

# How the cognitive reserve interacts with $\beta$ -amyloid deposition in mitigating FDG metabolism

## An observational study

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### Abstract

This observational study had the aim to assess the interaction between cognitive reserve (CR) and cerebrospinal fluid  $\beta$ -amyloid<sub>1-42</sub> ( $A\beta_{1-42}$ ) in modulating brain [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) metabolism in patients with moderate Alzheimer disease (AD).

Twenty-seven patients with probable AD and 25 neurological normal subjects (NNS) entered the study. All participants had an FDG-PET scan, and AD patients also received a lumbar puncture to measure  $A\beta_{1-42}$ , 181p-tau, and Tau concentrations. Based on years of formal education, AD patients were classified as highly educated-AD (years of formal education >5) or less educated-AD (years of formal education <5). By using a voxel-wise approach, we first investigated differences in the cerebral glucose uptake between AD and NNS, then we assessed the interaction between level of education (a proxy of CR) and cerebrospinal fluid biomarkers on FDG-PET metabolism in the patient groups.

Significantly lower glucose uptake was observed in the posterior cingulate gyrus, in the precuneus, in the inferior and medial temporal gyrus, and in the inferior parietal lobule of AD patients compared with NNS. A significant interaction was found between CR and  $A\beta_{1-42}$  values on brain metabolism in the inferior and medial temporal gyrus bilaterally.

The AD patients with higher CR level and marked signs of neuropathology showed glucose hypometabolism in regions typically targeted by AD pathology. This finding supports the hypothesis that CR partially compensates for the effect of  $A\beta$  plaques on cognitive impairment, helps in patients' clinical staging, and opens new possibilities for the development of nonpharmacological interventions.

**Abbreviations:** 181p-tau = hyperphosphorylated tau at threonine 181,  $A\beta_{1-42}$  =  $\beta$ -amyloid<sub>1-42</sub>, AD = Alzheimer disease, ADL = activities of daily living, CD = clock design, CR = cognitive reserve, CSF biomarkers = cerebrospinal fluid biomarkers, CT = computerized tomography, F = female, FAB = frontal assessment battery, FDG-PET = [18F]fluorodeoxyglucose positron emission tomography, GDS = 15-Item Geriatric Depression Scale, GU = cerebral glucose uptake, HE-AD = highly educated-AD, IADL = instrumental ADL, LE-AD = less educated-AD, M = male, MMSE = Mini Mental State Examination, NNS = neurological normal subjects, ROIs = regions of interest, SD = standard deviation, Tau = total tau.

**Keywords:** Alzheimer disease, cognitive reserve, CSF biomarkers, FDG-PET

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## 1. Introduction

Alzheimer disease (AD) is a neurodegenerative disorder that typically features memory deficits, followed by a progressive decrease of cognitive abilities.<sup>[1]</sup> The neuropathology in AD is characterized by a progressive accumulation of senile plaques and neurofibrillary tangles, which are responsible for neuronal death. A typical evolution of brain damage has been identified in AD brains, with an earlier and prominent involvement of the medial temporal lobes,<sup>[2]</sup> followed by involvement of lateral temporal, parietal, and frontal regions.<sup>[3]</sup> A number of studies investigated the sensitivity of specific biomarkers of AD pathology to discriminate between disease stages, and to provide measures of prognostic value.<sup>[4,5]</sup> Cerebral glucose uptake (GU), measured by brain [18F]fluorodeoxyglucose positron emission tomography (FDG-PET), and cerebrospinal fluid biomarkers (CSF biomarkers) are regarded as in vivo indicators of AD pathology. In particular, FDG-PET detects brain metabolism associated with synaptic activity and is considered as a proxy measure of neuronal integrity.<sup>[6,7]</sup> On FDG-PET, AD is characterized by a specific regional pattern of GU reduction in the posterior cingulate and in the parieto-temporal cortices.<sup>[8,9]</sup> AD symptoms essentially do not occur in the absence of hypometabolism, whose extent typically reflects the severity of cognitive impairment.<sup>[7]</sup>

