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**Amyloid positron emission tomography and cognitive reserve**

Bauckneht M *et al*. PET and cognitive reserve

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**Abstract**

Alzheimer’s disease (AD) is characterized by a non-linear progressive course and several aspects influence the relationship between cerebral amount of AD pathology and the clinical expression of the disease. Brain cognitive reserve (CR) refers to the hypothesized capacity of an adult brain to cope with brain damage in order to minimize symptomatology. CR phenomenon contributed to explain the disjunction between the degree of neurodegeneration and the clinical phenotype of AD. The possibility to track brain amyloidosis (Aβ) *in vivo* has huge relevance for AD diagnosis and new therapeutic approaches. The clinical repercussions of positron emission tomography (PET)-assessed Aβ load are certainly mediated by CR thus potentially hampering the prognostic meaning of Amyloid PET in selected groups of patients. Similarly, Amyloid PET and cerebrospinal fluid amyloidosis biomarkers have recently provided new evidence for CR. The present review discusses the concept of CR in the framework of available neuroimaging studies and specifically deals with the reciprocal influences between Amyloid PET and CR in AD patients and with the potential consequent interventional strategies for AD.

**Key words:** Cognitive reserve; Amyloid positron emission tomography; Mild cognitive impairment; Alzheimer disease; Brain

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**Core tip:** Given the large population of aging individuals and the consequent huge, progressive Alzheimer Disease (AD)-related healthcare costs, it is critical to find effective therapeutic strategies to mitigate the AD cognitive dysfunction. Accordingly, understanding the neurobiological mechanisms underlying cognitive reserve (CR) is of utmost importance. Instead, Amyloid positron emission tomography (PET) has recently improved our knowledge in the field of CR. The present review discusses the concept of CR in the framework of available neuroimaging studies and specifically deals with the reciprocal influences between Amyloid PET and CR in AD patients and with the potential consequent interventional strategies for AD.

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**INTRODUCTION**

AD is the most common neurodegenerative cause of dementia and affects around 10% of individuals over age 65 and up to 40% of individuals over age 85[1]. In 2010 it has been estimated that 4.7 million individuals aged 65 years or older were affected by AD in the United of States with the total number of people with AD dementia projected to be 13.8 million in 2050[1]. AD is characterized by a progressive deterioration in memory and other cognitive abilities as well as in capability for independent living. The course of AD is variable[2], but symptoms tend to develop over the same general steps: mild cognitive impairment (MCI) (which in typical forms begin with episodic memory impairment), slow, progressive affection of other cognitive domains and, eventually, dementia[3]. Amyloid deposition and tau pathology (neurofibrillary tangles, NFT) within the cerebral cortex are the neuropathological hallmarks of AD[4]. Several lines of evidence, demonstrated that AD is characterized by a non-linear progressive course and that several aspects may influence the relationship between cerebral amount of AD pathology and its clinical expression[3,5,6]. In fact, it has been shown that at least 20% of elderly people who are cognitively normal before death show postmortem findings sufficient to fulfill neuropathological criteria for AD[7,8]. On the other hand, several studies showed that biological factors such as the age of onset and the expression of Apolipoprotein E genotype, can be associated with a faster cognitive decline[9,10]. Similarly, increasing evidence has highlighted the role of oxidative stress in AD, because of the increased production of reactive oxygen species (ROS) and the influence of oxidative stress on brain energy metabolism[11].

Accordingly clinical expression of AD is critically affected by the resilience of the individual brain to molecular mechanisms and neuropathology[12]. These complex mechanisms have been historically referred to as Brain Cognitive Reserve phenomenon (CR[13]). CR refers to the hypothesized capacity of an adult brain to cope with brain damage in order to minimize symptomatology[13]. Individuals with high reserve are thought to have either higher number of neurons and synapses (“brain reserve”), and/or a better ability to put in place alternative strategies or compensatory mechanisms (“cognitive reserve”) than individuals with low reserve[12,14]. Therefore, CR phenomenon may also at least partially explain the disjunction between the degree of neurodegeneration and the clinical phenotype of AD.

