Brain Topogr (2011) 24:340–357
DOI 10.1007/s10548-011-0195-9

ORIGINAL PAPER

Structural and Functional Imaging Correlates of Cognitive and Brain Reserve Hypotheses in Healthy and Pathological Aging

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Received: 22 December 2010 / Accepted: 25 July 2011 / Published online: 19 August 2011

Abstract In the field of ageing and dementia, brain- or cognitive reserve refers to the capacity of the brain to manage pathology or age-related changes thereby minimizing clinical manifestations. The brain reserve capacity (BRC) hypothesis argues that this capacity derives from an individual's unique neural profile (e.g., cell count, synaptic connections, brain volume, etc.). Complimentarily, the cognitive reserve (CR) hypothesis emphasizes inter-individual differences in the effective recruitment of neural networks and cognitive processes to compensate for age-related effects or pathology. Despite an abundance of research, there is scarce literature attempting to synthesize the BRC the CR models. In this paper, we will review important aging and dementia studies using structural and functional neuroimaging techniques to investigate and attempt to assimilate both reserve hypotheses. The possibility to conceptualize reserve as reflecting indexes of brain plasticity will be proposed and novel data suggesting an intimate and complex correspondence between active and passive components of reserve will be presented.

Keywords Aging · Dementia · Brain reserve · Cognitive reserve · Neuroplasticity · MRI · Functional MRI · Cognition · Brain networks · Compensation

This is one of several papers published together in Brain Topography on the ''Special Issue: Brain Imaging across the Lifespan''.

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Introduction

Cognitive and Brain Reserve

Cognitive- or brain reserve refers to the hypothesized capacity of an adult brain to cope with brain pathology in order to minimize symptomatology (Stern 2002). Within the fields of ageing and dementia, the concept of reserve emerged from repeated observations of Alzheimer's Disease (AD) neuropathology in otherwise clinically healthy elders (Snowdon 2003) and by reported weak or absent associations between unique cognitive profiles and AD neuropathology (Driscoll et al. 2006). Two influential hypotheses have been proposed to account for these counterintuitive observations (Stern 2002). The first is the 'brain reserve capacity' (BRC) model. Largely concerned with anatomical correlates, the BRC suggests that passive factors (such as the number of synapses or brain volume) confer a particular capacity to endure neuropathological processes. With regards to dementia and pre-dementia conditions, the BRC serves to prolong the preclinical stage until a critical threshold is reached. Once the BRC is depleted by increasing levels of neuropathology, vulnerability to brain damage is unavoidable and, eventually, clinical and functional deficits become evident (Satz et al. 1993). This hypothesis predicts that individual differences in anatomy manifest in different levels of insult tolerance before clinical deficit emerges.

A proposed shortcoming of the passive (BRC) model is that it does not account for individual differences in

cognitive or functional processing. As such, an active or 'functional' model of reserve, the cognitive reserve (CR) hypothesis, was conceptualized (Stern 2002). In this hypothesis, CR reflects the inter-individual ability to use cognitive processes and brain networks in an effective way. With regards to healthy elders and patients with dementia, two mechanisms underlying CR have been proposed: neural reserve and neural compensation (Stern 2009). Neural reserve reflects strategies used by healthy individuals when coping with task demands and emphasizes pre-existing differences in neural efficiency or capacity. This reserve can take the form of using flexible brain networks or cognitive resources that are less susceptible to disruption. Neural compensation, on the other hand, refers to adopting new, compensatory brain networks after pathology has impacted those networks typically utilized for particular tasks. Neural compensation (and, accordingly, the CR hypothesis) emphasizes inter-individual differences in the ability to cope with age-related processes or AD pathology (Stern 2009).

Estimations of Reserve at an Individual Level

Precedent literature indicates that higher prevalence (Gurland et al. 1995; Mortel et al. 1995) or incidence (Stern et al. 1994; White et al. 1994) of AD and dementia in general is observed among elder populations with low levels of education. Conversely, prospective epidemiological and cross-sectional evidence reveals that higher ratings or highly qualified levels of education, occupation, and/or leisure activities protects against the appearance of clinical symptoms of dementia (e.g. Valenzuela and Sachdev 2006; Scarmeas 2007). Similarly, reduced intracranial volume or smaller head size, alone or in combination with low education, may confer an increased risk for cognitive decline and dementia (Schofield et al. 1995; Mortimer et al. 2003). Overall, the results obtained in these and other investigations identify variables that can be individually assessed by anthropometric or clinical evaluations which may provide good proxies or estimates of an individual's cerebral reserve.

It should be noted, however, that the best way to conceptualize and obtain measurements reflecting cerebral reserve remains open to debate. Too often, information regarding relevant genetic background is not combined with environmental variables that can affect reserve. Also, additional measures such as dietary habits, sleep habits, personality characteristics, and exposure to stressful events (all of which impact brain status in old age) should arguably be incorporated in studies considering reserve and dementia. Additionally, the need to conduct construct validation studies that define reserve in both neurophysiologic and cognitive terms has recently been strongly argued (Satz et al. 2010). At a conceptual level, Christensen et al. (2008) stressed that, in the field of reserve, correct methodological approaches can only be attained that combine measures of brain burden, reserve (i.e. education), and cognitive outcome. In order to present a new approach for describing in more operative terms the construct of reserve, Reed et al. (2010) have recently proposed a novel method for measuring and investigating CR termed the "prediction error", defined as the difference between the predicted cognitive performance by an individual with a specific level of pathology and said individual's *actual* performance. Clearly, further research is needed to clarify and determine how reserve can best be determined and/or measured.

Present Approach to Measure Reserve

Although the previous section highlighted the complexity of finding appropriate operational measures for the reserve construct, at a practical level, educational attainment estimates (with or without estimates of occupational achievement) have arguably been the most straightforward and successful reserve proxy utilized in the literature to date. While this may be a valid approach, it seems incomplete in the light of the aforementioned consideration. For example, there is evidence from epidemiological studies that additional life experiences, such as social or physical activity, may play as large a role as education in an individual's risk of developing dementia (Karp et al. 2006). Similarly, high levels of physical exercise and adherence to the Mediterranean diet were both independently associated with a lower risk of developing AD over 15 years (Scarmeas et al. 2009).

In this article, we will review the major publications available in the field of reserve as pertaining to ageing and dementia that utilize neuroimaging technology. We will place a specific emphasis on those studies performed by our group. Per reserve measurement, we have adopted an approach based upon that developed by Stern and colleagues (e.g. Stern et al. 2005). In short, we consider a single measure or score of CR for each participant (termed the 'composite CR score') which is subsequently regressed against structural and functional MRI parameters. This unique measure emerges from the integration of three major CR proxies as determined via a questionnaire developed by our institution (available upon request). More specifically, the first proxy we utilize is the Vocabulary Subtest of the WAIS 3rd version (WAIS-III) or the Word Accentuation Test (Del Ser et al. 1997)—an analogue to the National Adult Reading Test in the Spanish population. These tests infer the premorbid IQ which is thought to partially reflect an 'innate reserve capacity'. The second proxy we utilize reflects "education-occupation" and is coded using the

following ordinal values: 0 = no formal education, 1 = primary school, 2 = secondary education and 3 = superior or university education. Per 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) (Staff et al. 2004). The third proxy we utilize determines lifetime participation in leisure and cognitively stimulating activities, such as reading, writing, music playing, physical activities, and participation in social activities or groups.

Review of Imaging Studies of CR in Aging and Alzheimer's Disease

Previous Findings Concerning the Brain and Cognitive Reserve Hypotheses

Neuroimaging techniques offer an excellent methodological facility to investigate the neural implementation of the variables assumed to reflect reserve. As such, a relevant body of evidence using either functional (mainly PET and fMRI) or structural (mainly anatomical MRI) imaging is available in the ageing literature, generally addressing how CR or BRC proxies (e.g. education, occupation, leisure activities, head circumference) relate to parameters such as brain size or atrophy and to cerebral blood flow or glucose metabolism patterns as well as brain network utilization during cognitive demands.

