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Cognitive reserve modulates brain structure and cortical architecture in the Alzheimer's Disease

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Running head: Cognitive reserve and brain architecture in AD.

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Abstract

Aim: Cognitive reserve (CR) explains the individual resilience to neurodegeneration. The present study investigated the effect of CR in modulating brain cortical architecture. **Methods:** 278 individuals (110 AD, 104 a-MCI due to AD, 64 HS) underwent a neuropsychological evaluation and 3T-MRI. Cortical thickness (CTh) and fractal dimension (FD) were assessed. Years of formal education were used as an index of CR by which participants were divided in High and Low CR (HCR and LCR). Within-group differences in cortical architecture were assessed as a function of CR. Associations between cognitive scores and cortical measures were also evaluated. **Results:** A-MCI-HCR compared to a-MCI-LCR patients showed significant decrease of CTh in the right temporal and in the left prefrontal lobe. Moreover, they showed increased FD in the right temporal and in the left temporo-parietal lobes. Patients with AD-HCR showed reduced CTh in several brain areas and reduced FD in the left temporal cortices when compared with AD-LCR subjects. HS-HCR showed a significant increase of CTh in prefrontal areas bilaterally, and in the right parieto-occipital cortices. Finally, a-MCI-HCR showed significant positive associations between brain measures and memory and executive performance. **Discussion:** CR modulates the cortical architecture at pre-dementia stage only. Indeed, only patients with a-MCI showed both atrophy (likely due to neurodegeneration) alongside richer brain folding (likely due to reserve mechanisms) in temporo-parietal areas. This opposite trend was not observed in AD and HS. **Conclusions:** our data confirm the existence of a limited time-window for CR modulation at the a-MCI stage.

Keywords: cognitive reserve; Alzheimer's disease; Mild cognitive impairment; cortical thickness; fractal dimension.

INTRODUCTION

Alzheimer's Disease (AD) is the most common neurodegenerative disorder worldwide. AD implies biological, genetic and environmental factors that interact with each other producing a complex clinical picture with peculiar brain abnormalities. Brain morphology is known to modify over the lifespan with major changes occurring during development and aging [1].

The neocortex is the neuroanatomical substrate for processing of higher-level cognitive functions, while the white matter connects various brain regions to allow a network-based processing of information. The cortex is organized vertically into six different layers (or laminae) distinct from each other for neuronal composition and density [2]. In general, neuronal density and cortical thickness (CTh) are inversely correlated. This is the reason why associative areas are known to be thicker than primary sensory areas [3]. Over the last year it has been introduced a method of MRI data analysis called "Cortical thickness" (CTh), which is based on a voxel-wise processing of T1-weighted volumes [4-5]. CTh describes the distance between the inner and outer boundaries of gray matter using voxels or surface characteristics as a quantitative parameter [6]. CTh abnormalities can be considered as resulting from microstructural changes occurring in the brain tissue. Previous studies showed, in Alzheimer's disease brains, significant reductions of cortical thickness [7-8], and associations with neuropathological abnormalities [8,10]. CTh seems therefore to be a reliable proxy measure of AD neuropathology in vivo. Another measure that can be derived from T1-weighted volumes is fractal dimension (FD), which returns information on cortical complexity. FD is regarded as a quantitative index of roughness of the brain surface and is derived from folding properties of the cortex [8].

The surface area and cortical thickness are inheritable structural features, each one driven by specific genetic factors [11-12]. Additionally, these cortical features are susceptible to environmental factors [11,13]. The impact of environment on the brain structure and cognitive functions is well documented in both animal model and in human studies (please see [14] for a review). Neurogenesis, synaptogenesis, increased level of neurotrophic factors have been associated with enriched

environment exposure in animal experiments [14]. In clinical research, healthy life-styles including cognitive, social, physical stimulations, healthy diet, no smoking etc., have been associated with a higher brain resilience to neuronal damage [14-15]. All these studies fell in the framework of the cognitive reserve subject [16]. **It is well known that several factors can be considered as reserve-builders but** the most powerful one impacting on the individual cognitive reserve (CR) is the level of formal education. Several studies showed that education enhances the level of brain connectivity both inducing a synaptic increase [14,16-17], and stimulating behaviours oriented to more intense social and cognitive activities [17]. **In particular, education is an important environmental factor that pushes the motivation to engage stimulating cognitive activities during the entire lifespan [14]. Additionally, education is considered as a socialization factor that can promote more efficient learning strategies in response to request of the environment [14].**

It has been hypothesized that education modifies the relationship between accumulation of neuropathology and individual cognitive performances during aging [14-15]. Most previous studies used volumetric techniques such as voxel-based morphometry to investigate such an interaction [18-19]. However, the impact of reserve on cortical thickness has been so far only poorly explored [20-22]. Querbes and co-workers [20] by extracting a normalised thickness index from a pool of brain regions, reported a high predictive value for CTh in predicting the risk of conversion to AD in patients with Mild Cognitive Impairment and higher CR levels. A more recent study showed that individuals with higher CR and preserved cortical thickness are more protected against conversion to AD in a time framework longer than 7 years from clinical onset [21]. In addition, CR and cortical thickness had an independent impact on the risk of conversion to AD in those MCI patients who converted earlier than 7 years [21]. The effect of CR on the brain structures has been clearly demonstrated in animal models (see[14] for a review). In a rat model of AD it has been observed that physical exercise, traditionally considered as a reserve-builder [23-24], increases cortical thickness in motor areas as well as performance [25].

When considering FD, a recent study [26] analysed the association between this measure of brain complexity and cognition in patients with AD and fronto-temporal dementia (FTD). This study showed a similar pattern of FD changes between the two groups, involving the cingulate gyrus and insula, while different patterns of correlation were identified between FD and cognitive performances in either patient group. In more detail, significant correlations were observed between reduced FD in the superior temporal gyrus and isthmus of the cingulum, and memory performances in AD patients, while reduced FD in the inferior temporal, medial orbito-frontal cortex were associated to verbal fluency in FTD patients [26]. To the best of our knowledge, there are no published studies that investigated the relationship between CR and cortical complexity in both, healthy and pathological populations.

Aims of the present study were: i) to assess the effect of cognitive reserve (CR) in modulating cortical brain architecture in healthy elderly individuals and in patients with AD at different stages of disease progression; ii) to evaluate the association between CR and cortical complexity on the cognitive functioning of healthy individuals and patients with AD. To this purpose, we recruited a large cohort of participants assessing their CR, cognitive functions, and cortical thickness and complexity.

METHODS

Participants

A cohort of 278 participants, 110 with a diagnosis of probable AD (M/F=42/68; mean age=73.1, SD=6.5 years; mean years of formal education=9.7, SD=4.5), 104 with a diagnosis of amnesic MCI (a-MCI) (M/F=51/53; mean age=70.0, SD=7.9 years; mean years of formal education=9.9, SD=4.6), and 64 healthy elderly subjects (HS) (M/F=25/39; mean age=64.0, SD=9.4 years; mean years of formal education=13.3, SD=3.2) were enrolled in the study. They were consecutively recruited between January 2016 and December 2019 from the Specialist Dementia Clinic of Catholic University of Rome, and from Santa Lucia Foundation, IRCCS, Rome, Italy. The diagnosis of probable AD was formulated according to the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association (NINCDS-ADRDA) [27]. The diagnosis of a-MCI was performed according to current diagnostic criteria [28]. Patients could be either single- (n=54) or multiple (n=50) domain MCI, and had not to respond to the diagnostic criteria for major cognitive disorders [29], with a CDR [30] score not exceeding 0.5. As detailed below, medial temporal lobe atrophy was assessed in all subjects to confirm that they had an intermediate likelihood of underlying AD neuropathology, and to control for patients' homogeneity across high and low cognitive reserve groups. **In order to exclude individuals in a preclinical phase of cognitive decline from recruitment in the “healthy subjects” group, they had not to show** any significant medial temporal lobe atrophy or any **cognitive scores below the normality cut-off in each assessed cognitive domain**. All recruited subjects with a Hachinski score [31] higher than 4 were excluded. Major systemic, psychiatric, and other neurological illnesses were also carefully investigated and excluded in all participants. Finally, **in order to reduce any potential source of variability due to hemispheric dominance** subjects had to be right-handed, as assessed by the Edinburgh Handedness Inventory [32].