In this framework it has been hypothesized that not only duration of formal education, but also the quality of performance throughout the years can influence CR and the general brain reaction to AD pathology in clinical terms[12]. First evidence for CR date back to the ‘80s, when neuropathological studies highlighted the existence of subgroups of cognitively intact subjects matching criteria for AD at autopsy[7]. In the following decades, structural (MRI) and functional (MRI, SPECT and PET) studies have confirmed the existence of CR and allowed a better comprehension and anatomical localization of this phenomenon. In more recent years, the availability of new molecular probes sensitive to amyloid-beta (Aβ) deposition have allowed the *in vivo* demonstration of amyloid load by means of PET (Amy-PET)[15-18]. The possibility to track Aβ pathology *in vivo* has huge relevance for AD diagnosis and clinical trials. The oldest and more extensively studied PET tracer for Amy-PET is the Carbon11 labeled Pittsburgh compound B (PiB)[15]. More recently three fluorine18 labeled compounds have been developed. Following multicenter Phase 3 trials, they were all approved both in the United States and Europe to *in vivo* image amyloid plaques[18-20]. Accordingly, appropriate use criteria have been now proposed for the use of Amy-PET[21]. Although obtaining *in vivo* information about the presence of amyloid pathology allowed a greater accuracy in the work up of patients with suspected AD, the clinical repercussions of PET-assessed Aβ load are certainly mediated by CR. In fact CR can potentially hamper the prognostic meaning of Amy-PET at least in selected groups of patients. On the other side CR phenomenon itself has gained renovated interest from the possibility of knowing and *in vivo* localizing Aβ load by means of PET thus providing further evidence for a more etiopathological effect of CR[22,23]. Therefore on the one side, Amy-PET [and cerebrospinal fluid (CSF) amyloidosis biomarkers] provide new evidence for CR, on the other side, CR has clinical and pathophysiological repercussion for the study of AD, especially now, in the era of brain amyloidosis biomarkers. The present review discusses the concept of CR in the framework of available neuroimaging studies and specifically deals with the reciprocal influences between Amy-PET and CR in AD patients and with the potential consequent interventional strategies for AD.

**CONCEPT OF COGNITIVE RESERVE: PIONEERING STUDIES**

Historically the first model proposed to explain CR was referred to quantitative measures of head circumference, brain size[24], and synaptic or neuronal count[25]. According to this approach, individuals with more neurons required more brain damage to reach a threshold of clinically evident dementia (passive model of CR). However, since the first studies on CR, subjects with either greater brain size, quantities of neurons or synapses were demonstrated to have different epidemiological/demographic features that can be responsible for CR and thus can serve as proxies for reserve. These factors include measures of educational attainment and socioeconomic status, such as income or occupational attainment. Similarly, physical activity and cognitive activity even during midlife have been associated with a reduced risk of AD[26,27]. However, since the first studies education has probably been the most widely used proxy for CR. In fact level of education is relatively easy to ascertain. Moreover, proposed model fitted to the epidemiological evidence that higher incidence of AD and other dementia was observed among elder populations with low levels of education[27]. However, this epidemiological approach lacks of anatomic localization and produces only indirect (based on neuropsychology) evidence about brain functional damage and networking[28].

**CONRIBUTION OF NEUROIMAGING TO THE UNDERSTANDING OF CR**

Due to these limitations many groups turned to functional neuroimaging approach, which is able to provide a more precise proxy measure about CR *in vivo*, thus allowing a more comprehensive understanding and localization of this phenomenon. In fact, while neuropsychological test results are influenced by the cognitive ability of the patient and his/her motivation to perform the tests, the imaging-assessed brain impairment more closelyreflects the underlying brain damage (*i.e.,* neurodegeneration). In this line, functional neuroimaging supported the idea that even when neurodegeneration is higher in educated individuals, the clinical phenotype of AD may be similar to those in patients with lower education and less pathology[14]. Based on this integrated approach, CR can be defined as the difference between an individual’s expected (based on neuroimaging) and actual (assessed by neuropsychology) cognitive performance.

