of difficulty for all participants both within and between clinical groups, an aspect that by itself could lead to differential brain activity. Some previous studies (e.g. Habeck et al., 2003; Stern et al., 2003, 2005) adjusted the task difficulty so that all tested individuals performed at an equivalent level. Instead, we used recognition memory as a covariate in all analyses as a measure of control for this variable. However, no correlations were observed between memory performance and CR variables in any group, suggesting as in previous report (Stern et al., 2003) that it is unlikely that the relationship observed between fMRI and CR is an artifact of correlations between cognitive performance. A further limitation refers to the statistical approach. In the present report we did not analyze data using a multivariate approach to reveal networks underlying task performance during cognitive tasks. In exchange, we employed a general linear model (GLM) analysis only reflecting correlations and group differences between CR measures and task-related activations. Previous fMRI reports in similar samples have found complementary findings using both methodologies (Stern et al., 2003; Habeck et al., 2003). Thus, future studies using multivariate approaches such as functional connectivity may reveal dynamic associations between CR variables and brain activity among distinct clinical groups.

Conflict of interest

There are no actual or potential conflicts of interest.

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