The major neuroimaging studies testing the BRC hypothesis in elder populations (i.e. how education, intelligence, or intracranial volumes relate to structural brain parameters such as brain volume, atrophy, or white matter damage) have been recently reviewed in a comprehensive article by Christensen and colleagues (2008). The principal conclusions of this investigation were: (1) Measures of reserve, notably of intelligence, associate with larger brain volumes in healthy elders (particularly cortical volumes). However, this relationship appears to weaken with advancing age. (2) There is some evidence that high reserve (education and intelligence) protects against progressive brain burden (mainly brain atrophy or WMH). Unfortunately, longitudinal studies are scant and there is no clear data reflecting premorbid intelligence estimations or education and the *rate* of change in brain structures. (3) There are probably additional factors unaccounted for in these investigations that interact with current reserve measures. These factors likely include smoking, alcohol consumption, genetic factors, hypertension, vascular disease, toxic or nutritional factors, etc.

Following this review, several relevant studies were published investigating the passive or BRC hypothesis. For example, Perneczky et al. (2010) examined brain atrophy measures, Teipel et al. (2009) utilized diffusion tensor imaging analysis, and Querbes et al. (2009) analyzed cortical thickness patterns. These three studies all confirmed earlier MRI-volumetric observations (Kidron et al. 1997) which indicated that, when considering individuals with established dementia at comparable levels of clinical severity, higher levels of reserve (as determined by educational or occupational attainments) related to greater amounts of brain damage. Together, these and previous observations reinforce the core notion of the brain reserve hypothesis indicating that greater amount of brain pathology can be tolerated amongst patients with higher proxies of reserve. This results in reduced impact on clinical manifestations. On the other hand, in healthy populations, Rovio et al. (2010) have demonstrated a positive impact of midlife physical activity on total brain, total gray matter, and regional gray matter densities in the middle frontal gyrus late in life. Also, Valenzuela et al. (2008) and Christensen et al. (2009) have published two of the few longitudinal studies investigating the impact of reserve measures amongst healthy elders. In the Valenzuela et al. investigation, lifestyle engagement in complex activities was found to be associated with diminished rates of hippocampal atrophy during a 3-year follow-up. Conversely, Christensen and colleagues failed to observe a protective effect of high education or larger intracranial volume against baseline brain atrophy or WMHs rates (Christensen et al. 2009).

Two relevant conclusions can be drawn from these latter investigations. First, the impact of reserve on structural brain parameters as measured by neuroimaging techniques may be regionally specific. This is most clearly exemplified by the investigation of Valenzuela and colleagues (2008) wherein CR modulated the rate of atrophy in the hippocampus but not the brain as a whole. Second, in general, inverse associations are observed between brain integrity measures and reserve estimates for healthy and patient populations (positive for controls and negative for patients). However, this remains a controversial finding as Querbes et al. (2009) observed that higher education related to thinner cortical mantle in temporal and posteriomedial regions amongst both healthy elders and patient populations. This observation adds to earlier reports by Coffey et al. (1999) that healthy elders with higher education exhibited greater brain atrophy. Therefore, whereas higher reserve appears to confer with higher capacity to resist neuropathology in clinical populations, reserve measurements have generated mixed correlations within normal elder groups.

As regards the major studies using functional neuroimaging techniques, the parameters and findings are summarized in Table 1. Investigations performed at rest have consistently shown an inverse association between regional

Table 1 Studies using functional neuroimaging techniques to investigate the reserve hypothesis in young subjects, healthy elders and patients with Alzheimer's disease

Study	Samples	Reserve proxies	Methods	Imaging measures/techniques	Main findings
Stern et al. (1992)	58 AD	Education	Comparison among 3 groups with distinct levels of education	At rest ^{33}Xenon inhalation-PET; Regional cerebral blood flow	Matched for clinical severity, more educated patients showed depleted blood flow in parietotemporal regions
Stern et al. (2003)	19 healthy young adults	Estimates of premorbid IQ	Regression analysis	fMRI: two conditions (low/titrated) of encoding and recognition task	There were areas across subjects where significant positive or negative correlation between change in activation from low to titrated demand and NART exists. This differential processing may help explain individual differences in capacity and may underlie reserve against age-related pathologic changes
Stern et al. (1995)	51 AD	Occupational demands in interpersonal skills, physical demands	Partial correlations (controlling for relevant demographic characteristics) between occupation and cortical perfusion. Multiple regression analysis	At rest ^{33}Xenon inhalation-PET; Regional cerebral blood flow	There was less relative perfusion in the parietal region in subjects whose occupations were associated with higher interpersonal skills and physical demands factor scores. Occupational experience may provide a reserve that delays the clinical manifestation of AD
Alexander et al. (1997)	46 AD 41 HE	Estimates of premorbid IQ, word reading ability	Partial correlations (controlling for relevant demographic characteristics) between occupation and cortical perfusion. Multiple regression analysis	At rest [^{18}F]-2-fluoro-2-deoxy-D-glucose-PET Cerebral metabolism	Estimates of premorbid intellectual ability were inversely correlated with cerebral metabolism in the prefrontal, premotor and left superior parietal association regions. Higher levels of premorbid ability are associated with greater pathophysiological effects o AD among patients of similar dementia severity
Habeck et al. (2003)	17 healthy young adults	Years of education and IQ indices	Regional covariance analysis	fMRI: two condition (low/titrated demand) of non-verbal recognition task	Different approach to task used by individuals with more and less CR. Change in network expression across the low and titrated conditions correlated with CR after partialing out the influence of task performance, suggesting reserve-related physiological differences
Scarmeas et al. (2003b)	17 healthy young adults, 19 HE	Years of education and IQ indices	Multiple regression analyses. Identification of brain regions where regression slopes differed between two groups	$H_2{}^{15}$ O-PET serial recognition memory task under two condition: non memory and titrated demand.	Brain regions showing systematic relationships between CR and brain activation differ as a function of aging, suggesting compensation mechanisms in those brain areas.
Scarmeas et al. (2003a)	9 early AD, 16 HE	Education, estimated premorbid IQ and intellectual, social and physical activities	Multiple regression analyses	At rest $H_2{}^{15}$ O-PET	At a given level of clinical disease severity, there is a greater degree of pathology in temporal and temporal-occipital-parietal association cortices in patients with AD who have higher activity scores. This inverse relation is still when controlling for education and IQ.
Scarmeas et al. (2004)	12 AD, 17 HE	Years of education and IQ indices	Multiple regression analyses. Identification of brain regions where regression slopes differed between the two groups	$H_2{}^{15}$ O-PET memory task for nonverbalizable shapes under two conditions (low/titrated demand)	Brain regions where systematic relationships between subjects' education-IQ and brain activation differ as a function of disease status may mediate differential ability to cope with clinical manifestations of AD