Thanks to their diagnostic accuracy, CSF biomarkers are also used in the clinical diagnosis of AD, and include markers of neurofibrillary degeneration (ie, total tau [Tau] and hyperphosphorylated tau at threonine 181 [181p-tau] proteins) and  $\beta$ -amyloid deposition ( $A\beta$  peptides 1 to 42 [ $A\beta_{1-42}$ ]). The use of low CSF- $A\beta_{1-42}$  levels as a marker for AD pathology has been validated in several studies, although variability exists in the definition of cut-off values for normality.<sup>[10,11]</sup>

The relationship between AD pathology and cognition is increasingly recognized to be complex, and not linear. The concept of cognitive reserve (CR) was introduced to account for the gap existing between the extent of brain tissue damage and the clinical symptoms observed at individual level.<sup>[12]</sup> According to this assumption, AD patients with higher as compared with those with lower CR would require a more severe accumulation of AD pathology to exhibit the same level of cognitive impairment.<sup>[12]</sup> This is supported by evidence from PET studies, indicating an inverse relationship between GU and years of formal education (a proxy measure of static CR) in patients with different forms of neurodegenerative dementia.<sup>[6,13]</sup>

There are several studies that examined the role of CR in AD.<sup>[12,14–17]</sup> However, all these studies lack more direct indexes of pathological load that, in AD, may be given by measures of  $\beta$ -amyloid deposition. To the best of our knowledge, there are few studies only that correlated CSF assessment of  $\beta$ -amyloid with patients' levels of CR,<sup>[18–20]</sup> whereas 2 studies used  $\beta$ -amyloid PET imaging.<sup>[21,22]</sup>

The aim of this study was to examine the interaction between CSF  $A\beta_{1-42}$  and education (a proxy of CR<sup>[23]</sup>) on brain FDG-PET metabolism in patients with moderate AD.

## 2. Materials and methods

### 2.1. Patients

Twenty-seven patients with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and by Alzheimer's Disease and Related Disorders Association diagnostic criteria<sup>[24]</sup> (mean [SD] age: 71.5 [8.0] years; F/M: 19/8; mean [SD] years of formal education: 7.3 [3.3]) were consecutively recruited from the Clinic of Nervous System Diseases of OORR Foggia (Italy) between September 2012 and June 2013. In all patients, alternative neurological and psychiatric diagnoses were carefully investigated and excluded, based on blood tests (complete blood count, liver, kidney, and thyroid function tests, serum cobalamin and folate, syphilis serology) and conventional magnetic resonance imaging (MRI) (T2 and T1-weighted images, fluid-attenuated inversion recovery [FLAIR] images; diffusion-weighted images). After recruitment, patients underwent a detailed neuropsychological evaluation, CSF assessment, and FDG-PET, as detailed below. Twenty-five older neurological normal individuals (NNS) (mean [SD] age: 68.2 [7.0] years; F/M: 12/13; mean [SD] years of formal education: 7.8 [4.5]) were selected from the database of the Institute of Nuclear Medicine (OORR Foggia, Italy) and used as control group for FDG-PET data analysis. All these subjects suffered from cancer with no signs of brain involvement as assessed by neurological and neuropsychological examination, MRI (or postcontrast computerized tomography [CT]), and visual assessment of FDG-PET images.

For the purposes of the principal aim of this study (interaction between CR and AD pathology as assessed by FDG-PET and CSF biomarkers), AD patients were divided in 2 subgroups based on

their level of formal education. They were therefore classified in those highly educated-AD (HE-AD) and less educated-AD (LE-AD) patients using the median years of formal education (ie, 5 years) of the whole patient group as cut-off.

The study was approved by the Ethics Committee of OORR, and all subjects gave written informed consent before taking part in the study.