To elucidate these mechanisms, several imaging studies have originally used resting regional cerebral blood flow (rCBF) PET measurement as a surrogate of AD pathology[29]. In these studies correlation between rCBF on one side and education and life-time activities score on the other was tested and an inverse correlation with rCBF in temporal-parietal-occipital areas was demonstrated in AD patients[29].

Similar results were obtained by means of 3D magnetic resonance imaging (MRI) analysis demonstrating that education increases regional cortical thickness in healthy controls, while it is inversely correlated with regional cortical thicknesses in temporal, parietal and occipital regions in AD patients[30]. Finally, FDG-PET studies demonstrated that reserve mechanism are already at work in patients with amnestic mild cognitive impairment (aMCI) and prodromal Alzheimer’s disease (pAD) patients[14,31]. In fact, even in this early stages, AD patients with higher education showed more severe and extended “posterior” AD typical brain hypometabolism with respect to poorly educated patients expressing the same level of cognitive symptoms[14,31]. This means that in early stage of disease CR may have meaningful repercussions for the clinical diagnosis of AD as highly educated prodromal AD patients can clinically hide the disease for a longer period of time. Accordingly, new lines of research focused on the mechanism(s) specifically allowing highly educated AD to cope with their greater brain damage. These mechanisms, evaluated by means of functional MRI and H215O PET activation studies as well with resting FDG PET, allowed to develop the so-called “active model” of CR[29,32]. As CR allows maintenance of effective function across a wide range of activities despite the presence of brain pathology, it can be hypothesized that a specific network (or multiple integrated networks) are able to sustain CR and thus patients’ cognitive function and independent activities of daily leaving[33,34]. To investigate this hypothesis, Stern’s group[35] carried out a fMRI study by scanning young and elder subjects while performing two different tasks underlying two different cognitive domains and activations were regressed onto putative CR variables. A common network was actually identified including bilateral superior and medial frontal gyri thus suggesting a central role of the frontal cortex in CR- mediating mechanism[35]. Another possible strategy to identify a specific CR network is the so-called metabolic connectivity analysis of brain 18F-FDG PET studies[36]. In fact by calculating correlation coefficients -or pattern of intercorrelations- between values of FDG uptake, it is possible to estimate the functional association between cerebral areas[36]. Therefore interregional correlations of metabolic glucose rates can be regarded in terms of “traffic (metabolic-functional connectivity) in the anatomical ‘roads’ present in the brain” which, by contrast, can be investigated by other neuroimaging methods such as diffusion tensor imaging’[37,38]. Morbelli *et al*[14] investigated functional mechanisms underling CR in 64 early stage AD patients and 90 healthy controls who underwent brain 18F-FDG PET. Highly and poorly educated subjects were compared bidirectionally and with age and education-matched controls. It was indeed demonstrated that although AD-typical damage is more prominent in highly educated subjects, highly educated pAD have also a relatively higher metabolic levels with respect to poorly educated patients in the right inferior, middle, and superior frontal gyri with respect to less educated AD subjects.

These regions, which corresponded to the right dorsolateral prefrontal cortex (DLFC), were then included as covariates in the subsequent metabolic connectivity analysis in highly and poorly educated AD patients. As the results, in highly educated AD patients, metabolism of the DLFC correlated significantly with that of several cortical areas in both hemispheres, while it was basically only auto correlated in poorly educated AD. Accordingly this metabolic connectivity analysis supports the existence of a network mediating CR and is anatomically consistent with a crucial role of lateral frontal cortex in CR-mediating mechanism. However, all these analyses did not completely elucidate whether these functional networks are due to preserved functional connections that are physiologically present in more educated subjects (*i.e.*, the brain reserve component of cognitive reserve) or to the recruitment of alternative neural networks able to support cognitive function just in the presence of disease related damage elsewhere (*i.e.,* the brain compensation component of cognitive reserve)[33]. To specifically address this aspect, the same analysis was extended to the control groups and demonstrated that the large bilateral fronto-temporal-limbic metabolic network related to CR was actually present and topographically similar in highly educated controls. However this network was quantitatively less pronounced with respect to highly educated AD patients thus demonstrating that CR in early AD patients with a high level of education is a result of both neural reserve and neural compensation[14]. The importance of reinforcement in brain connectivity in healthy elders was further confirmed in a multimodal imaging study involving thirty-six healthy elders presenting normal cognition and a negative florbetapir-PET scan[39]. In fact, seed connectivity analyses of resting state fMRI showed that education was positively related to the magnitude of functional connectivity between the anterior cingulate cortex and the hippocampus as well as the inferior frontal lobe, posterior cingulate cortex and angular gyrus.