The study was approved by the Ethics Committee of Santa Lucia Foundation and written informed consent was obtained from all participants and or their legal guardians before study initiation. All procedures performed in this study are in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Neuropsychological assessment

All participants underwent an extensive neuropsychological covering all cognitive domains: a) verbal episodic long-term memory: 15-Word List (Immediate, 15-min Delayed recall and recognition) [33]; Short Story Test (Immediate and 20-min Delayed recall) [34]; b) visuo-spatial long-term memory: Complex Rey's Figure (Immediate and 20-min Delayed recall) [34]; c) short-term and working memory: Digit span (forward and backward) and the Corsi Block Tapping task (forward and backward) [35]; d) executive functions: Phonological Word Fluency [33] and

Modified Card Sorting Test [36]; e) language: Naming objects subtest of the BADA (“Batteria per l’Analisi dei Deficit Afasici”, Italian for “Battery for the analysis of aphasic deficits”) [37]; f) Reasoning: Raven’s Coloured Progressive Matrices [33]; g) constructional praxis: copy of simple drawings with and without landmarks [33] and copy of Complex Rey’s Figure [34]; h) general cognitive efficiency: Mini Mental State Examination (MMSE) [38-39]. For the purposes of the current study, focussed on the cognitive reserve, neuropsychological scores were not adjusted for age and education, as previously reported [18].

Classification criteria to define the level of cognitive reserve.

As previously reported [18], we divided participants on the basis of their level of formal education as proxy measure of CR. Within each group, the years of formal education were transformed into z scores, and individuals reporting a z score ≤ 0 were considered as having a low cognitive reserve (AD-L_{CR}; n= 58; a-MCI-L_{CR}=58 and HS-L_{CR}=44). Conversely, individuals with a z score > 0 were considered having a high cognitive reserve (AD-H_{CR}; n= 52; a-MCI-H_{CR}=46 and HS-H_{CR}=20). Individuals with high and low cognitive reserve were equally distributed across groups. Table 1 summarizes the principal characteristics of all subjects.

MRI acquisition

Image acquisition and pre-processing of volumetric images to assess cortical thickness

All participants underwent MRI-3T brain scanning (Siemens, Medical solutions, Erlangen, Germany) including the following acquisitions: (a) dual-echo spin echo (DE-SE) (TR=5000 ms, TE=20/100 ms); (b) fast-fluid attenuated inversion recovery (FLAIR) (TR=8170 ms, TE=96 ms, TI=2100ms); (c) 3D T1-weighted (TR=7.92 ms, TE=2.4 ms, TI=210 ms, flip angle = 15°). For the dual-echo and FLAIR scans, 52 contiguous interleaved axial slices were acquired with a 2 mm slice thickness, with a 192 x 256 matrix over a 256 mm x 256 mm field of view, covering the whole brain. The T1-weighted volumes were acquired in a single slab, with a sagittal orientation and 224 x 256 matrix size over a 256 x 256 mm² field of view, with an effective slice thickness of a 1mm.

The T1-weighted images were pre-processed by using the pipeline for surface-based morphometry included in CAT-12 (Computational Anatomy Toolbox 12), a toolbox of SPM 12 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Briefly, a projection-based thickness estimation was used to compute the cortical thickness (CTh), the central surface and the FD [40], including the partial volume correction, the sulcal blurring and asymmetries corrections. CAT-12 permits to repair topological defects, using a method based on spherical harmonics [41] and to re-parameterize the surface mesh into a common coordinate system using a specific algorithm to reduce the area distortion [42]. Then an adapted two-dimensional diffeomorphic DARTEL algorithm was used for the spherical registration of the brain surface. Finally, a smoothing with a Gaussian kernel of 15 mm (FWHM) was applied to each dataset.

Medial temporal lobe atrophy

The Medial Temporal lobe Atrophy scale (MTA) [43] was employed on T1-weighted volumetric images to assess the severity of atrophy in each subject. This scale provides a rating score from 0 to 4, with scores > 1.5 [44] indicating significant atrophy. For each subject we averaged the scores obtained in the right and left hemispheres to obtain a single measure of medial-temporal lobe atrophy.

Statistical analyses

Demographical features, clinical and neuropsychological features

SPSS-20.0 (<https://www.ibm.com/it-it/analytics/spss-statistics-software>) was used to assess group differences in demographic and clinical variables by using a series of two-way 3 by 2 ANOVAs, with a 3 level Group (AD vs. a-MCI vs. HS) and a 2 level CR (High vs. Low). Variables included age, years of formal education, the MTA scores, the MMSE scores and neuropsychological scores. Twenty two-way ANOVAs were performed to assess differences in the neuropsychological scores, and to avoid the type-I error Bonferroni's correction was applied (p value threshold $\alpha=$

0.05/20=0.003). Tukey test was used as post-hoc analysis of ANOVAs. Gender distribution across groups was assessed by using Chi-square.

Cortical thickness and fractal dimension analyses

The MRI data analyses were performed in the framework of the General Linear Model by using CAT-12 (Computational Anatomy Toolbox in SPM12)

(<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Two-sample t test models were used for voxel-wise comparisons of cortical thickness and FD between subjects with low and high CR within each diagnostic group (AD-L_{CR} vs. AD-H_{CR}; a-MCI-L_{CR} vs. a-MCI-H_{CR}; and HS-L_{CR} vs. HS-H_{CR}, respectively). Age, intracranial volumes (TIV, obtained as sum of grey matter, white matter and cerebrospinal fluid) and MMSE scores were always used as covariates of no interest. **Although cortical thickness or other surface measures are usually not dependent on TIV, in the CR framework TIV is considered as a proxy measure of brain reserve. To reduce this potential confounding factor on the impact of cognitive reserve on ChT and FD we chose to enter TIV as nuisance variable into the analyses.**

Moreover, a series of multiple regression models were used to assess the potential association between cortical thickness, FD and performance obtained at neuropsychological tests. Intracranial volumes and MMSE scores were again entered as covariates of no interest. All results were accepted if survived at correction for multiple comparisons ($p < 0.05$ FWE at cluster level).

Results

Demographic and clinical characteristics

There was a significant main effect of Group in age ($F_{2,269} = 28.9$, $p < 0.001$) due to the fact that both patients' groups were older than HS (all $p < 0.001$ in the Tukey post-hoc analysis); no significant main effect of CR-level ($F_{1,269} = 0.85$, $p = 0.356$) or Group by CR-level interaction ($F_{2,269} = 0.45$, $p = 0.640$) were observed. With respect to years of formal education, as expected, there was a significant main effect of Group ($F_{2,269} = 76.3$, $p < 0.001$), main effect of CR-level ($F_{1,269} = 624.7$,

$p < 0.001$) and a significant Group by CR-level interactions ($F_{2,269} = 8.43$, $p < 0.001$). Moreover, there were significant main effects of Group ($F_{2,269} = 168.3$, $p < 0.001$) and of CR-level effect ($F_{1,269} = 10.7$, $p = 0.001$) in the MMSE scores. The first effect was due to the fact that AD patients reported lower MMSE scores than those with a-MCI and HS, while a-MCI patients showed lower scores than HS (all $p < 0.001$ in the Tukey post-hoc analysis). The main effect of CR-level indicated that individuals with high CR (regardless of their diagnostic group belonging) showed higher MMSE scores than individuals with low CR. No significant Group by CR-level interaction was observed ($F_{2,269} = 0.50$, $p = 0.629$) in all studied groups. Finally, there was a significant main effect of Group in the MTA scores ($F_{2,269} = 72.1$, $p < 0.001$), because AD patients showed more atrophy in the hippocampus than a-MCI patients and HS, and a-MCI patients showed more atrophy than HS (all $p < 0.001$ in the Tukey post-hoc analysis). No other significant differences were observed between groups and subgroups. Finally, patients with a-MCI showed a significant difference in sex distribution when stratified for their CR-level. This difference was due to the a-MCI-L_{CR} group that included more females than the a-MCI-H_{CR} group ($\chi^2 = 8.64$, d.f. = 1, $p = 0.033$).