### 2.2. Neuropsychological assessment

All patients underwent a neuropsychological examination, measuring global cognitive functioning (by the Mini Mental State Examination [MMSE]), verbal long-term memory (by the Story Recall test), verbal and spatial short-term memory (by Digit Span, forward and backward and the Corsi Block Tapping Test), visuospatial (by the Clock Design [CD]), and executive abilities (by the Frontal Assessment Battery [FAB], Phonemic and Semantic Fluencies), and attention (by the Attentional Matrices). Mood disorders were assessed using the 15-item Geriatric Depression Scale [GDS]. Activities of daily living (ADL) and instrumental ADL (IADL) were used to evaluate patients' functional impairments.

### 2.3. CSF biomarkers

Lumbar puncture was performed in all recruited patients. CSF was collected in 12-mL polypropylene tubes, and centrifuged at 2171g for 10 minutes (3400 rpm) within 2 hours. A small amount of CSF was used for routine analysis, including total cell count, bacteriologic and microbiologic examinations, total protein, and glucose levels. CSF was aliquoted in polypropylene tubes and temporarily stored at  $-22^{\circ}\text{C}$  to quantify, within 1 month after collection,  $A\beta_{1-42}$ , 181p-tau, and Tau concentrations (Innotest ELISA; Innogenetics, Ghent, Belgium). Table 1 summarizes the mean (SD) values of  $A\beta_{1-42}$ , 181p-tau, and Tau for each patient subgroup.

### 2.4. PET scan acquisition and data processing

Subjects had to fast for approximately 12 hours before FDG injection. Before examination initiation, blood glucose levels were always checked and had to be inferior to 140 mg/dL. Subjects were injected an activity of FDG equal to 37 MBq/7 kg of their body mass, according to the following formula: activity to be administered = [(mass of the patient/7)  $\times$  37]. Brain scanning started 30 minutes after intravenous (i.v.) administration of the radiopharmaceutical tracer, using a layers Discovery PET/CT 600 system (GE Healthcare). CT temporal resolution was 0.25 seconds, whereas PET spatial resolution was 2.14 mm (FWHM). CT scans served for attenuation correction. Images were reconstructed using a 3-dimensional filtered back-projection method, for a total examination duration of 6 to 8 minutes. PET images were reconstructed in repetitive Recon or Osem mode, processed with 3DSSP, and evaluated by 2 independent nuclear specialists.

### 2.5. FDG-PET statistical analyses

Statistical analyses were performed at the Neuroimaging Laboratory of Santa Lucia Foundation (Rome, Italy). FDG-PET interfiles were converted to Neuroimaging Informatics Technology Initiative format and preprocessed according to the PET protocol implemented in SPM8 ([www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/))

**Table 1****Principal demographic and clinical characteristics of groups with Alzheimer disease.**

	HE-AD (n = 12)	LE-AD (n = 15)	P
Mean (SD) age, y	68.6 (7.2)	73.9 (7.6)	NS*
Sex (female/male)	8/4	10/5	NS†
Mean (SD) MMSE score	17.5 (6.2)	17.9 (4.7)	NS*
Mean (SD) ADL score	4.3 (0.9)	3.8 (1.3)	NS
Mean (SD) IADL score	3.4 (1.8)	3.8 (1.9)	NS
Mean (SD) GDS score	5.25 (3.4)	7.5 (4.5)	NS
Mean (SD) y of formal education	10.4 (2.5)	4.7 (0.7)	<0.001*
Mean (SD) of Aβ <sub>1-42</sub> values, pg/mL	465.8 (140)	534.8 (183.6)	NS*
Mean (SD) of 181p-tau values, pg/mL	93.3 (65.6)	62.7 (39.8)	NS*
Mean (SD) of Tau values, ng/mL	694.9 (570)	616.3 (461.7)	NS*

Aβ<sub>1-42</sub> values = beta-amyloid<sub>1-42</sub> values, ADL = activities of daily living, GDS = 15-Item Geriatric Depression Scale, HE-AD = highly educated Alzheimer disease, IADL = instrumental ADL, LE-AD = less educated Alzheimer disease, MMSE = Mini-Mental State Examination, NS = not significant, SD = standard deviation.