**IMPLICATION OF CR FOR CLINICAL USE AMYLOID IMAGING.**

Amy-PET offers great promise to facilitate the evaluation of patients in a clinical setting, to improve our understanding of AD pathophysiology and to advance the development of effective therapy.

*In vivo* PET studies have shown an increased uptake of amyloid ligand 11C-labeled Pittsburgh Compound B ([11C]PIB) and fluorinated Amy-PET tracers in AD and mild cognitive impairment patients, especially in the frontal, parietal, and temporal cortices and in the posterior cingulate, which indicates an increased amyloid accumulation in these areas[40,41]. However, in agreement with reports that significant Aβ deposits can be found in the brain of cognitively normal elderly individuals at autopsy, Amy-PET studies revealed that 20%-40% of cognitively unimpaired individuals over the age of 65 years can have brain uptake above a predetermined threshold for AD in at least one region of interest[42,43]. This evidence can be at least partially linked to CR phenomenon. In fact it was further demonstrated that even in patients with AD, the well-known greater posterior hypometabolism present in highly educated pAD is paralleled by a greater Amy-PET tracer’s uptake especially in the ventrolateral frontal cortex[44]. While only longitudinal evaluation of Amy-PET positive cognitively normal subjects can allow to access their long term outcome, this evidence have important diagnostic repercussion. In fact as CR is influenced by several (often measurable) epidemiological and social factors, these factors could be taken into account to support the final diagnosis of probable AD by means of Amy-PET or CSF amyloidosis biomarkers. Kemppainen *et al*[44] tested this hypothesis by assessing whether factors thought to influence the association of AD pathology and dementia help to accurately identify dementia of the Alzheimer type when considered together with Amy-PET. They generated receiver operating characteristic curves to compare the predictive accuracy of using Amy-PET alone or Amy-PET together with the above mentioned factors with the aim to tell apart AD patients from subjects with normal cognition. In this study, factors reported to influence associations between AD pathology and dementia demonstrated to improve the predictive accuracy of amyloid imaging for the identification of symptomatic AD. In fact, if a scan is performed and found positive (*i.e.,* in depressed patients with concurrent cognitive impairment), the risk of incidental brain amyloidosis must be taken into consideration when defining probable diagnosis and planning subsequent management[45]. In this scenario high prognostic value of Amy-PET is present in case of a negative scan thus virtually excluding AD and encouraging a more vigorous evaluation of alternative diagnoses and treatment (for example when differential diagnosis was defined with respect to depression)[45]. By contrast to exclude the presence of “incidental” positivity of Amy-PET the use of different biomarkers (*i.e.,* biomarkers of neurodegeneration) can be proposed to support a diagnosis of AD. In fact glucose hypometabolism as assessed by means of 18F-FDG PET as well as brain atrophy are more directly associated with neurodegeneration and thus with concurrent cognitive function[46]. Noteworthy, if CR phenomenon is at work, PET-assessed hypometabolism might be markedly reduced even in presence of a mild cognitive impairment. The validity of this approach have been recently confirmed by a large retrospective multicenter study showing that, in clinical setting, the combined use of both amyloid and neuronal injury markers offers the most accurate prognosis in MCI patients[47]. Besides underlying the importance of integrating Amy-PET with neurodegeneration biomarkers, the issue of positive Amy-PET in cognitive normal subjects further supports the need of a standardized approach to Amy-PET quantification. In fact, to date there’s still considerable variability in the numbers reported as quantitative outcome measures of tracer retention. Many international efforts are ongoing to address the problem of Amy-PET quantification[48]. Besides the increased accuracy and consistency potentially provided by tracer binding quantification, a further possible benefit would be related to the possibility of defining three ranges of amyloid deposition: (1) the amyloid-negative range; (2) the “AD-like” range; and (3) the “just-positive” range[48,49]. A greater comprehension of this latter range may be of interest to better differentiated ‘incidental’ amyloid load from amyloid load in the AD-like range in cognitively intact subjects with greater CR.