Table 1 continued

Study	Samples	Reserve proxies	Methods	Imaging measures/techniques	Main findings
Springer et al. (2005)	21 healthy young adults, 29 HE	Years of education	Repeated measures analysis of covariance/ multivariate analysis	fMRI: memory task, encoding/recognition	Brain regions associated with education and overall memory ability, differ with age. This regions either showed no overlap between young and HE or were inversely related, suggesting that the reorganization of brain function in HE may be a type of CR
Stern et al. (2005)	20 young adults, 17 HE	Years of education, IQ indices	Covariance analysis	$H_2{}^{15}$ O PET: two conditions (low/titrated demand) of a recognition	Young individuals with higher CR showed increased expression of the topography of the task network across the two conditions, suggesting a neural manifestation of innate or acquired reserve. HE with higher cognitive reserve showed decreased expression of the topography across tasks, suggesting some functional reorganization of the network used by the young
Perneczky et al. (2006)	93 patients with mild AD, 16 HE	Years of education	Voxel-based linear regression analysis of rCMRglc with years of education	^{18}F-FDG-PET	Inverse association between years of schooling and glucose metabolism, suggesting that education is associated with brain reserve
Kemppainen et al. (2008)	12 high-educated and 13 low-educated cognitively comparable groups	Years of education	Voxel-based statistical analyses: between group comparison, two sample t-test	PET: Pittsburgh compound B (PiB) and ^{18}F-fluorodeoxyglucose	High-educated patients showed increased PiB uptake in the lateral frontal cortex compared with low-educated and significantly lower glucose metabolic rate in the temporoparietal cortical regions compared with low-educated patients, suggesting more advanced pathological and functional brain changes in high-educated patients
Stern et al. (2008)	40 young adults, 18 HE/24 young adults, 21 HE	IQ indices	Canonical variates analysis	fMRI: two tasks with different processing demands: delayed item reponse task with letters or shapes	There was a brain pattern that manifested relationships between load-related encoding activation and CR variables across the letter and shape task in young but not in HE. This pattern could represent a general neural implementation of CR
Roe et al. (2008)	161 HE, 37 AD	Years of education	Multiple regression	PET: Carbon 11-labeled Pittsburgh Compound B ([^{11}C]PiB)	[^{11}C]PiB interacted with years of education in predicting scores on neuropsychological test. The performance on these measures increased with increasing education for participants with elevated PiB uptake, supporting the hypothesis that cognitive reserve influences the association between Alzheimer disease pathological burden and cognition
Roe et al. (2010)	180 HE, 25 AD	Years of education and occupation	Logistic regression	PET: Pittsburgh compound B (PiB)	Greater educational attainment was associated with a lower likelihood of AD and reserve variables influence associations between AD pathology and dementia. This variables improve the predictive accuracy of amyloid imaging for the identification of symptomatic AD

AD Alzheimer's disease, *HE* healthy elders, *CR* cognitive reserve, *fMRI* functional magnetic resonance, *HE* healthy elders, *PET* positron emission tomography, *PiB* Pittsburgh compound B, *rCMRgl* regional cerebral metabolism rate of glucose

blood flow and reserve measurements evidencing those patients with higher estimates of reserve can tolerate more advanced stages of the disease. These associations appear mainly in pathology-relevant areas such as the temporo-parietal cortices in AD and occipital areas in dementia with Lewy bodies (Pernezcky et al. 2009).

FMRI and PET are best suited to investigate the CR hypothesis (via cognitive activation studies) and studies to date have focused primarily on memory tasks. Those investigations performed in young subjects have successfully indentified patterns of brain activity that change with increasing cognitive loads as a function of inter-individual differences in reserve estimations (Stern et al. 2003; Habeck et al. 2003). The comparison between young and elderly subjects has further revealed reserve-related differential activation patterns and inverse associations between CR estimates and the expression of task-specific networks. Scarmeas et al. (2003b), using rCBF-PET, a nonverbal recognition task, and a composite measure derived from education and IQ, evidenced several regions where brain activity was correlated with CR estimates during task performance but where there were slope differences between young and healthy elders. Here, there were regions with a more positive slope in young populations suggesting both an increased capacity to invoke said networks in high CR individuals and an effect reduction with increased age. Also, several areas showed opposing slopes in the correlation between brain activity and CR estimates, probably evidencing compensatory reorganizations of brain function in the face of age-related changes. Similarly, Stern et al. (2005), employing fMRI, observed that young individuals with high reserve exhibited increased expression of an age-related topography network as task difficulty increased and a concomitant decreased expression as a function of CR in elders. Springer et al. (2005), also using fMRI, found that education correlated positively with frontal activity in healthy elders and negatively in young individuals during memory tasks. This suggests that the frontal cortex is engaged as an alternative network to aid cognitive function in the older individuals.

In the case of dementia, studies combing functional activation and CR measures are somewhat scarce. Scarmeas et al. (2004), using the same PET and nonverbal recognition task reported above, observed an inverse correlation between regional cerebral blood flow and CR estimates. Here, correlations were more positive in visual and temporal areas for healthy elders and for more positive in the precentral gyrus and hippocampus for patient populations. Together, reports employing functional neuroimaging techniques during cognitive activation studies provide evidences that CR modulates the expression of brain networks in young and aged populations. In younger populations, findings reflect evidence for neural efficiency or capacity linked to CR, whereas in elder and clinical populations CR correlated compensatory mechanisms are frequently evoked.

Evidences from Our Group Using MRI in Healthy Ageing and Early Stages of Dementia

It is clear the investigations conducted to date using neuroimaging techniques have offered valuable information regarding the impact of cognitive and/or brain reserve estimations on the anatomofunctional characteristics of the ageing brain, with and without dementia. Still, several critical questions need to be addressed. These questions have served as the driver for our laboratory. The remainder of this review will focus on the findings obtained by our group with regards to the following issues:

- First—although considerable data exploring how brain function *or* brain structure reflects reserve proxies was available in the literature, there was very limited information integrating functional neuroimaging and morphological data in the same populations. This was something we determined to undertake.
- Second, studies to date have included healthy elders, AD patients, or a combination of both, but rarely subjects at prodromal stages of dementia (i.e. MCI patients). We reasoned that including all three of these groups in our investigations would allow a better understanding of how CR enables individuals to cope with brain damage across the ageing or disease span.
- Third, with regards to activation or functional neuroimaging studies, there is scant data reflecting CR related brain activity changes across distinct cognitive domains. Seminal studies undertaken by the group of Yaakov Stern at Columbia University used different verbal and object memory tasks with fMRI or PET (see Table 1). However, the impact of CR on brain networks supporting other cognitive functions relevant to dementia, such as language or visuoperceptive processes, has remained largely unexplored. Interestingly, some of these functions may be preserved in the early or prodromal stages of dementia. As such, relevant investigations using neuromaging techniques could help us to determine if structural–functional changes as a function of CR are implemented in patients before clinical manifestation has occurred.
- Fourth, as reported above, morphological and 'at rest' functional neuroimaging studies suggest regional specificity for the implementation of reserve. Also, in functional activation studies, brain regions influenced by CR across distinct populations imply areas that, in the previous literature, have been directly or indirectly linked to the processing of specific types of cognitive

task (i.e. Scarmeas et al. 2003b). On the other hand, it has been proposed that CR may affect cognitive tasks via a common mechanism, whereby a general CR network is expressed across a wide range of cognitive tasks (i.e. Stern et al. 2008). A major objective of our investigations was thus to provide further evidence for the existence of a specific, a common, or a combined mechanism for the implementation of CR.

Findings in Healthy Elders

A repeated observation of our different investigations integrating functional imaging, structural MRI parameters, and CR proxies suggests that, amongst healthy elders, higher CR scores relate to better preserved global and regional cerebral brain volumes and to reduced recruitment of brain networks during cognitive demands. In our first report (Solé-Padullés et al. 2009), we evidenced that healthy seniors scoring higher in our CR questionnaire were characterized by larger brains (corrected by age, gender, and intracranial volume) and showed negative associations between CR and brain activity (within the bilateral frontal lobes and cerebellum, the right temporal cortex, and the left thalamus) during a visual encoding task. This effect was observed after adjusting for cognitive performance in the subsequent recognition memory test (Fig. 1, encoding representation). Both CR related brain structure and function estimates were further replicated in a second investigation using voxel-based morphometry (VBM) analyses to illustrate regional gray matter volume changes as related to CR variations (as opposed to the whole-brain measurements used above) (Bartrés-Faz et al. 2009). In this study, higher CR scores corresponded to larger GM volumes in frontal and parietal areas (Fig. 1, gray matter results). In this study we also administered a working memory N-back task within the fMRI scanner. When brain activity was regressed against the CR composite variable, we observed reduced cerebral activity in the WM-network in those individuals with higher CR estimates (Fig. 1, working memory representation). Finally, using biological parametric mapping (BPM) to precisely adjust, in a voxel-by-voxel manner, the effects of brain atrophy on brain activity and revealed that BOLD changes linked to CR could not be further observed.