All these data are summarised in Table 1.

Neuropsychological assessment

Table 2 shows between-group differences in neuropsychological measures. There was significant main effect of Group in each administered test due to the fact that patients with AD showed lower scores than patients with a-MCI and HS, and, in turn, a-MCI patients reported worse scores than HS. In addition, there was significant main effect of CR-level (better scores shown by participants with high CR level compared to those with low CR level regardless of their diagnostic group belonging), in the immediate recall of 15-Word list, in the Digit span backward, in the phonological verbal fluency, in the Raven's Progressive Matrices, in the copy of drawings and in the copy of Rey's Figure. Finally, there were no significant Group by CR-level interactions.

Cortical thickness and Fractal dimension analyses

Patients with AD-H_{CR} showed reduced CTh compared to AD-L_{CR} patients in several brain areas including the left post central gyrus (BA3), the left parieto-occipital cortices (i.e., precuneus and primary visual cortex; BA7, BA17), the left cingulate cortex (BA31) and the right inferior frontal gyrus (BA44), and the medial part of the right temporal gyrus (BA20, BA21, BA37) (See Figure 1 panel A and table 3). A-MCI-H_{CR} patients compared to a-MCI-L_{CR} patients showed a significant decrease of CTh in the right temporal lobe, including the inferior temporal and fusiform gyri (BA38, BA20, BA21), and in the left prefrontal lobe (BA6, BA8, BA9) (Figure 1, panel B and Table 3). Moreover AD-H_{CR} showed increased CTh compared with AD patients with low CR in the left anterior cingulate cortex (BA32), in the prefrontal cortex (BA9) and in the left inferior and medial temporal gyri (BA21, BA37) (see Figure 2A and Table 3). Finally, HS-H_{CR} compared to HS-L_{CR} showed a significant increase of cortical thickness in the prefrontal areas of the left (BA6, BA8, BA9) and right (BA10 BA11, BA44, BA47) hemisphere, and in the right parieto-occipital cortices (BA39 and BA19) respectively (see Figure 2B and Table 3).

When considering FD, we found in AD-H_{CR} patients compared with AD-L_{CR} patients reduced complexity in the left temporal cortices (BA22 and BA37) (Figure 3 panel A, Table 4). On the contrary, a-MCI-H_{CR} showed a significant increase of the FD compared with a-MCI-L_{CR} patients in the right temporal (BA38) and in the left temporo-parietal lobes (in posterior part of BA21, BA37, BA39) (Figure 3 panel B, Table 4).

No differences in FD were found when comparing HS with low and high CR.

Relationship between neuropsychological tests and Cortical thickness and Fractal dimension

A significant positive association was found in the AD-H_{CR} group between patients' performance on the 15-Word List (immediate recall) and their cortical thickness in the left posterior parietal cortex, in the left inferior temporal gyrus, and in the bilateral middle temporal gyrus. In the same group, a significant positive association was found between patients' scores on the Raven's Progressive Matrices and cortical thickness in their right frontal pole (see Figure 4, panel A). When considering

the a-MCI-H_{CR} group, a significant positive association was found between patients' scores at the digit span backward and CTh in the left inferior frontal gyrus (Figure 4, panel B). The HS-H_{CR} group showed positive association between scores on the Raven's Progressive Matrices and CTh in the pre-central gyrus and post-central gyrus and in the precuneus bilaterally. In the same group, a significant positive association was found between scores on the Copy of Drawings test and CTh in the right precentral and inferior frontal gyri (Figure 4, panel C). No significant associations were identified in all diagnostic groups for individuals with low cognitive reserve.

When considering FD, we observed a significant positive association in a-MCI-H_{CR} Digit span backward scores and FD in the left middle temporal gyrus. Finally, in the a-MCI-L_{CR} group, a significant positive association was found between scores on the 15-Word List and FD in the left middle temporal gyrus (Figure 5).

No additional associations were found between FD and cognitive scores from any other group.

Discussion

The importance of studying cortical thickness and brain complexity across normal and pathological brain aging is to detect detailed interactions between cerebral functions and dysfunctions and brain architecture. Previous studies have already demonstrated the presence of reduced thickness in AD brains at different disease stages [6,9]. The novelty of the current study was to use the measure of cortical thickness and fractal dimension to detect the modulation of CR on the neuropathology of AD. Our main finding is that the effect of CR reflects on cortical thickness and fractal dimension across aging, whose modifications account for individual performance on various cognitive domains. Overall, our findings further support the Stern's hypothesis that patients with higher CR need to accumulate more neuropathology than individuals with low CR to exhibit the same level of cognitive impairment [45]. In addition, our findings in healthy elderly individuals indicate that some cortical areas play a key role in brain maintenance. Specifically, all prefrontal areas found to be thicker in HS, are involved in executive functions, which are essential for cognitive flexibility and

make the brain more adaptable to social and environmental demands. Furthermore, the present study indicates that CTh and FD can be considered as reliable structural biomarkers for studying gray matter changes across AD evolution. In fact, they not only return a peculiar picture of degeneration for the different AD stage, but they are also influenced by the individual's enriching life experiences, measured through cognitive reserve.

We used here a static index of reserve, derived from the years of formal education, to assess the effect that CR has in modulating CTh and FD (a measure of cortical complexity).

Both, a-MCI and AD patients were older than HS as shown by the main effect of Group, but there was no significant effect due to the CR level or significant Group by CR level interaction. For this reason, in order to control the age effect, MRI analyses were performed within groups. We also observed a significant main effect of CR in the absence of any group interaction. This is due to the fact that subjects with high reserve have a significantly higher global cognitive function than those with low reserve, regardless of their diagnostic group belonging.

From a neuropsychological viewpoint, we found, as expected, a significant main effect of Group in several cognitive measures due to the fact that AD patients showed lower performances than a-MCI and HS, and a-MCI patients performed worse than HS in memory and executive functions. We observed also a main effect of CR level. Indeed, participants with higher CR showed better performances than those with lower CR in tests assessing episodic memory, phonological verbal fluency, reasoning and constructional praxis.

When considering the CTh in the groups of participants with high and low CR we found that, in AD patients, subjects with high CR showed thinner thickness in the left post- central gyrus, in the left parietal operculum, in the left superior parietal gyrus, in the left primary visual cortex, in the left cingulate gyrus, in the right medial temporal gyrus and in the right inferior frontal gyrus. Patients with a-MCI- H_{CR} showed reduced thickness in the left supplementary motor cortex, in the superior frontal gyrus, in the left temporal pole, inferior temporal and fusiform gyri.

More remarkably, we observed reduced cortical thickness in both patients with AD and a-MCI with high CR when compared to those with low CR. In particular, the areas in the right medial temporal gyrus (BA20/21) were thinner in both AD-H_{CR} and a-MCI-H_{CR}. These brain areas are known to be crucial for long-term memory, and the present results reinforce the idea that they are involved since early stages of AD [46-47]. However, some cortical areas showed different anatomical patterns of atrophy in patients with AD and a-MCI. In particular, AD-H_{CR} patients compared with AD-L_{CR} showed reduced thickness in a cluster included the post-central gyrus (BA3), the precuneus (BA7) and the posterior cingulate cortex (BA31). The precuneus and the posterior cingulate cortex have been previously recognised as involved in memory functioning [48-50]. AD-H_{CR} patients showed also thinner thickness in the BA44 (i.e., Broca's area), which is implicated in speech production. Recently, we demonstrated that this same area accounts for deficit in constructional apraxia in AD patients [51], indicating a more widespread role for the Broca's area in the pathophysiology of AD. Moreover, AD-H_{CR} compared with AD-L_{CR} patients showed thicker CTh in the left anterior cingulate cortex (BA32), in the prefrontal cortex (BA9) and in the left inferior and medial temporal gyri (BA21, BA37). All these regions are extensively involved in higher-level cognitive functions. We hypothesise that a thicker CTh may account for a better cognitive profile in the AD-H_{CR} compared to the AD-L_{CR} group. This view is reinforced by the correlations observed between the same brain regions and memory and reasoning performances in AD-H_{CR} patients.