\* Two-sample *t* test.

† Chi-square test; statistical threshold ( $P < 0.05$ ).

). Briefly, images were first realigned, normalized, and smoothed using a 12-mm FWHM Gaussian kernel. Differences in regional GU uptake were first investigated between all AD patients against NNS using a 2-sample *t* test design. Then, interactions between education levels and each CSF biomarker (ie, Aβ<sub>1-42</sub>, 181p-tau, and Tau) on FDG-PET metabolism were investigated in AD patients only. Patients were grouped in HE-AD and LE-AD, and individual concentrations of each CSF biomarker were entered in the design matrix as covariate of interest. Statistical tests were all performed considering the whole brain, and results were considered as statistically significant for *P* values Family-Wise Error cluster-level corrected <0.05. Each set of clusters resulted as statistically significant were used as regions of interest (ROIs) to extract, in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), GU values at a single-subject level. These values were used to plot results in as measures proportional to GU.

### 3. Results

#### 3.1. Demographic, clinical, and cognitive characteristics of patients subgroups

When comparing AD patients with NNS, there were no significant differences in age, sex, and years of formal education. No subject was bilingual. When comparing HE-AD with LE-AD patients, there were no significant differences in demographic features, MMSE, GDS, ADL, and IADL scores, and CSF

biomarkers (Table 1). Additionally, there were no significant differences in the cognitive functions between HE-AD and LE-AD patients.

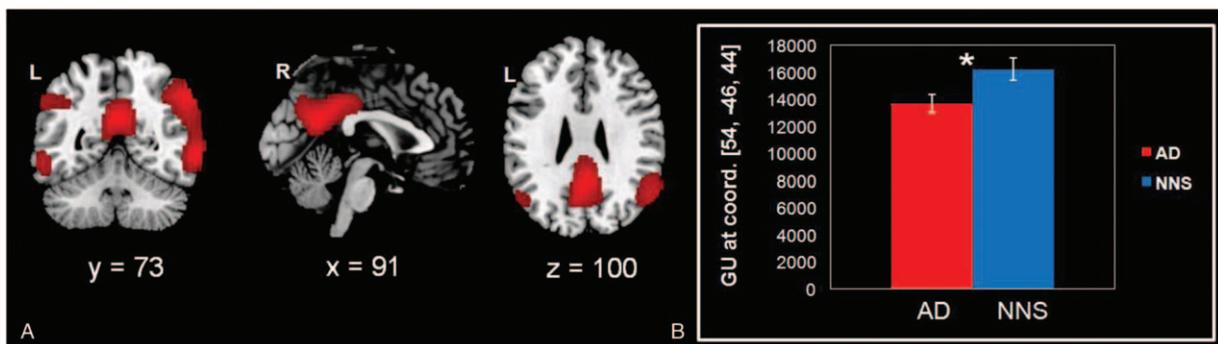
#### 3.2. Conventional brain MRI

Conventional brain MRI images were examined by an expert radiologist, who confirmed the expected pattern of brain atrophy in all AD patients (irrespective of individual CR level), which was dominated by a bilateral tempore-parietal distribution.