Reduced activity in language-related areas as a function of CR loads in healthy elders (as compared to clinical populations) was observed in a further investigation which included independent samples and a linguistic comprehension task. This was a passive task aimed at investigating an unaffected clinical domain in patients (see below). The task consisted of listening to spoken narratives of everyday events with neutral emotional content as previously employed by our group (Fernández-Espejo et al. 2008). In this study, we also analyzed the deactivation BOLD signals with a particular focus on the anatomical areas comprising the default-mode network (DMN). The DMN includes functionally connected regions, mainly prefrontal dorsal and ventral medial regions, the posteromedial cortex (the posterior cingulate, precuneus and retrosplenial cortex) and inferior parietal areas (Buckner et al. 2008). This system is

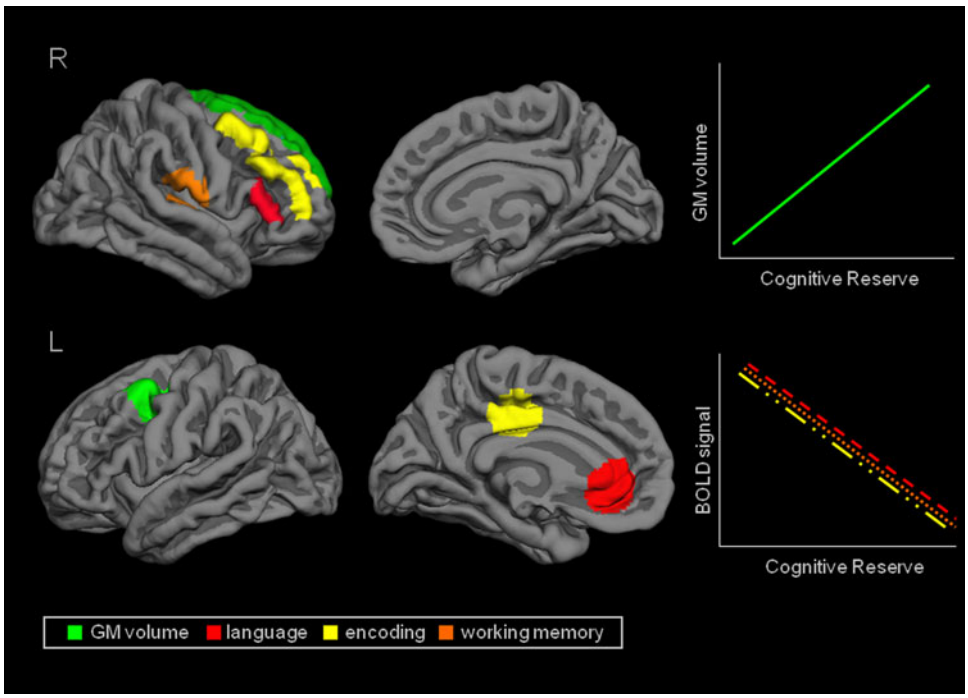

Fig. 1 Schematic representation of the associations between CR composite measures, regional brain volumes and brain activity across distinct cognitive tasks in our healthy elders. Note that for brain volume correlations are positive (see also Solé-Padullés et al., 2009) whereas for brain activity they are negative. Also note that for this latter association, the frontal lobes are involved in the three cognitive tasks investigated. Language activations reflect areas where correlation slopes between BOLD signal changes and CR were more negative for healthy elders than for patients (MCI or AD)

more active during passive task conditions (e.g. passive fixation, rest) than during goal-directed tasks and is dysfunctional in the early stages of AD, including MCI and, to a lesser extent, typical ageing (Lustig et al. 2003). In our study we observed evidence that CR modulates not only task-related brain activation areas but also deactivations of the DMN. Healthy elders with higher scores in the CR questionnaire expressed less deactivation of this network (Fig. 1, language representation). Since the degree of deactivation of the DMN is thought to reflect cognitive effort in elders (Persson et al. 2007), this pattern of decreased task-related activation in the language network and reduced deactivation in the DMN in high CR elders suggests more efficient neural resources and more automatic or effortless processing (Bosch et al. 2010a).

Our structural brain findings among healthy elders in the first study conferred with previous evidence suggesting larger or more preserved brains as a function of CR variables. In a subsequent study, we examined if this relationship was also observed when considering white matter (WM) integrity. The impetus to focus on WM was motivated by the lack of significant associations between CR and GM measures in our aforementioned report utilizing a linguistic task (Bosch et al. 2010a). We hypothesized that white matter changes (which appear early in the course of the ageing process) might represent a more sensitive anatomic substrate associated with the CR construct in a healthy sample. Also, former investigations have reported that highly educated individuals maintained increased tolerance of white matter damage and, accordingly, minimized cognitive manifestations (Dufouil et al. 2003; Nebes et al. 2006). However, whereas these studies analyzed either WM volumes or white matter hyperintensities, we employed diffusion tensor imaging (DTI) and the fractional anisotrophy (FA) metric, a parameter that provides quantitative measures of the integrity of WM fiber tracts. During this study, we also investigated if expected CR-FA associations would be anatomically specific (i.e. if they would prevail in areas reflecting age-related WM loss among healthy elders in regions showing pathological FA decreases) among the patient groups. Regarding healthy elders, we observed that CR status was only related to WM integrity in the *genum* of the corpus callosum. According to previous literature (Medina and Gaviria 2008 and to our earlier DTI study whereby 'age related' and 'AD-typical' topography patterns of WM loss of integrity were reported (Bosch et al. 2010b), effects to this area corresponds more to typical aging and are less characteristic of early dementia.

While this latter result suggests regional specificity for the neural implementation of CR among healthy elders, an unexpected finding suggested that the observed correlation between CR composite score and WM integrity in the anterior corpus callosum was *negative* (greater CR corresponded to lower FA values). These findings are reminiscent of formerly reported inconsistencies in the literature concerning correlations between CR estimates and imaging parameters denoting brain integrity among controls. In this particular case, as prefrontal WM represents of earliest change incurred during the process of physiological ageing, a possible interpretation is that higher CR may suggest a greater capacity to tolerate age-related structural damage without concomitant impact on cognitive performance. In fact, we observed positive correlations between CR and neuropsychological evaluations in this sample (Arenaza-Urquijo et al. 2011). An alternative, and arguably more intriguing, explanation may be that some of our cognitively normal subjects were harboring some sort of preclinical AD pathology. Within this context, it is important to note that current research criteria for AD emphasize the need to identify very early stages of dementia or at-risk dementia conditions (Dubois et al. 2010). The use of biomarkers is essential to this endeavor. One of the earliest AD biomarkers appears to be reduced cerebrospinal fluid CSF amyloid-β_{1-42} ($A\beta_{1-42}$) levels (Sunderland et al. 2003) and may reappear several years before clinical manifestations (Jack et al. 2010a, b). The point here is that subsets of elders who appear cognitively normal do in fact have AD, pathologically speaking. Therefore, we conducted a subsequent study after CSF $A\beta_{1-42}$ values were obtained from a sample of cognitively preserved elders. The results (depicted in Fig. 2) show a clear interaction between WM integrity and CR as a function of the $A\beta_{1-42}$ biomarker: while healthy elders with normal levels of $A\beta_{1-42}$ showed the expected positive correlation reflecting more preserved WM structure as a function of CR, a negative association is observed for individuals with reduced $A\beta_{1-42}$.