Patients with a-MCI-H_{CR} showed reduced thickness in the prefrontal lobe, including the supplementary motor area (SMA) (BA6) and the dorsolateral prefrontal cortex (BA8, BA9). The SMA, is implicated in "internally-generated" planning of movements, in the planning of sequences of movements, and in motor coordination [51-52], and BA8 and BA9 have been found involved in the executive functions in both healthy controls and neurological patients [53]. In particular the dorsolateral prefrontal cortex is involved in working memory [54].

Some brain areas such as BA9 and prefrontal regions appeared to be thinner in the a-MCI-H_{CR} and thicker in the AD-H_{CR} group, which is counterintuitive. Longitudinal studies are needed to clarify this issue.

Conversely, individuals in the HS-H_{CR} group compared to those with low CR, showed an increase of cortical thickness in the same prefrontal areas. This finding is consistent with a previous study from Kim and co-workers [55], which showed a protective effect of education on cortical thickness mainly in the prefrontal parietal and occipital regions of healthy elderly subjects.

When considering FD, we observed an opposite pattern of complexity in AD and a-MCI patients. Indeed, AD-H_{CR} showed reduced FD than AD-L_{CR} in the left medial temporal gyrus, while a-MCI-H_{CR} showed increased FD in the same cortical area and in the right temporal pole. Interestingly, FD changes were observed in the mesial temporal lobe structures, which are critical for the memory disorders observed in AD. King and co-worker [8] observed reduced FD in patients with AD compared to healthy controls in several brain areas from the temporal lobe, in the mammillary bodies and in the superior and inferior colliculus. In line with this observation we speculate that the progression of neurodegeneration reduces the complexity of brain cytoarchitecture, resulting in a minor folding pattern, with a modulation of CR.

It is remarkable that a different trend was observed in a-MCI patients only. Indeed, in a-MCI-H_{CR} patients lower CTh corresponded to a greater folding in the temporal-occipital regions of both hemispheres. This effect seems to disappear at more advanced disease stages. In fact, AD patients with high CR compared to those with low CR, showed less cortical complexity in the left temporal lobe, alongside a decrease in CTh. According with Im et al., [56] cortical thickness and FD share approximately 50% of variance and the non-total correspondence between the two morphometric measures could be found in the modality (how and where) of occurrence of brain atrophy. FD is known to depend on the volumetric changes of the white matter and the lateral ventricles, which structurally support the cerebral folds [8,56]. These subcortical atrophying processes, which are

well delineated in patients AD, cannot be detected yet in subjects with mild cognitive impairment. This means that cognitive reserve modulates cortical FD in AD and MCI in relation to the different level of atrophy. However further studies on the relationship between CR and FD and brain atrophy are needed to clarify these aspects.

We observed also positive associations between cortical complexity measures and cognitive tests. Specifically, patients with AD-H_{CR} showed a positive association between cortical thickness in the mesial temporal lobe structures and long-term episodic memory and cortical thickness in the frontal pole and reasoning ability. While a-MCI-H_{CR} patients showed positive associations between thicker thickness (and also FD in turn) in the left inferior frontal gyrus and scores on verbal working memory tests; finally, HS-H_{CR} individuals showed a positive association between thickness in the fronto-parietal areas and reasoning and between the inferior frontal and precentral gyri and constructional praxis abilities. These associations highlight the strict relationship between the integrity of cortical structures and cognition and the protective effect of cognitive reserve.

In conclusion, a detailed analysis of cortical complex architecture help understanding the role played by cognitive reserve in modulating the effect of AD neuropathology on different cognitive functions. Beyond the speculative interest of this investigation, we believe that this approach is potentially useful when stratifying patients for clinical trials. Recruiting individuals with different levels of cognitive reserve means introducing a remarkable source of variability that might mitigate the effect of interest.

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Conflict of interests

None of the Authors has any conflict of interest to disclose.

Figure legends

Figure 1. Reduced cortical thickness in patients with AD and a-MCI

Panel A illustrates the reduction of cortical thickness in AD-H_{CR} compared to AD-L_{CR} patients in several brain areas including the post central gyrus, the parieto-occipital cortices, the cingulate cortex in the left hemisphere and the inferior frontal gyrus, the medial part of the temporal gyrus in the right hemisphere. In panel B a-MCI-H_{CR} patients showed a significant decrease of cortical thickness compared to a-MCI-L_{CR} patients in the right inferior temporal and fusiform gyri, and in the left prefrontal lobe. The statistical comparisons were overlapped on MRIcron ch2bet template (<https://www.nitrc.org/projects/mricron>).

Abbreviations: AD-H_{CR}= Alzheimer's Disease with high cognitive reserve; AD-L_{CR}= Alzheimer's Disease with low cognitive reserve; a-MCI-H_{CR}= amnesic Mild Cognitive Impairment with high cognitive reserve; a-MCI-L_{CR}= amnesic Mild Cognitive Impairment with low cognitive reserve; L=Left; R=Right.

See text for further details.

Figure 2. Increased cortical thickness in patients and healthy subjects

Figure 2A illustrates patients AD-H_{CR} with increased cortical thickness compared with AD patients with low CR in the left anterior cingulate cortex, in the prefrontal cortex and in the left inferior and medial temporal gyri. Finally, individuals HS-H_{CR} compared to HS-L_{CR} showed a significant increase of cortical thickness in the prefrontal areas bilaterally, and in the right parieto-occipital cortices. The statistical comparisons were overlapped on MRIcron ch2bet template (<https://www.nitrc.org/projects/mricron>).

Abbreviations: AD-H_{CR}= Alzheimer's Disease with high cognitive reserve; AD-L_{CR}= Alzheimer's Disease with low cognitive reserve; HS-H_{CR}= Healthy Subjects with high cognitive reserve; HS-L_{CR}= Healthy Subjects with low cognitive reserve; L=Left; R=Right.

See text for further details.

Figure 3. Fractal dimension

Panel A shows reduction of fractal dimension in AD-H_{CR} patients compared with AD-L_{CR} patients in the left temporal cortices. Panel B shows increase of fractal dimension in a-MCI-H_{CR} compared with a-MCI-L_{CR} patients in the right temporal and in the left temporo-parietal lobes.

The statistical comparisons were overlapped on MRICron ch2bet template

(<https://www.nitrc.org/projects/mricron>).

Abbreviations: AD-H_{CR}= Alzheimer's Disease with high cognitive reserve; AD-L_{CR}= Alzheimer's Disease with low cognitive reserve; a-MCI-H_{CR}= amnesic Mild Cognitive Impairment with high cognitive reserve; a-MCI-L_{CR}= amnesic Mild Cognitive Impairment with low cognitive reserve.

L=Left; R=Right.

See text for further details.

Figure 4. Associations between cortical thickness and cognitive tests

Panel A reports significant positive associations in the AD-H_{CR} group between patients' performance on the 15-Word List (immediate recall) and their cortical thickness in the left posterior parietal cortex, in the left inferior temporal gyrus, and in the bilateral middle temporal gyrus. In the same group, a significant positive association was found between patients' scores on the Raven's Progressive Matrices and cortical thickness in their right frontal pole. Panel B shows positive association in the a-MCI-H_{CR} group between patients' scores on the digit span backward and cortical thickness in the left inferior frontal gyrus. Panel C illustrates in the HS-H_{CR} group positive associations between scores at the Raven's Progressive Matrices and cortical thickness in the pre-central gyrus and post-central gyrus and in the precuneus bilaterally and between scores at the Copy of Drawings test and cortical thickness in the right precentral and inferior frontal gyri.

The statistical comparisons were overlapped on MRICron ch2bet template

(<https://www.nitrc.org/projects/mricron>).

Abbreviations: AD-H_{CR}= Alzheimer's Disease with high cognitive reserve; AD-L_{CR}= Alzheimer's Disease with low cognitive reserve; a-MCI-H_{CR}= amnesic Mild Cognitive Impairment with high

cognitive reserve; a-MCI-L_{CR}= amnesic Mild Cognitive Impairment with low cognitive reserve; HS-H_{CR}= Healthy Subjects with high cognitive reserve; HS-L_{CR}= Healthy Subjects with low cognitive reserve. L=Left; R=Right.