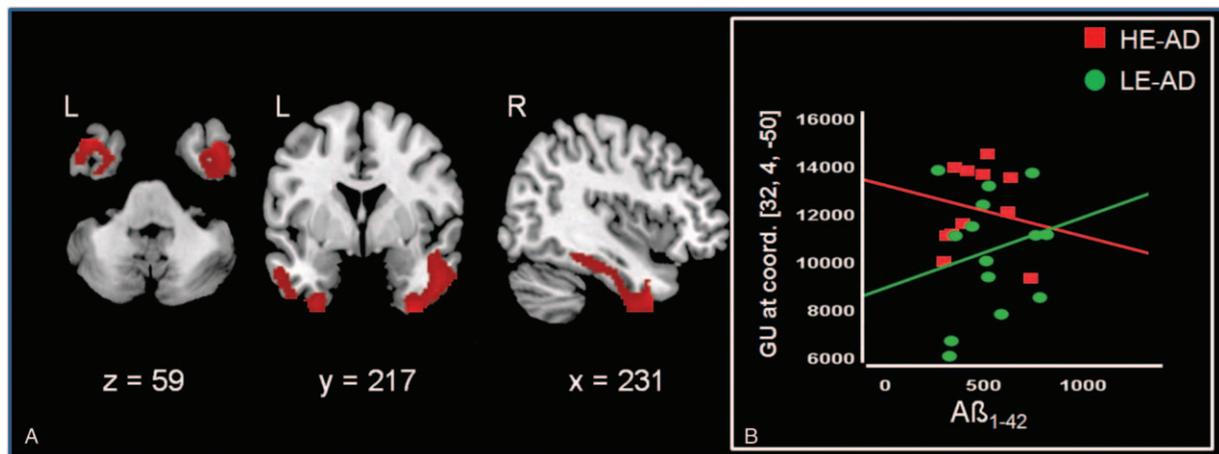
#### 3.3. FDG-PET

Between-group comparison revealed significant clusters of low GU in AD compared with NNS in the posterior cingulate gyrus and precuneus, in the inferior and medial temporal gyrus, and in the inferior parietal lobe bilaterally (Fig. 1 and Supplemental Table 2, <http://links.lww.com/MD/B624>).

In AD patients, the interaction between CR and CSF-biomarkers on FDG-PET metabolism returned significant results when considering β-amyloid levels only. Selective modulation of CR on brain metabolism was found in the inferior and medial temporal gyrus bilaterally (Supplemental Table 3, <http://links.lww.com/MD/B624>). Such an interaction was driven by a negative association between CSF β-amyloid levels (inversely correlated to amyloid plaque deposition) and GU in HE-AD patients, and a direct association in LE-AD patients (Fig. 2).



**Figure 1.** Pattern of GU between AD and NNS. Panel A shows regions of significant difference (FWE,  $P < 0.05$  at cluster level) in values of GU between AD and NNS in bilateral posterior cingulate, precuneus, and lateral parieto-occipital cortices. Panel B shows the plot of between-groups significant differences ( $P = 0.003$ ) in GU located in the right parieto-occipital cortex. Areas of GU are shown in red and overlaid onto a T1-weighted template. MNI coordinates are reported for each section. Abbreviations: AD = Alzheimer disease, FEW = Family-Wise Error, GU = glucose uptake, L = left, NNS = neurological normal subjects, R = right (see text for further details).



**Figure 2.** Interaction between education and  $A\beta_{1-42}$  values in 2 patient groups. Panel A shows regional changes in GU between AD divided in those with a higher (HE-AD) and those with a lower educational level (LE-AD) in the inferior and medial temporal gyrus (statistical threshold set to FWE,  $P < 0.05$  at cluster level). Areas of GU are shown in red and overlaid onto a T1-weighted template. MNI coordinates are reported for each section. Panel B shows interaction between GU in the inferior and medial temporal gyrus bilaterally and CSF  $A\beta_{1-42}$ , in which patients with higher educational level (HE-AD) showed reduced metabolism than those with lower educational level (LE-AD). Abbreviations: AD=Alzheimer disease, CSF  $A\beta_{1-42}$ =cerebrospinal fluid beta-amyloid<sub>1-42</sub>, FWE=Family-Wise Error, GU=glucose uptake, HE-AD=highly educated-AD, L=left, LE-AD = less educated-AD, NNS=neurological normal subjects, R=right (see text for further details).