Findings in MCI and Dementia

In our investigations, the comparison between healthy elder and MCI and AD patients per brain function and structure correlates to CR proxies provides an interesting double dissociation. In most cases, and in clear opposition to cognitively healthy individuals, the correlation between CR and brain anatomy is negative in patient populations and CR is related to a higher expression of functional networks during cognitive demands. This was the case in our first investigation which included a visual encoding task whereby positive fMRI activations with regards to CR ratings were observed amongst AD patients in the lingual gyrus and anterior cingulate (Solé-Padullés et al. 2009; Fig. 3, encoding representation). Further analyses revealed regions of interaction where the regression slope between CR and brain activity was more negative for controls than for AD patients in the superior temporal gyrus and parietal

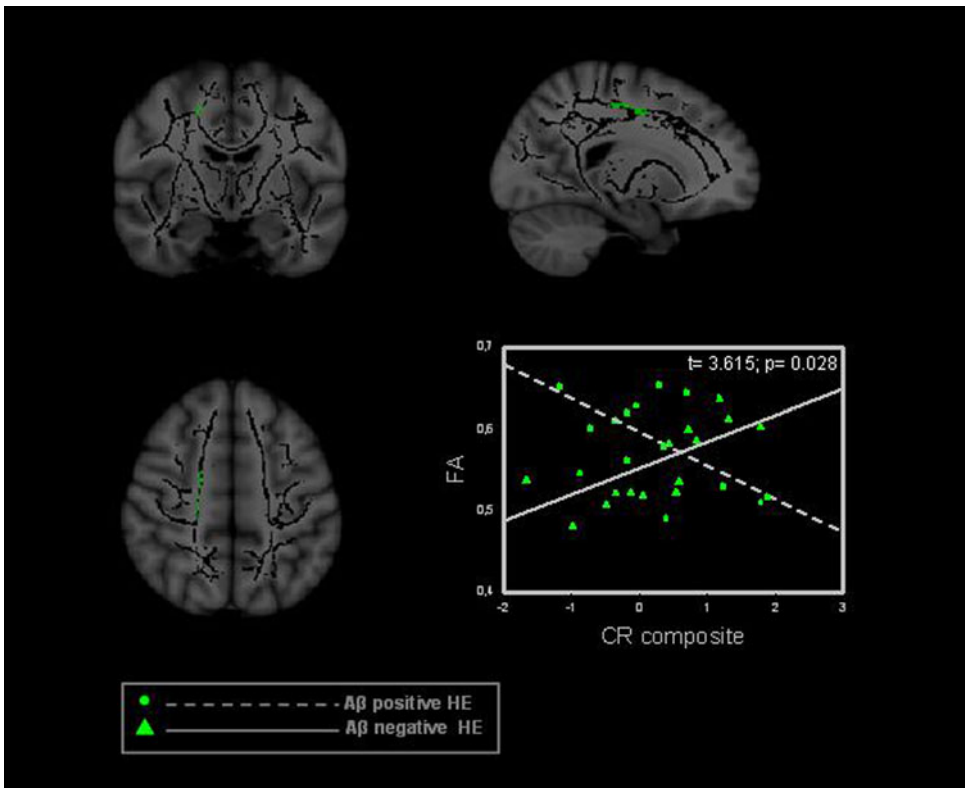

Fig. 2 Interaction between white matter integrity (FA) and an estimation of cognitive reserve in elders with preserved cognitive function but differing for as CSF Aβ_{1-42} levels. Note that in subjects with abnormally low values (the Aβ positive HE group) the correlation is negative reflecting reduced white matter integrity in high CR individuals. This association is reversed in the group exhibiting normative CSF Aβ_{1-42} values (the Aβ negative HE group)

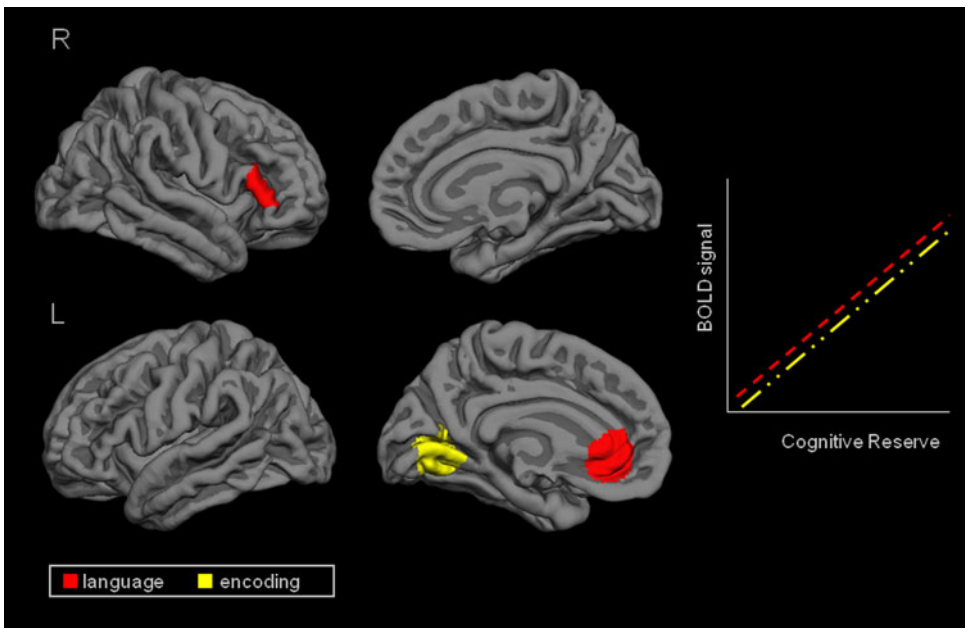

Fig. 3 Schematic representation reflecting the positive associations observed between CR composite measures, and brain activity in a language and memory encoding tasks in our patients (see also Fig. 4b for positive correlations between CR and fMRI signal in a complex visual task among MCI patients). Language activations reflect areas where correlation slopes between BOLD signal changes and CR were more positive for patients (MCI or AD) than for healthy elders

lobule. Of note, these fMRI findings were observed in the context of greater whole brain atrophy both in MCI and AD patients with high CR. This provides general support for the brain reserve conceptualizations.

Similarly, in our aforementioned DTI study, the expected negative associations between CR estimates and WM integrity where clearly reported in the patient groups. The affected regions were characteristic of AD, including relevant association, commissural, and limbic pathways (Bosch et al. 2010b) including all segments of the corpus callosum, the bilateral cingulate bundle, the inferior and superior longitudinal fasciculi, and the inferior fronto-occipital bundle (Arenaza-Urquijo et al. 2011). These findings align nicely with the only other available