See text for further details.

Figure 5. Associations between Fractal dimension and cognitive tests

Positive associations in a-MCI-H_{CR} is observed between Digit span backward scores and Fractal dimension in the left middle temporal gyrus. Moreover, in the a-MCI-L_{CR} group, a significant positive association was found between scores on the 15-Word List and FD in the left middle temporal gyrus. The statistical comparisons were overlapped on MRICron ch2bet template (<https://www.nitrc.org/projects/mricron>).

Abbreviations: a-MCI-H_{CR}= amnesic Mild Cognitive Impairment with high cognitive reserve; a-MCI-L_{CR}= amnesic Mild Cognitive Impairment with low cognitive reserve. L=Left.

Table 1. Principal demographic and clinical characteristics of the participants.

	Participants					
	AD-H _{CR} N=52	AD-L _{CR} N=58	a-MCI-H _{CR} N=46	a-MCI-L _{CR} N=58	HS-H _{CR} N=20	HS-L _{CR} N=44
Mean (SD) Age [years] ^a	73.2 (6.8)*#	72.9 (6.2)*#	70.2 (8.9)&	71.1 (7.1)&	62.2 (9.5)	64.4 (9.4)
Mean (SD) education [years] ^a	13.7 (2.5)*§	6.1 (2.6)*	14.6 (2.1)&§	6.2 (1.7)&	16.9 (0.2)§	11.6 (2.6)
Sex (M/F) ^b	19/33	23/35	30/16	21/37	7/13	18/26
Mean (SD) MMSE score ^a	22.3 (4.1)* #§	20.6 (4.1)*#	27.7 (1.7)&§	26.5 (1.9)&	29.6 (0.9)§	28.8 (1.3)
Mean (SD) MTA score ^a	2.9 (0.7)*#	2.9 (0.9)*#	2.1 (0.8)&	1.9 (0.8) &	0.7 (0.5)	0.8 (0.8)

^aTwo-ways ANOVA; ^bChi-square; Post-hoc comparisons: *AD vs. HS p-value<0.05; #AD vs. a-

MCI p-value<0.05; &a-MCI vs. HS p-value<0.05; § High-CR >Low-CR p-value<0.05.

Abbreviations: AD-L_{CR}: Alzheimer's Disease patients with low cognitive reserve; AD-H_{CR}:

Alzheimer's Disease patients with high cognitive reserve; a-MCI-L_{CR}: amnesic Mild

Cognitive Impairment patients with low cognitive reserve; a-MCI-H_{CR}: amnesic Mild

Cognitive Impairment patients and high cognitive reserve; HS-L_{CR}: healthy subjects with low

cognitive reserve; HS-H_{CR}: healthy subjects with high cognitive reserve; MMSE: Mini

Mental State Examination; MTA: medial temporal lobe scale. See text for further details.

Table 2. Performance obtained by participants on neuropsychological testing.

Neuropsychological tests	Participants						Two-ways ANOVA		
	AD-H _{CR}	AD-L _{CR}	a-MCI-H _{CR}	a-MCI-L _{CR}	HS-H _{CR}	HS-L _{CR}	Group effect	CR level effect	Group x CR level
<u>Verbal episodic memory</u>									
15-Word List:									
Immediate recall (cut-off ≥ 28.5)	19.5 (8.3)*#§	17.7 (7.1)*#	29.2 (7.9)&§	25.5 (7.7)&	47.0 (1.8)§	40.7 (9.6)	F _{2,269} =173.1 p<0.001	F _{1,269} =13.9 p<0.001	F _{2,269} =1.4 p=0.247
Delayed recall (cut-off ≥ 4.6)	1.3 (1.3)*#	1.3 (1.5)*#	4.2 (2.8)&	3.7 (2.4)&	7.7 (1.5)	9.5 (2.1)	F _{2,269} =233.9 p<0.001	F _{1,269} =6.7 p=0.010	F _{2,269} =2.4 p=0.094
Recognition <i>hit rates</i>	8.4 (0.5)*#	8.5 (0.4) *#	11.1 (0.5)&	10.8 (0.4)&	13.8 (0.9)	13.6 (0.5)	F _{2,269} =43.2 p<0.001	F _{1,269} =0.06 p=0.811	F _{2,269} =0.11 p=0.896
Recognition <i>false</i>	6.3 (0.7)*	6.6 (0.7)*	3.9 (0.7)	4.2 (0.7)	1.1 (1.2)	1.2 (0.8)	F _{2,269} =17.9 p<0.001	F _{1,269} =0.12 p=0.732	F _{2,269} =0.01 p=0.991
Short Story:									
Immediate recall (cut-off > 3.1)	2.4 (2.0)*#	2.1 (2.0)*#	4.7 (1.6)&	4.0 (1.9)&	6.5 (1.2)	5.6 (1.5)	F _{2,269} =66.2 p<0.001	F _{1,269} =5.7 p=0.018	F _{2,269} =0.48 p=0.621

Delayed recall (cut-off \geq 2.8)	0.9 (1.4)*#	0.9 (1.8) *#	4.0 (2.0)&	3.7 (2.2)&	5.9 (1.5)	5.6 (1.4)	$F_{2,269}=104.7$ p<0.001	$F_{1,269}=0.4$ p=0.517	$F_{2,269}=0.2$ p=0.814
<u>Visuo-spatial episodic memory</u>									
Rey's Complex Figure:									
Immediate recall (cut-off > 6.4)	3.0 (3.5)*#	2.6 (3.0)*#	10.2 (8.2)&	6.7 (4.8)&	14.8 (5.9)	14.9 (7.0)	$F_{2,269}=71.1$ p<0.001	$F_{1,269}=2.9$ p=0.091	$F_{2,269}=2.3$ p=0.106
Delayed recall (cut-off \geq 6.3)	3.0 (3.3)*#	2.0 (2.7)*#	9.6 (6.7)&	6.8 (5.2)&	15.9 (5.4)	15.0 (6.0)	$F_{2,269}=111.3$ p<0.001	$F_{1,269}=5.4$ p=0.021	$F_{2,269}=0.9$ p=0.409
<u>Verbal short-term memory</u>									
Digit Span forward (cut-off > 3.7)	5.1 (1.1)*	4.8 (1.1)*	5.6 (1.0)&	5.0 (0.9)&	6.5 (1.0)	6.2 (1.2)	$F_{2,269}=31.2$ p<0.001	$F_{1,269}=8.1$ p=0.005	$F_{2,269}=0.36$ p=0.697
Digit Span backward	3.2 (1.3)*#§	2.5 (1.7)*#	4.0 (0.9)&§	3.1 (1.3)&	4.8 (0.9)§	4.4 (0.8)	$F_{2,269}=31.8$ p<0.001	$F_{1,269}=15.6$ p<0.001	$F_{2,269}=0.6$ p=0.505
<u>Visuo-spatial short-term memory</u>									
Corsi Span forward (cut-off \geq 3.5)	3.4 (1.5)*#	3.2 (1.5) #*	4.4 (0.8)&	4.0 (0.5)&	6.5 (1.0)	6.2 (1.2)	$F_{2,269}=53.3$ p<0.001	$F_{1,269}=4.8$ p=0.028	$F_{2,269}=0.17$ p=0.845