**IMPLICATION OF AMYLOID IMAGING FOR COMPREHENSION OF CR**

Many implications have been derived from CR for the clinical use of Amy-PET. Similarly, CR has gained new evidence and new interest from the availability of Amy-PET. As mentioned, patients with mild AD dementia and higher education (*i.e.,* 15 or more years of education) were found to have higher uptake of amyloid PET tracers in the frontal cortex compared with patients with lower education (*i.e.,* 6 years of education)[6]. These results confirm that highly educated individuals manifest mild AD later on in the clinical course of the disease when more Aβ pathology is present thus supporting CR hypothesis.

However the availability of this information during life and the possibility to correlate this finding with other biomarkers have provided novel evidence for CR. This information can be relevant for AD model approach and biomarkers cascade in more comprehensive way. In fact, Chetelat *et al*[50] correlated Amy-PET and brain structure data and cognitive performance in subjects with and without memory complaints. They demonstrated that Amy-PET positive subjects without memory complaints had larger temporal lobes and better verbal learning performance than Amy-PET negative controls. On the opposite, Amy-PET positive subjects with subjective memory complaints had smaller regional brain volumes and worse global cognition than Amy-PET with memory complaints. Altogether these finding allow to propose a general model of interpretation. In fact the larger temporal lobes may have been crucial for Amy-PET positive subjects to maintain their cognitive ability while Amy-PET positive subjects with memory complaints might originally have less gray matter than those without memory complaints, and therefore had less CR[50,51]  (Figure 1). Accordingly the availability of Amy-PET and this multi-biomarker approach provided *in vivo* evidence that improving brain structure (*i.e.,* through cognitive or physical activity) may help compensate for AD related damage.

**NEW PERSPECTIVE ON AMYLOID PET AND CR**

Given the large population of aging individuals and the consequent huge, progressive AD-related Healthcare Costs, it is critical to find effective therapeutic strategies to mitigate the AD cognitive dysfunction. Understanding the neurobiological mechanisms underlying CR is thus of utmost importance. First studies trying to simulate, measure and possibly influence the effect of CR on AD were performed in animal models. Environmental enrichment paradigms has been developed in rodents by manipulating the complexity of their social, cognitive, and sensorial environments[52]. These models are ideal to experimentally measure the effect of environmental stimulation on cognitive reserve. In addition, previous studies demonstrated that environmental enrichment triggers structural and biochemical modification on neurons[53], stimulates hippocampal neurogenesis in adult animals[54] and attenuate cognitive decline in transgenic models of familial AD[55]. Animal models may also serve to better define the specific age and time-frame in which exposure to environmental enrichment can still trigger functional compensation and mitigate memory dysfunction. Finally, the effect of environmental stimulation on neuropathological hallmarks of AD can be assessed ex vivo for example in mouse model of the disease. In this framework, Verret *et al*[22] examined whether exposure of a Tg2576 transgenic mouse model of AD to environmental enrichment at a specific period during the amyloidogenic process favored the establishment of a cognitive reserve. They demonstrated that environmental stimulation during early adulthood of mice—before amyloidogenesis has started - reduced the severity of AD-related cognitive deficits more efficiently than exposure later in life, when the pathology is already present. More importantly they highlighted *ex vivo* that, early-life environmental stimulation, slightly reduced forebrain surface covered by amyloid plaques (while not significantly impact remodeling in the hippocampus). These findings may open new scenarios related to the effect of CR in AD patients as they might suggest that cognitive activity may even modify amyloid deposition, rather than just compensating for it[51]. Amy-PET and CSF biomarkers may allow to test this hypothesis *in vivo* in humans. In this framework, Landau *et al*[17] aimed to assess the association between lifestyle practices (cognitive and physical activity) and β-amyloid deposition, measured with positron emission tomography using carbon [11C]-PIB, in healthy elderly. Greater participation in cognitively stimulating activities across the lifespan, but particularly in early and middle life, was associated with reduced [11C]PIB uptake (taken into account age, sex, and education). Moreover, among older controls, those who were more involved in cognitively stimulating activities across the lifespan (especially during young and middle age) had brain amyloid levels comparable to young controls, while those who were poorly cognitively active had amyloid levels similar to AD patients. Other studies reported that CR-related factors such as physical exercise correlated with less Aβ accumulation, however results are not always consistent. In fact in some cases those effects reached significance only in ApoE4 carriers[56] and in other studies no evidence was highlighted concerning an effect of lifetime cognitive stimulation on the level of Aβ accumulation regardless of ApoE genotype[57].