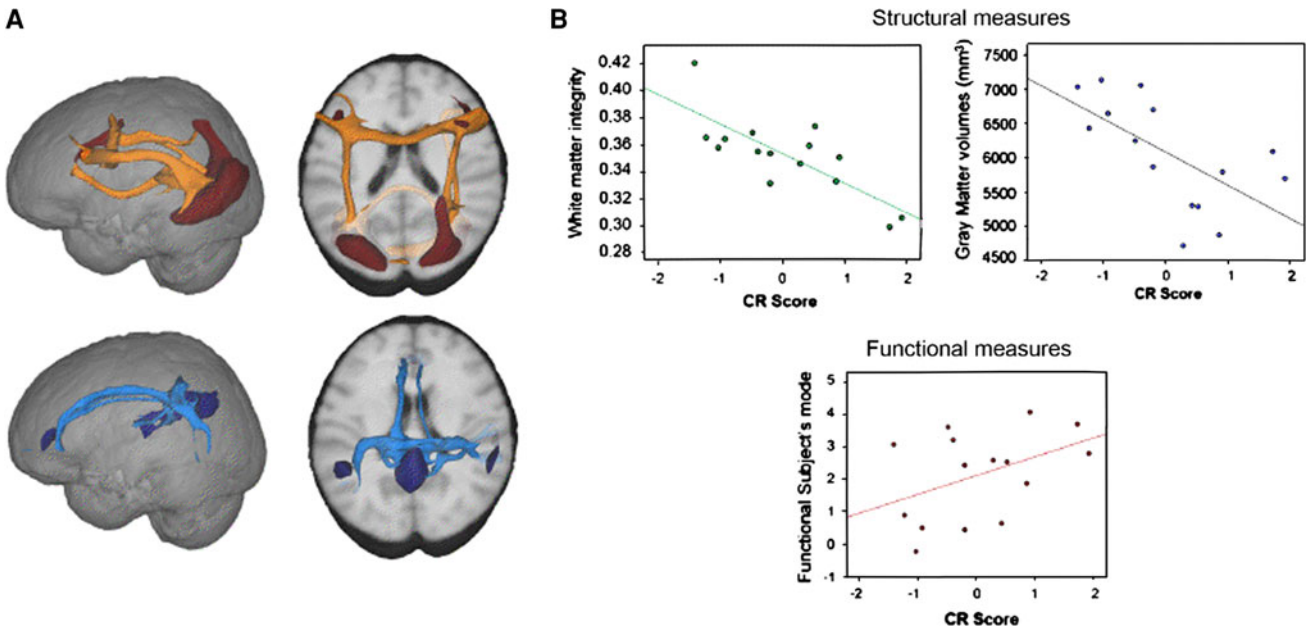

Fig. 4 **a** Multimodal integration of fMRI, DTI and cortical volumetric data showing a brain network related to complex visual processing among amnestic MCI patients (see main text). **b** Correlations between CR composite measures and the structural and functional components of this network. Note that higher CR MCI patients showed increased atrophy in cortical areas and reduced white matter integrity in the connecting fiber tracts. These patients also showed more robust activations and deactivations during task performance in the same cortical areas

investigation exploring a similar hypothesis (Teipel et al. 2009). This latter report, however, did not include an MCI group, for which we observed the strongest negative associations between WM integrity and CR estimates in 'AD-typical' areas. On the other hand, regions showing 'normal age-related' changes were much less involved in these negative associations. This fact reinforces the notion of regional specificity when exploring structural brain correlates of the CR construct. A further interesting finding (examined in greater detail below) is that, at follow-up, 5 of the 16 MCI patients had progressed to AD. These 5 cases had the highest scores in CR evaluations.

In the final two investigations that will be reviewed here we examined if functional and structural information derived from MRI acquisitions in MCI and AD patients could capture CR related reorganizations or compensations implicated in the performance of cognitively preserved tasks. We first used the passive language comprehension test (referenced above), a skill judged to be clinically unaffected both in a sample of MCI and early AD patients. This notion was confirmed as, prior to entering the scanner, it was verified all patients could understand the utilized sentences correctly and performed within normal limits in the Auditory Comprehension subtest of the Boston Diagnostic Aphasia Examination (BDAE, Goodglass and Kaplan 1972). In this report, as compared to healthy elders, we were able to demonstrate increased activity patterns in areas directly implicated in language processing (Fig. 3, language representation) and more marked deactivation of the DMN amongst both MCI and AD patients with higher estimations of CR. Accordingly, it seems that greater task-induced activations and greater reallocations of processing resources from the DMN occurred in these patients. These results can be viewed as evidences that, at least in early stages of dementia, high CR relates to facilitation of the deactivation of the DMN during cognitive demands. This is relevant as areas showing BOLD changes comprised posteromedial regions, which are critically affected in the early stages of dementia (Minoshima et al. 1997; Scahill et al. 2002; Anchisi et al. 2005; Pengas et al. 2010). Additionally, *deactivation* deficits in this location have a predictive role in the progression of MCI to dementia (Petrella et al. 2007).

Anatomofunctional covaraitions related to CR estimates were further corroborated in a posterior study including pure amnestic MCI patients and employing an adaptation of a visuoperceptive test validated in this population (Rami et al. 2007). Here, as in the previous investigation, we verified that all patients included performed within normal limits in this test for age, gender and educational norms (this was, in fact, the reason why this study was only focused on MCI—we were unable to determine normal cognitive functioning amongst AD patients). This investigation included multi-modal MRI, integrating fMRI, DTI, and GM-volumetry measurements. Our first analyses combined fMRI data with and independent component analysis (ICA) to describe the functional network whose

BOLD signal time-courses covariated positively with processing of complex visual stimuli and negatively with the DMN (Sala-Llonch et al. 2010a). The fMRI results served as the basis to define the underlying anatomical network whereby we extracted gray matter volumes of the activated and deactivated regions and estimated the integrity of WM fibers connecting the involved cortical regions (Fig. 4a). As regards to CR, and in clear accordance with our previous findings, we observed that MCI cases with higher estimates of CR showed more atrophy in the cortical GM areas of this network and reduced integrity in the fibers connecting these regions. Complimentarily, the brain activity of patients with high CR estimates suggested a greater need to employ functional brain resources (Sala-Llonch et al. 2010b, Fig. 4b).

Summary and Further Directions

Reversed Associations Between CR Estimates in Both Functional and Structural Brain Measures in Patients and Healthy Elders

Among patients, our studies globally support the BRC hypothesis in its more basic conceptualization. Accordingly, when we studied patients at a comparable level of clinical severity (all MCI cases included were of the amnestic type and of similar clinical level of alteration—all AD patients were mild, GDS = 4), high reserve patients appeared to have an increased ability to cope with neuropathology (Katzman et al. 1988; Snowdon 2003) as reflected by increased whole brain (Solé-Padullés et al. 2009), gray matter (Sala-Llonch et al. 2010b), or WM (Arenaza-Urquijo et al. 2011) damage. In this vein, the most novel of our findings is that WM microstructural damage in MCI patients with high reserve reflects WM areas typically damaged during AD. Further, we observed that those MCI patients with higher reserve (greater WM damage) more commonly progressed to AD in our follow-up study (Arenaza-Urquijo et al. 2011). At a functional level it should be noted that across all the cognitive domains tested (memory encoding, language comprehension, and complex visual functions) we always observed positive associations between CR estimates and BOLD activity that showed more positive associations in patients than in controls (except for deactivations of the DMN). In general, these findings suggest that in early or prodromal stages of dementia, the overuse of functional networks has the potential to counteract structural brain deficit. This capacity is particularly maintained in high CR patients, despite more advanced neuropathological damage.

Conversely, among healthy elders, our findings evidence positive associations between brain volumes or measures of integrity and estimates of reserve. Our DTI study (excluding those individuals with preclinical AD—positive for CSF biomarker) confirms that positive relationships prevail and that previous negative associations (i.e. Querbes et al. 2009; Coffey et al. 1999) may have been confounded by this or other factors. Within this context, fMRI results evidenced decreased BOLD responses among high CR elders across episodic memory, working memory, and language domains. In general, these findings align with the concept of increased neural efficiency in high CR individuals (i.e. less activity for same performance). According to the CR terminology (Stern et al. 2009), increased neural compensation may also explain our findings if the networks covariating with CR were different in healthy elders than in young individuals (i.e. they were using alternate networks as the ones employed by the 'optimal' young brain). However, we did not include this latter group in our fMRI studies.

Overall, the impact of CR among healthy elders may reflect some sort of neuroprotection. This suggests that lifetime variables linked to high CR do not moderate the relationship between brain burden and cognitive functioning, but act directly upon brain health (Christensen et al. 2009). One important conceptual point when measuring reserve (as presented here) is that structural and functional neuroimaging findings in aged populations are thought to reflect *accumulated effects of lifetime exposure* to particular environments. On the other hand, interventions based on augmenting complex mental activity during senescence may help to slow the rate of age-related cognitive decline (Gates and Valenzuela 2010). Under this assumption, it might be interesting to employ advanced neuroimaging techniques to directly compare groups of elders that have similar overall estimations of CR but distinct lifetime reserve factor periods. For example, exposure to high quality intellectual, social, or physical environments during childhood and early adulthood may have a greater impact on the ageing brain than similar exposure during advanced adulthood. However, the possibility also exists that 'late-life only exposure' may result in clear, positive manifestations, including reduced impact of age-related brain changes. From a neuroimaging standpoint, it would be interesting to study if associations between CR measures and cerebral network reorganizations during cognitive demands are qualitatively comparable across such groups. Such information could help to provide scientific bases for implementing integrative education programs combining intellectual, social, and physical stimulation—particularly among old-adults or elders that were raised in unfavorable environments. Current approaches to measure CR, such as that developed by Valenzuela and Sachdev (2007) which separate evaluations into distinct lifetime periods (before 30 years, 30–60 year, and after retirement), in combination

with advanced neuroimaging techniques should help to shed light on this and similar issues.