Corsi Span backward	3.2 (1.9)*	2.5 (1.7)*	4.1 (1.1) &	3.6 (1.2)&	4.8 (0.9)	6.3 (0.8)	F _{2,269} =12.5	F _{1,269} =5,6	F _{2,269} =2.39
							p<0.001	p=0.019	p=0.094
<u>Executive functions</u>									
Phonological verbal fluency	22.4 (10.0)*#§	17.4 (9.9)*#	32.9 (9.1)&§	23.2 (8.6)&	42.5 (10.5)§	36.2 (10.0)	F _{2,269} =73.5	F _{1,269} =30.9	F _{2,269} =1.5
(cut-off ≥ 17.3)							p<0.001	p<0.001	p=0.226
Modified Card Sorting Test:									
Criteria achieved (cut-off ≥ 17.3)	2.3 (1.1)*#	2.0 (1.6)*#	4.2 (2.0)&	3.1 (1.8)&	6.0 (0.3)	5.6 (1.1)	F _{2,269} =71.7	F _{1,269} =6.9	F _{2,269} =1.8
							p<0.001	p=0.009	p=0.174
<u>Reasoning</u>									
Raven's Progressive Matrices	21.6 (7.6)*#§	18.1 (7.7)*#	27.0 (4.9)&§	23.5 (5.4)&	32.1 (3.7)§	31.6 (3.3)	F _{2,269} =73.4	F _{1,269} =10.6	F _{2,269} =1.33
(cut-off ≥ 18.9)							p<0.001	p=0.001	p=0.267
<u>Language</u>									
Naming of objects	25.4 (2.7)*#	23.4 (1.1)*#	28.9 (0.9)	27.9 (1.7)	29.7 (0.3)	28.9 (0.5)	F _{2,269} =22.9	F _{1,269} =3.5	F _{2,269} =0.34
(cut-off ≥ 22)							p<0.001	p=0.062	p=0.716
<u>Constructional praxis</u>									

Copy of drawings (cut-off ≥ 7.1)	7.8 (3.6)*#§	6.4 (3.2)*#	10.1 (1.4)&§	8.2 (2.0)&	11.3 (0.9)§	11.0 (1.1)	F _{2,269} =48.7 p<0.001	F _{1,269} =14.5 p<0.001	F _{2,269} =1.9 p=0.138
Copy of drawings with landmarks (cut-off ≥ 61.8)	57.1 (21.8)*#	51.3 (21.4)	68.1 (1.7)	63.3 (9.8)	69.4 (0.6)	69.3 (0.7)	F _{2,269} =23.6 p<0.001	F _{1,269} =3.28 p=0.072	F _{2,269} =0.64 p=0.527
Rey's Complex Figure-Copy (cut-off ≥ 23.7)	21.9 (12.2)*#§	18.2 (11.6)*#	30.8 (6.5)&§	25.1 (8.1)&	33.1 (3.4)§	32.4 (2.7)	F _{2,269} =35.6 p<0.001	F _{1,269} =8.2 p<0.001	F _{2,269} =1.4 p=0.257

Two-ways ANOVA; Post-hoc comparisons: *AD vs. HS p-value<0.05; #AD vs. a-MCI p-value<0.05; &a-MCI vs. HS p-value<0.05; § High-CR >Low-CR p-value<0.05. In bold p-values surviving after Bonferroni's correction ($p \leq 0.003$).

Abbreviations: AD-L_{CR}: Alzheimer's Disease patients with low cognitive reserve; AD-H_{CR}: Alzheimer's Disease patients with high cognitive reserve; a-MCI-L_{CR}: amnesic Mild Cognitive Impairment patients with low cognitive reserve; a-MCI-H_{CR}: amnesic Mild Cognitive Impairment patients and high cognitive reserve; HS-L_{CR}: healthy subjects with low cognitive reserve; HS-H_{CR}: healthy subjects with high cognitive reserve; See text for further details.

Table 3. Cortical thickness in the participants according with their cognitive reserve's level

Group	Brain region	Side	Size	MNI coordinates			Z	p-level FWE- cluster level
				x	y	z		
AD-H_{CR}<AD-L_{CR}								
	Post central gyrus	L	26555	-46	-14	30	24.2	<0.001
	Inferior Frontal gyrus			-39	21	22	14.5	
	Orbitofrontal cortex			-36	33	-11	10.9	
	Primary visual cortex	L	20891	-17	-75	4	18.3	<0.001
	Fusiform gyrus			-30	-54	-8	15.2	
	Parietal operculum	L	3821	-53	-40	29	16.1	0.014
	Superior Parietal cortex	L	4354	-31	-55	54	6.24	0.006
	Supramarginal gyrus			-45	-47	42	5.35	
	Cingulate gyrus	L	3779	-14	-45	35	6.15	0.015
	Precuneus			-15	-46	54	4.08	
	Medial temporal gyrus	R	3564	52	-41	-3	3.25	0.021
	Inferior Frontal gyrus	R	4418	57	20	16	2.65	0.005

	Medial frontal gyrus		38	9	40	2.61		
<hr/>								
a-MCI-H_{CR}<								
a-MCI-L_{CR}								
	Supplementary motor cortex	L	4565	-8	7	44	3.40	0.001
	Superior Frontal gyrus			-7	28	58	2.93	
	Temporal pole	R	5770	52	12	17	3.53	<0.001
	Inferior Temporal gyrus			55	20	-35	3.21	
	Fusiform gyrus			29	2	-41	2.81	
<hr/>								
AD-H_{CR}>AD- L_{CR}	Supplementary motor cortex	L	8215	-4	-8	54	6.48	<0.001
	Frontal pole			-7	59	29		
<hr/>								
	Middle Temporal gyrus	L	11720	-64	-51	1	6.47	<0.001
	Supramarginal gyrus			-57	-27	30		
<hr/>								
	Posterior cingulate cortex	L	1564	-5	-53	12	6.32	<0.001
<hr/>								
HS -H_{CR}>HS- L_{CR}								
	Precentral gyrus	L	3015	-29	-3	46	3.24	0.024
	Medial frontal gyrus			-38	25	43	2.86	

Parietal	R	6227	62	-19	18	4.13	<0.001
operculum							
Inferior Frontal			49	10	16	3.19	
gyrus							
Medial	R	4204	52	-49	8	3.59\	0.001
temporal gyrus							
Superior			51	-34	1	2.44	
Temporal gyrus							
Anterior	R	3131	5	20	32	3.13	0.016
Cingulate							
cortex							
Paracingulate			11	36	25	2.69	
gyrus							
Frontal pole	R	3461	35	50	13	3.11	0.008
Orbitofrontal			28	22	-22	2.35	
cortex							

Abbreviations: AD-L_{CR}: Alzheimer's Disease patients with low cognitive reserve; AD-H_{CR}:

Alzheimer's Disease patients with high cognitive reserve; a-MCI-L_{CR}: amnesic Mild Cognitive

Impairment patients with low cognitive reserve; a-MCI-H_{CR}: amnesic Mild Cognitive Impairment

patients and high cognitive reserve; HS-L_{CR}: healthy subjects with low cognitive reserve; HS-H_{CR}:

healthy subjects with high cognitive reserve; L= left; R=Right.

See text for further details

Table 4. Fractal dimension in the participants according with their cognitive reserve's level

Group	Brain region	Side	Size	MNI coordinates			Z	p-level FWE- cluster level
				x	y	z		
AD- H_{CR}<AD- L_{CR}								
	Medial temporal gyrus	L	3856	-52	-53	5	3.37	0.001
	Superior Temporal gyrus			-61	-31	0	3.04	
a-MCI- H_{CR} > a- MCI-L_{CR}								
	Temporal pole	R	2715	45	12	-32	3.89	0.019
	Fusiform gyrus			36	-31	-26	2.75	
	Medial temporal gyrus	L	3654	-59	-43	-11	4.11	0.002
	Lateral Occipital gyrus			-45	-64	12	2.40	

Abbreviations: AD-L_{CR}: Alzheimer's Disease patients with low cognitive reserve; AD-H_{CR}:

Alzheimer's Disease patients with high cognitive reserve; a-MCI-L_{CR}: amnesic Mild Cognitive

Impairment patients with low cognitive reserve; a-MCI-H_{CR}: amnesic Mild Cognitive Impairment patients and high cognitive reserve; L= left; R=Right.

See text for further details.