#### 4. Discussion

This study investigated the impact of CR on brain metabolism in AD, by controlling for the load of AD pathology assessed by CSF biomarkers. We first replicated previous findings by comparing all AD patients (irrespective of their CR level) and healthy controls. Consistent with previous literature,<sup>[8,9]</sup> patients with AD reported a significant decrease of GU in the cingulate gyrus and precuneus and in parieto-temporal regions.

Then, we examined the interaction between CR and specific measures of brain pathology on brain functioning. As expected by a consecutive patient recruitment, HE-AD and LE-AD patients were similar for demographic and clinical characteristics, and years of disease onset. According to our analysis,  $\beta$ -amyloid was the only biomarker showing an interaction between CR and brain metabolism. This is not surprising for several reasons, including the central role of  $\beta$ -amyloid accumulation in AD pathophysiology,<sup>[25,26]</sup> and its partial dissociation from phenomena of neuronal death.<sup>[27]</sup> Conversely, tau tangle formation is known to reflect neuronal loss, thus being strictly associated with cognitive impairment beyond any potential effect of CR.<sup>[28]</sup>

The main finding of the current study is the interaction between patients' CR and  $\beta$ -amyloid deposition on metabolism in the medial temporal lobes, which have been previously shown as particularly sensitive to  $A\beta_{1-42}$  level.<sup>[29,30]</sup> In HE-AD patients, CR was inversely associated with GU, whereas the opposite effect was observed in LE-AD patients. This is in line with the CR theory and with a number of previous neuroimaging studies, indicating a compensatory effect of CR against accumulation of pathological damage.<sup>[14]</sup> In other words, our findings suggest that, at least in early/moderate stages of AD, CR compensates neurodegeneration and allows the maintenance of patients' cognitive performance as previously argued by others.<sup>[14,31,32]</sup> The selective anatomical distribution we found in the medial temporal lobes of our patients is consistent with their clinical presentation, which was in all cases amnesic. However, it has been recently shown that AD also includes atypical variants (ie, nonamnesic AD)<sup>[33-36]</sup> and that they are more common than it was thought before.<sup>[33]</sup> Further studies are needed to clarify

whether the effect of CR we described here can be extended also to patients with atypical AD. This is relevant not only for speculative reasons on the pathophysiology of AD. Indeed, in the absence of treatments, with the ability of modifying the natural history of the disease, CR might open to potential interventions to mitigate the impact of AD. This is particularly relevant for patients at early or even preclinical AD stages. As recently reported by Ewers et al, CR interacts with individual  $\beta$ -amyloid status on brain metabolism in the temporo-parietal lobes of cognitively normal individuals.

Local GM volumes of these parietal association regions were found to be less atrophic in AD patients with higher as compared with those with lower education levels.<sup>[32]</sup>

This study suffers from some limitations, including sample size and assessment of CR based on education only. Subjects serving as controls (even if with no signs of brain involvement as assessed by neurological and neuropsychological examination) suffered from cancer.

Nevertheless, our patient sample was well-selected and clinically homogeneous. With respect to education, this is certainly a simplistic way for measuring CR. However, education is one of the most widely used and reliable proxy measure of CR in literature, thus facilitating a comparison between current findings and previous studies.<sup>[23]</sup> In addition, it is important to highlight that the motivation behind choosing education as a proxy for CR is that, although occurring early in life, education tends to influence lifestyle throughout the entire life.

In conclusion, this supported evidence for the role played by CR theory in neurodegeneration, by assessing *in vivo* the severity of AD pathology in patients at a moderate stage of disease. Due to the experimental design, the main potential sources of sample variability were well-controlled, thus identifying the specific interaction between subjective level of CR and accumulation of AD pathology. This is relevant for clinical reasons as we currently do not have reliable prognostic measures on patient clinical outcome to be applied at a single subject level. Understanding the protective role of CR might improve our prognostic accuracy in clinical practice, and also in patients' stratification for future clinical trials.

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