Specific and General Brain Networks for Reserve?

Using both structural and functional MRI technologies in healthy elders and patients, we have observed that the neural implementation of reserve entails regional specificity and that this effect depends upon both the population considered and the cognitive domain tested. For example, WM integrity associations with CR shifted from typical age-related areas in the healthy elder group to AD-typical regions in MCI and AD patients (Arenaza-Urquijo et al. 2011; Bosch et al. 2010b). Further, in our first fMRI study, higher expression of brain networks in the fusiform or lingual gyri as a function of CR were observed in AD patients as compared to healthy elders. This likely reflects reorganizations due to compensatory functional responses in the face of either neuropathological abnormalities in these particular regions or secondary changes in response to damage in earlier affected structures (i.e. entorhinal cortex; Solé-Padullés et al. 2009). These results are in accordance with previous findings (Pernezcky et al. 2009) using PET and demonstrating education mediated attenuation of the impact of brain damage on everyday functioning in BA 19, a region know to be primarily affected by pathology in dementia patients with Lewy bodies.

CR also appears to modulate brain activity in the networks activated during specific cognitive tasks. In this vein, and despite the fact that we performed whole brain analyses in the working memory (Bartrés-Faz et al. 2009) and language studies (Bosch et al. 2010a), CR negatively covariated with BOLD signals in brain regions related these cognitive functions. The topographical map of covariations between CR and brain activity in the language (Bosch et al. 2010a) and visuoperceptive (Sala-Llonch et al. 2010b) studies, in addition to supporting regional specificity, further provide evidence that functional reorganization occurs as a function of CR during the performance of low-difficulty tasks both in healthy elders and patients.

Despite these observations, a more general inspection of our results reveals that changes of brain activity as a function of CR in areas of the medial and lateral portions of the frontal lobes are a common. Thus, among healthy elders, negative correlations were observed in the inferior precentral gyrus (BA 6) in the WM study (Bartrés-Faz et al. 2009) and the medial frontal gyrus (BA 6) and anterior cingulate (BA 24) in the memory encoding study (Solé-Padullés et al. 2009). Similarly, in the language study, more negative correlations in the inferior (BA 44, 46), middle and superior frontal (BA 6) gyri and the anterior cingulate cortex (BA 24, 32; Bosch et al. 2010a) were reported for healthy elders than for patients. These results are reminiscent of an earlier fMRI investigation which implied the superior, middle, and medial frontal lobes were related to CR across two working memory tasks with two levels of difficulty (Stern et al. 2008). Though it may be argued that these regions represent further task-specific associations, an alternate view suggests they reflect a general 'cognitive reserve network' linked to control processes (Stern 2009). Under this assumption, this network would not be linked to any task-specific function but, instead, to the overall capacity of the individual to cope with pathology or age-related brain changes.

Finally, it should be noted that based on functional age-related changes, two models of neural compensation have been proposed, which could also partially account for the frontal lobe activations reported above linked to CR measurements. The HAROLD model (Cabeza 2002) posits that hemispheric asymmetry reduction occurs in prefrontal cortex in old adults compared to young. Even if this model was firstly noted in episodic memory retrieval, it has been largely supported by functional neuroimaging evidence in other domains (working memory, perception and inhibitory control; for a review see Dolcos et al. 2002). Thus, in the line of our conclusions when considering CR mechanisms it seems that this asymmetry change in older adults is reflective of a general aging phenomenon rather than a task-specific occurrence (Cabeza 2002). In direct support of the HAROLD model as a compensation mechanism, there is further the recent observations by Manenti et al. (2011) using repetitive transcranial magnetic stimulation (rTMS) to transiently interfere both encoding and retrieval associative memory processes in healthy older adults. The authors observed that left DLPFC rTMS during encoding only resulted in a disruptive effect among elders exhibiting low memory performance at baseline but not among high performing elders, suggesting that the underlying mechanisms supporting memory accuracy in this latter group imply more distributed, recruitment of the contralateral DLPFC to counteract age-related functional brain loss. The second model, the PASA model reflects a posterior-anterior shift in aging and has been typically attributed to functional compensation. PASA model posits an age-related reduction in occipitotemporal activity coupled with an age-related increase in frontal activity. This pattern was first reported in a PET study (Grady et al. 1994) studying perception of faces and locations. Although it was suggested as a compensatory mechanism for sensory processing deficits, it has been observed across different cognitive (attention, visual perception, visuospatial processing, working memory, episodic memory encoding, episodic memory retrieval; see Davis et al. 2008).

Both, HAROLD and PASA models imply that more distributed or shifted brain activity within the frontal lobes reflect functional compensatory mechanisms, in the sense

that elders able to recruit these patterns more effectively exhibit better performances in cognitive evaluations. Therefore the association between frontal lobe activity as a fundamental compensatory mechanisms is generally aligned with the abovementioned conclusions of CR studies. It should be noted however that as suggested by Stern et al. (2003) and employed in the present review, the definition of compensation linked to CR is not necessarily related to the maintenance of *optimal* function but to concept of efficiency (in healthy elders) or to allow some degree of function, even if it is less effective than 'normal' function (Stern et al. 2003).

Overall, our findings support the notion that CR is expressed through both regionally specific areas and common brain networks. Concerning this later claim, it should be noted that we have provided the first available evidence indicating CR estimations modulate DMN activity in the face of cognitive demands. Complex brain functions depend critically on dynamic interactions between distributed brain regions transiently interacting to perform a particular neural function. Abnormalities in the interactions of network components play a critical role in common and devastating neurological and psychiatric disorders including dementia. Furthermore, damage to specific functional connectivity networks can lead to distinct neurological syndromes (Seeley et al. 2009). To date, the DMN represents the best-characterized large scale human brain network and its activity can be investigated at rest or during task demands where its fluctuations covariate during a variety of distinct cognitive processes (including self-referential thinking, autobiographical memory, envisioning the future, theory of mind or moral decision making—Buckner et al. 2008).

In our study, we investigated deactivations of the DMN anatomical areas within the context of a language task and found that CR did, indeed, modulate its activity. However, most recent fMRI techniques studying functional connectivity within brain regions, rather than simply activation measured as the strength of the BOLD signal, have confirmed that connectivity is also impaired in dementia populations (Greicius et al. 2004), and in at-risk subjects (Hedden et al. 2009; Mormino et al. 2011). Functional connectivity measures are also known to be related to the cognitive performance in healthy aging (Sambataro et al. 2010). Finally, Fleisher et al. suggested that functional connectivity as studied with resting-fMRI paradigms might be more appropiate than typical task-activation paradigms to identify functional pathology associated with risk of dementia (Fleisher et al. 2009). Together, all these findings suggest that the functional connectivity patterns within the DMN would show modulations as regards CR estimations among HE and early dementia patients. Future research should investigate if some of the other characterized 'large scale networks', such as those linked with cognitive or control mechanisms (see Van den Heuvel and Hulshoff Pol 2010 for a review of the principal resting-state networks), show particularly strong associations with CR estimates in healthy ageing and how this is modified by progressive neurodegeneration.