Table 5 Relationship between neuropsychological tests and Cortical thickness and Fractal dimension

Group	Neuropsychological test	Brain region	Side	Size	MNI coordinates			Z	p-level FWE-cluster level
					x	y	z		
Cortical thickness									
AD-HCR									
	15-Word List IR	Posterior parietal lobe	L	1372	-46	-63	20	4.39	<0.001
		Middle temporal gyrus	L		-49	-57	12	3.63	
		Inferior temporal gyrus	L	563	-58	-44	-12	3.75	0.03
		Middle temporal gyrys	R	863	61	-48	4	4.08	0.006
	Raven's Progressive Matrices	Middle frontal gyrus	R	1216	46	7	47	3.75	0.001
		Precentral gyrus	R		38	2	33	3.60	
		Frontal pole	R	545	16	45	34	3.73	0.037

a-MCI-	Digit Span	Inferior	L	531	-45	26	4	5.04	0.030
H_{CR}	backward	frontal							
		gyrus							
HS-H_{CR}	Raven's	Precentral	L	1150	-24	-30	55	4.86	<0.001
	Progressive	gyrus							
	Matrices								
		Postcentral	L	2385	-50	-17	50	4.30	<0.001
		gyrus							
		Precuneus	L	581	-8	-68	26	3.69	0.016
		Precentral	R	985	15	-30	59	4.04	0.001
		gyrus							
	Copy of Drawings	Precentral	R	630	24	-8	48	4.53	0.011
		gyrus							
		Inferior	R	653	38	17	22	4.22	0.009
		frontal							
		gyrus							
<hr/>									
Fractal									
dimension									
a-MCI-	Corsi span forward	Middle	L	649	-63	-41	-11	4.06	0.007
H_{CR}		temporal							
		gyrus							
a-MCI-	15-Word List IR	Middle	L	471	-51	-22	-12	4.04	0.028
LCR		temporal							
		gyrus							

Figure 1.

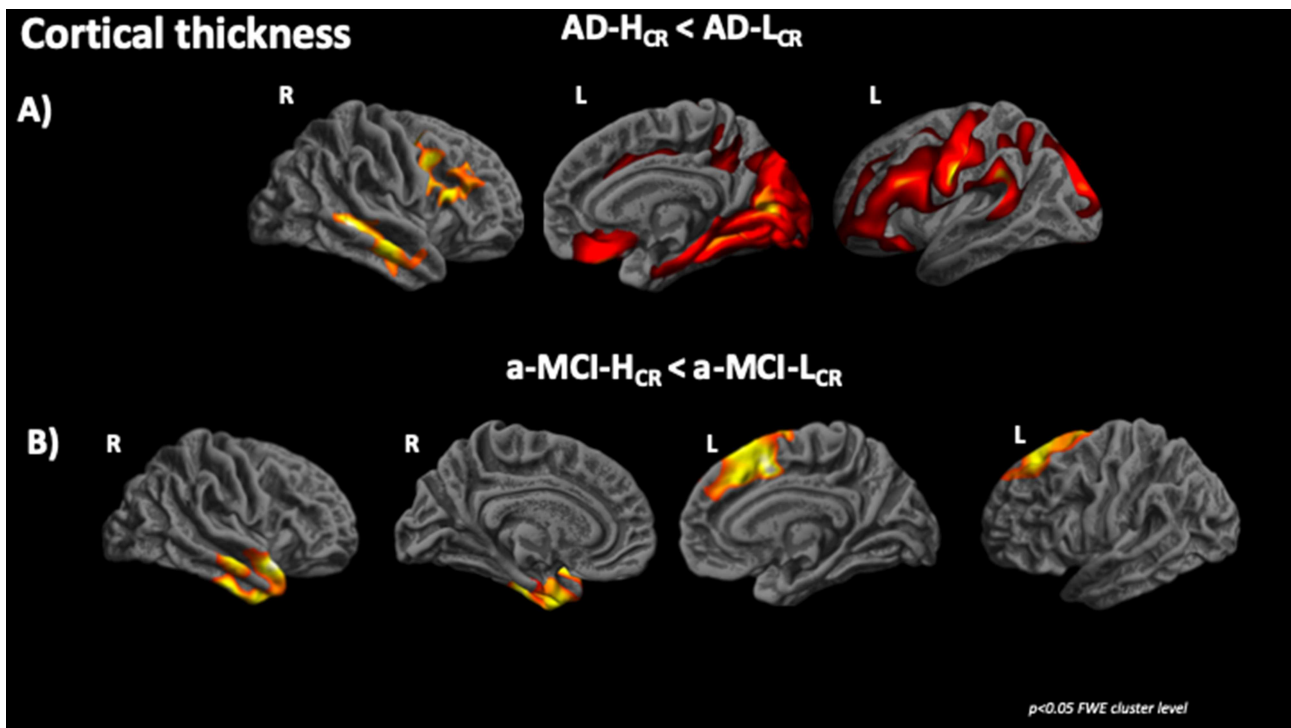


Figure 2.

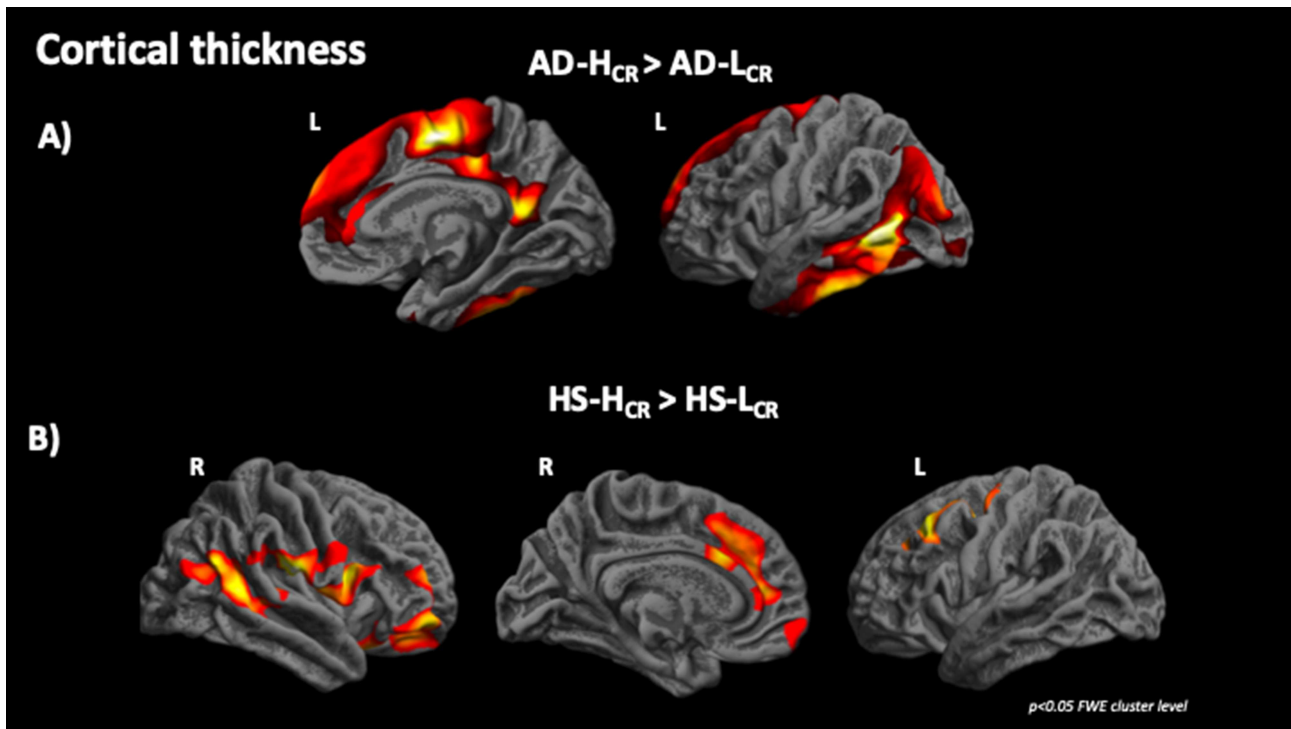


Figure 3.