Accordingly is still a matter of debate if cognitive/physical stimulation can really modify the underlying pathology of AD or if CR just gives a resilience to it (as in the original definition of CR[13]). However even in this latter case the availability of amyloidosis and neurodegeneration AD biomarkers can further clarify and possibly localize mechanism of resistance to AD-related damage. In other words: should we just define CR as the use of pre-existing and/or compensative network or can we hypothesized that brains/neurons in subjects with higher CR may be less damaged by AD-related pathology and thus may demonstrate less neurodegeneration? A first answer to this question has been provided by Almeida *et al*[58] who aimed to measure whether cognitive reserve could weaken the relationship between age and AD biomarker levels. A cross-sectional cohort of 268 individuals (211 cognitively normal and 57 cognitively impaired subjects; average age 62 years) was evaluated with respect to Aβ42, t-tau, and p-tau immunoassays. The authors found that the difference in CSF phosphorylated tau (p-tau) and total tau (t-tau) between younger and older people was larger in subgroup of subjects with less than 16 years of education than it was in the subgroups with at least 16 years of schooling. These findings suggest that education could attenuate age-related increment in CSF p-tau and t-tau and might suggest a more general effect on age-related neurodegeneration. However, although raising interesting possibility and stimulating new interventional strategies in AD patients, this evidence need to be further tested especially with respect to its relevance for the future onset of dementia. In the next future, the availability not only of Amy-PET but also of Tau imaging (and thus the possibility to quantify and anatomically localize neurodegeneration[59]) will allow to track and localize the pathological biomarkers cascade of AD in earlier stage of the illness (Figure 1). In fact, given models in which molecular pathologic changes (β-amyloid deposition) may temporarily precede neurodegeneration by a substantial of time period[60], evaluation of just one of these two types of biomarkers do not allow to direct measure resilience to AD-related damage. Once entity, time-frame and individual peculiarity of this resilience will be identified, a more precise model of CR and its consequences on AD clinics will be defined thus finally elucidating (and selecting patients) for CR-related interventional approaches.

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**Figure 1** **Schematic representation of the possible mechanisms mediating the effect of cognitive reserve** **on the onset of Alzheimer’s dementia and corresponding expected results on 18F-FDG and amyloid positron emission tomography.** According to hypothesis (A) cognitive reserve (CR) would simply delay the clinical expression of the disease. In fact despite amyloid positron emission tomography (PET) and FDG PET marked positivity patients are able to delay symptoms thanks to compensative functional networks and/or structural features such as larger temporal lobe volume[14,51]. Hypothesis (B) admits an opposite scenario in which, CR would prevent/delay amyloid deposition and Alzheimer’s dementia (AD) pathology and thus neuronal damage and dementia onset[17]. Finally hypothesis (C) could coexist with either of the first two and would explain the effect of CR as a sort of brain resilience despite AD pathology thus allowing a relatively preserved 18F-FDG PET scan for a longer period of time[59]. Amy-PET: Amyloid PET; ++: Markedly positive scan; +: Positive scan; -: Negative/relatively preserved scan.