Coupling Between Brain Function and Structure Related to the Reserve Construct

Results summarized thus far provide support and evidence in support of the brain reserve hypothesis and the cognitive reserve hypothesis (Stern 2002). Direct comparisons or analysis of both brain structure and function relative to CR were undertaken in two of our studies. The first focused on healthy elders and used biological parametrical mapping (BPM) for a precise voxel-by-voxel corregistration between fMRI patterns linked to an N-back task and regional GM volumes, both regressed against composite CR estimates. As reported above, neural efficiency for those with high CR (reflected by reduced activations within the same level of behavioral performance) was entirely accounted for by the underlying GM volumes in those specific regions. The second investigation studied the same functional and anatomical substrates as a function of CR within MCI patients and combined fMRI, GM, and DTI. Here it was also evident that fMRI activity increases coexisted with underlying cortical atrophy and loss of WM integrity in the precise connecting pathways. However, in a later study utilizing a passive language task, we could not find changes in the observed associations between CR estimates and fMRI activation or deactivation responses when analyses were adjusted according to gray matter volumes. This latter result may suggest that when the cognitive task tested is very simple or automatic, active compensatory brain mechanisms are more sensitive and better reveal brain changes linked to CR proxies.

Present and future approaches to the study of reserve

Since different approaches, applications and suggestions for advancing in the field of reserve have been deeply discussed (see Satz et al. 2010; Jones et al. 2011) the aim of this section is to summarize and briefly address a few suggestions to develop new and possibly more sensitive measures or indexes of reserve.

Firstly, as pointed out by Stern (2009), cognitive processes linked to CR have a physiological basis and exposure to CR environments during neurodevelopment results in changes in brain structure. Similarly, brain responses associated with complex mental activity or CR, such as molecular changes, neurogenesis, synaptogenesis, dendritic field size changes, or angiogenesis (reviewed in Valenzuela and Sachdev 2006), are difficult to situate within the

'dynamic-static' continuum of brain changes. In this complex scenario an approach based on MRI technology and without longitudinal data can only partially capture the interactions that influence brain changes linked to reserve. Still, at this broad level, our findings indicate that in general inter-individual differences linked to the expression of CR networks cannot be fully understood without taking into account the precise underlying brain anatomy. Hence and when focusing on neuroimage techniques, further neuroimaging studies of CR should combine functional and structural brain connectivity analyses to advance the investigation of the intimate relationship between structural and functional components of CR. For example, the application of methodology allowing for the investigation of spatial patterns common across different MRI modalities (specifically DTI and resting-state) such as joint ICA (Teipel et al. 2010) may provide important information relevant to the field of CR. Similarly, examining the efficiency, clustering, and/or centrality of complex networks via the construction complex interregional correlate graphs (Zhu et al. 2010) or other multi-level techniques (Bullmore and Bassett 2011) may reveal datum which may further propel the field of CR forward.

Secondly, as stated above, with the shift of the conceptual paradigm in the early detection of dementia towards the use of biomarkers (Jack et al. 2010a, b), advances in imaging neuropathology, notably amyloid but eventually other markers, in combination with the study of CSF profiles, may offer a new paradigm to study reserve along the continuum from healthy subjects to AD patients. Particularly, since amyloid burden has been suggested as an early, accurate diagnostic tool for AD (Mathis et al. 2007; Weiner 2009), the contribution of these studies to the assessment of reserve could partially cope with some of the limitations mentioned in the introduction, providing an objective measure of brain burden. Thus, it is possible now to study patients with the same level of pathology and different cognitive strengths and more interestingly, healthy elders harboring AD pathology, defined as preclinical AD in the new lexicon (Dubois et al. 2010). In our view, understanding the neuroprotective mechanisms of these subjects showing no cognitive decline despite AD pathology could be a key to understand the cerebral basis of reserve. If neuroprotective or compensatory mechanisms are explaining the delayed onset of symptoms, identifying those mechanisms and the associated variables (i.e. level of education) could provide a new perspective to the study of reserve. In this regard Cohen et al. (2009) observed predominantly negative correlations between metabolism and PiB retention in AD but positive correlations within MCI group suggesting that higher basal metabolism might be a mechanism of brain reserve protecting against clinical conversion from MCI to AD. Finally, greater temporal volume in healthy controls harboring amyloid deposition has been described (Chetelat et al. 2010). This result might be interpreted as a brain reserve or compensatory mechanism delaying the effects of β-amyloid on cognition. Overall, these studies provide evidence consistent with CR hypothesis using variables as markers of CR (Kemppainen et al. 2008; Roe et al. 2010; Rentz et al. 2010) or directly suggesting BRC mechanisms (Cohen et al. 2009; Chetelat et al. 2010).

Finally, besides the terms of 'compensation' (Cabeza 2002), 'neural reserve' or 'neural efficiency' (Stern 2009), the neural plasticity model can also conceptually account for the morphological and functional brain mechanisms linked to CR. Brain plasticity is an intrinsic property of the nervous system (Pascual-leone et al. 2005) and despite age limits the capacity for plastic changes (Wagner et al. 2000) it is maintained throughout all life-span (Pascual-leone et al. 2005; Greenwood and Pasasuranam 2010). In this light, a myriad of animal studies demonstrate structural and functional brain reorganizations or adaptations after exposure to enriched environments or to nervous system injuries (Draganski and May 2008). In a similar vein, neuroimaging investigations performed in old-adult humans have observed dynamic changes in brain structure after cognitive or physical training programs, resulting in expansions of gray (Boyke et al. 2008) and white (Colcombe et al. 2006) matter volumes including increased regional cortical thickness (Engvig et al. 2010), as well as a more effective usage of cortical functional networks, (Kirchhoff et al. 2011). These results are generally viewed as evidencing neuroplastic adaptations to adjust to perturbations in the external environment or internal milieu. Although the nature of the underlying cellular events accounting for these neuroimaging findings in humans is almost unknown, and may involve among others aspects such as glial proliferation, angiogenesis or neuogenesis (Draganski and May 2008), they might be primarily linked to spine and synapse turnover mechanisms, as adaptations can occur rapidly, within a range of a single week (Driemeyer et al. 2008).

Furthermore, in the ageing literature the Scaffolding Theory of Aging and Cognition (STAC; Goh and Park 2009) considers neuroplasticity as a fundamental mechanism accounting for the expanded brain activity and recruitment of additional areas (particularly in the frontal lobes), probably emerging to counteract the deleterious effects of increasing age on brain macroscopy, but also to boost hippocampal activity during learning through a top-down modulation process over dysfunctional core plastic mechanisms such as long term potentiation (LTP). In connection with the postulates of CR this model of neuroplasticity predicts that scaffolding and developing effective neural structures will be favored among individuals frequently engaging novel activities including new

learning, physical activity and participation in cognitive training programs.

In summary, conclusions raised from all these lines of evidence closely mirror the characteristics of brain function and structure related to CR measures reviewed in this manuscript. Therefore, one possible conceptual approach is to consider reserve as an index of plasticity. Within this view, lifetime exposure to high CR environments, interacting with genotype predispositions, could confer to particular individuals an increased cerebral plasticity potential. Here, and similarly as the two-step model of plasticity evoked by Pascual-Leone and coworkers (2005), lifetime exposure (particularly early life exposure) to high CR environments may impact onto the formation and development of the 'primary neural pathways' characteristics. Subsequently, when age-related or neuropathological brain changes emerge and individuals need to counteract them when confronted to particular social or cognitive challenges, this higher 'baseline adaptative neuroplasticity' may operate as providing greater dynamic capacity for adjusting and remodeling cortical modules (i.e. cortical circuits), particularly prefrontal networks (Mercado 2008). This would in turn favor more efficient cognitive processing strategies (Mercado 2008) or more stable behavioral phenotypes among patients in the initial stages of dementia. Within this idea in mind, a first step in this line of research could be to conduct investigations aimed to study the relationship between measures of cortical plasticity sensitive to the ageing process, such as the ones obtained by combining TMS with electromyography or electroencephalography (Freitas et al. 2011), with classical estimations of CR in HE and demented patients.

Acknowledgments Supported by a Spanish Ministerio de Ciencia e Innovación research grant (SAF2009-07489) to D.B.-F. E.M.A-U was funded by a predoctoral grant from the Generalitat de Catalunya. The authors thank Roser Sala-Llonch for her help during figure designing and Jared C. Horvath for his excellent review of the English language.

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