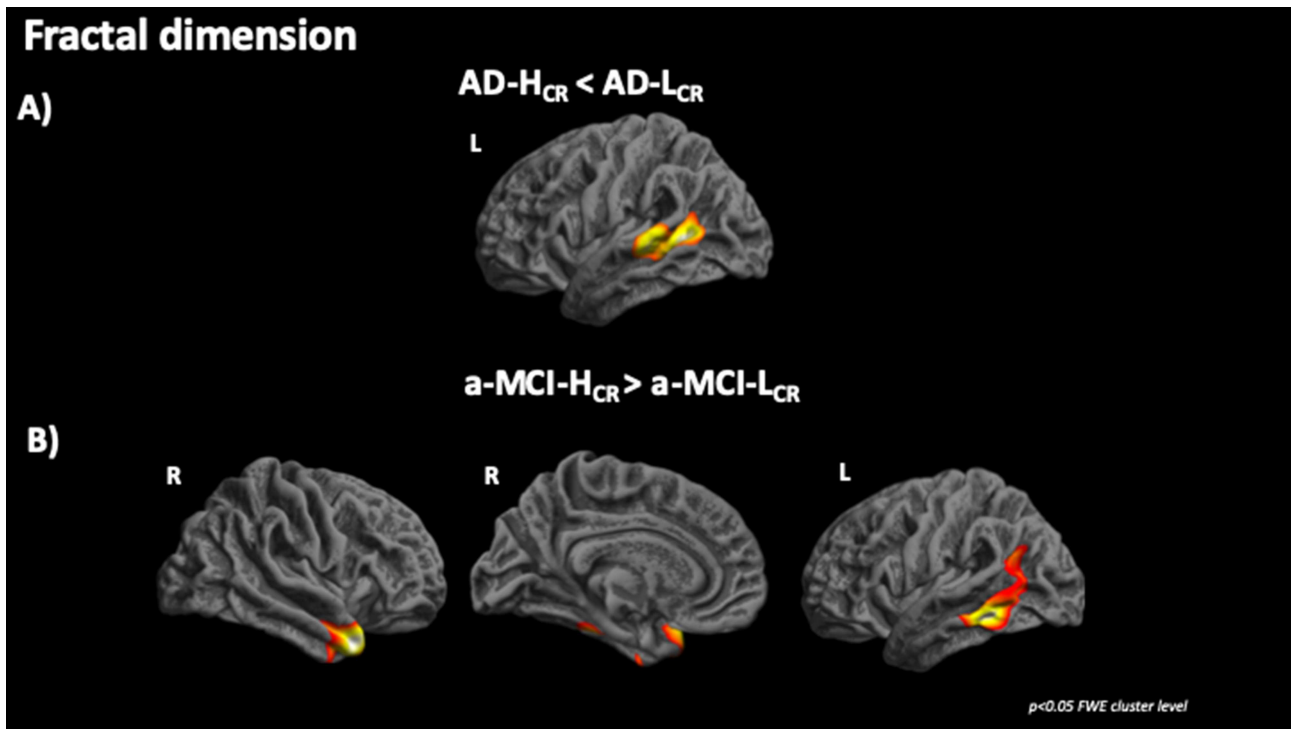


Figure 4.

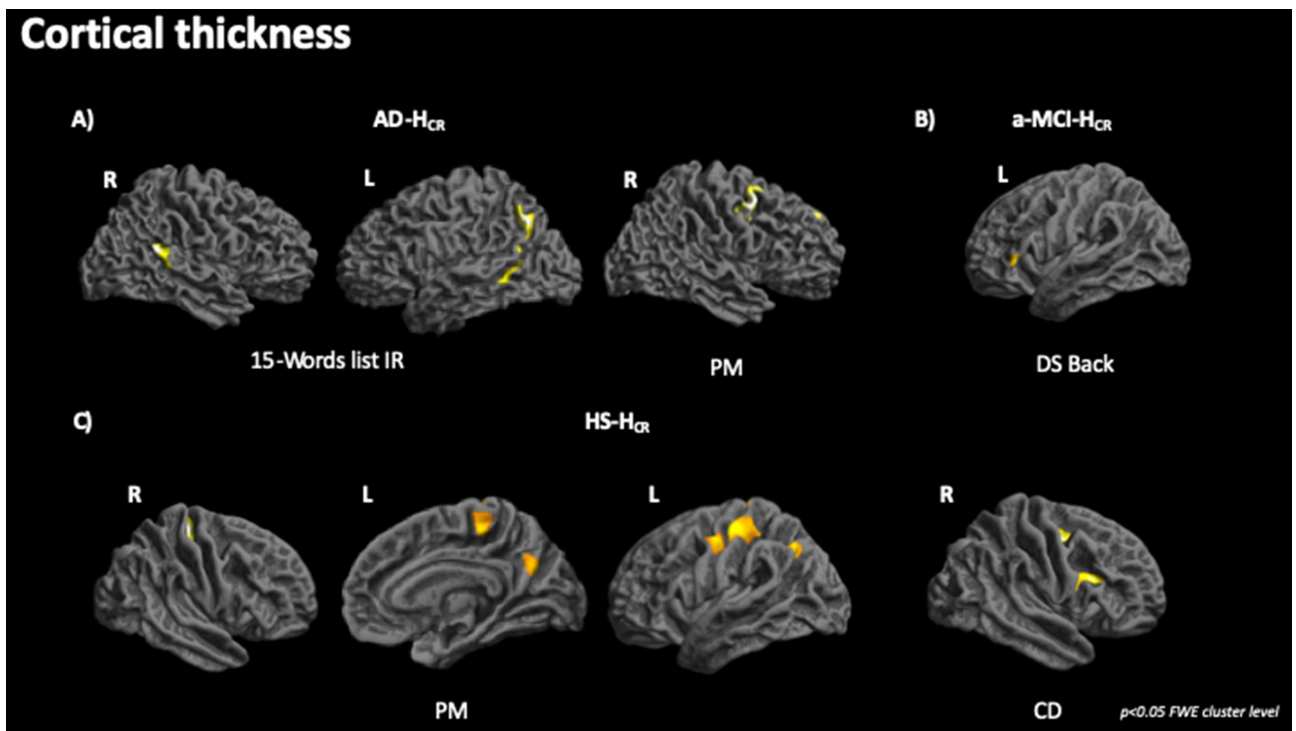
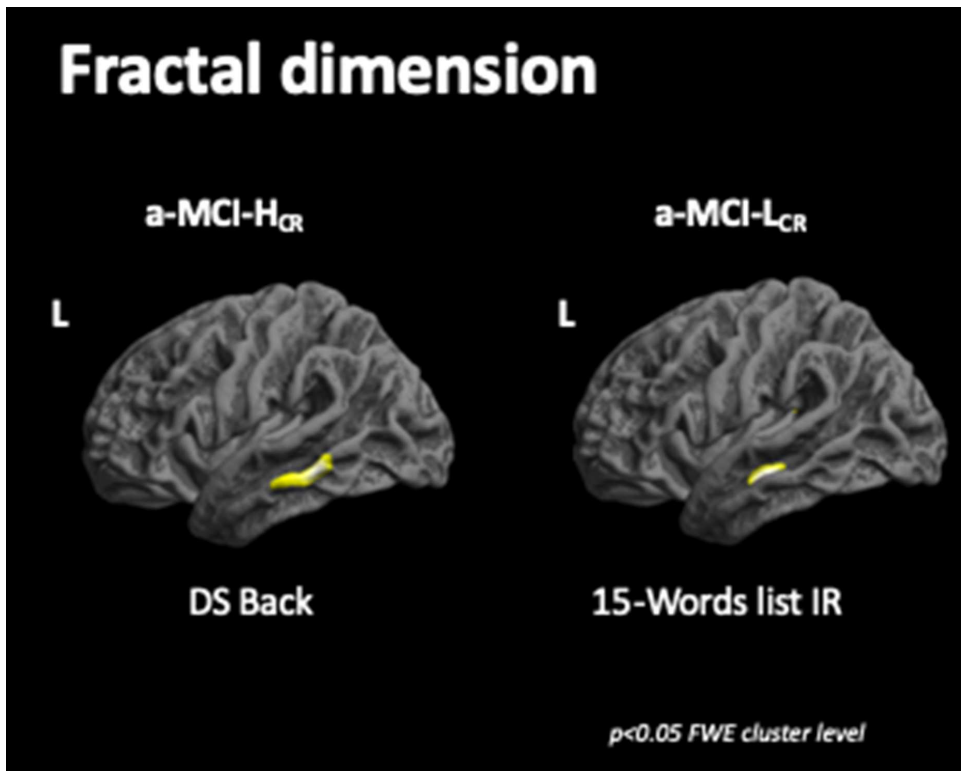


Figure 5.



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