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Understanding the effect of cognitive/brain reserve and depression on regional atrophy in early Alzheimer's disease

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Abstract

Introduction: Depression in patients with mild cognitive impairment (MCI) and dementia of the Alzheimer's type (AD) is associated with worse prognosis. Indeed, depressed MCI patients have worse cognitive performance and greater loss of gray-matter volume in several brain areas. To date, knowledge of the factors that can mitigate this detrimental effect is still limited. The aim of the present study was to understand in what way cognitive reserve/brain reserve and depression interact and are linked to regional atrophy in early stage AD.

Methods: Depression was evaluated with the Patient Health Questionnaire-9 in 90 patients with early AD, and a cut-off of ≥ 5 was used to separate depressed ($n = 44$) from non-depressed ($n = 46$) patients. Each group was further stratified into high/low cognitive reserve/brain reserve. Cognitive reserve was calculated using years of education as proxy, while normalized parenchymal volumes were used to estimate brain reserve. Voxel-based morphometry was carried out to extract and analyze gray-matter maps. 2×2 *ANCOVA*s were run to test the effect of the reserve-by-depression interaction on gray matter. Age and hippocampal ratio were used as covariates. Composite indices of major cognitive domain were also analyzed with comparable models.

Results: No reserve-by-depression interaction was found in the analytical models of gray matter. Depression was associated with less gray matter volume in the cerebellum and parahippocampal gyrus. The brain reserve-by-depression interaction was a significant predictor of executive functioning. Among those with high brain reserve, depressed patients had poorer executive skills. No significant results were found in association with cognitive reserve.

Conclusion: These findings suggest that brain reserve may modulate the association between neurodegeneration and depression in patients with MCI and dementia of the AD type, influencing in particular executive functioning.

Keywords: Alzheimer's disease, depression, brain reserve, cognitive reserve, voxel-based morphometry

1. Introduction

The prevalence of depression among people affected by mild cognitive impairment (MCI) and early Alzheimer's disease (AD) has been reported to be high, with figures that vary between 30% and 50% [1]. Affective symptoms have been found to increase psychological burden in caregivers [2] and to have a huge impact on quality of life of patients [3], who are more likely to access care facilities at a time earlier than non-depressed patients [4]. Depression in patients with AD may play a specific role in accelerating cognitive decline, as found by a longitudinal study that reported a faster drop in Mini Mental State Examination scores of depressed patients [5]. Moreover, depressive symptoms also affect specific cognitive functions, such as episodic memory and working memory [6] and executive functions in people with MCI [7].

Neuroimaging investigations have shown that depression may worsen the evolution of AD-related neurodegeneration by fostering loss of gray matter. Indeed, a study that used voxel-based morphometry (VBM) found that the co-presence of MCI and depression influences the reduction of volume in frontal and temporal areas [8]. Consistently, depressed patients with AD, compared to those without depression, showed greater reduction of gray-matter volume in the left inferior temporal gyrus [9]. Another study found that depressive symptoms were instead associated with cortical thinning in parietal and temporal areas in this same diagnostic population [10].

Two major factors have long been hypothesized to account for resilience against neurodegenerative diseases like AD: brain and cognitive reserve [11]. These concepts may explain, in different neurodegenerative conditions, the difference observed between the degree of brain damage and the manifestation of clinical symptoms [12].

Brain reserve refers to the structural architecture of the brain and it is considered a passive model of resilience: the more brain tissue, the more neuropathological damage necessary to

cross a threshold that would cause deficits to emerge [13]. Differently, cognitive reserve is an active model that describes reserve in terms of flexibility of brain functioning implemented during one's whole life course [13]. Cognitive reserve has mainly been assessed indirectly, by means of proxies such as education, level of occupation, mental and physical leisure activities [14]. Different studies have shown that both reserve factors seem to have a neuroprotective role against the clinical manifestation of AD [15,16].

In other words, high levels of brain and cognitive reserve do not prevent the accumulation of brain pathology due to AD, but do modulate the symptomatic manifestations [17]. Indeed, despite the ongoing progressive pathology, high cognitive reserve might preserve cognitive functioning by optimizing the use of brain networks, characterized by greater efficiency or capacity, or by fostering compensatory mechanisms [18]. On this note, a VBM study found more severe gray matter atrophy in medial temporal areas (particularly susceptible to AD pathology) in MCI patients with high cognitive reserve, compared to those with low cognitive reserve [19]. The former group showed also larger gray-matter volume in fronto-parietal associative regions and better cognitive performance on tasks of visual-spatial and executive abilities.

Hence, cognitive/brain reserve and depression appear to have opposite effects on brain atrophy and cognitive functioning. In a recent work, Opdebeeck et al. [20] investigated in a sample of older adults without neurodegenerative diseases whether high cognitive reserve (measured as a composite score including education, occupation and social and cognitive engagement) could mediate the negative association between mood disturbance and cognitive functioning. They found that cognition was significantly worse in elderly with depression and low cognitive reserve compared to those with high cognitive reserve.

Based on the limited number of studies on the structural brain changes associated with depression in patients with MCI and AD and the scarce knowledge about the factors that can

mitigate the detrimental effect of this neuropsychiatric symptom on neurological functioning, we investigated the possible interaction between depression and measures of cognitive and brain reserve. We chose to rely on a non-clinical cut-off to establish the presence of depressive symptoms, rather than to use a measure of depressive symptoms that would highlight symptoms of a severity of clinical relevance. We did so to focus on the mechanisms that link reserve and the depression continuum in more general terms without the need to refer exclusively to clinically-relevant stages.

2. Material and methods

2.1. Sample

One-hundred-and-forty-five patients with a clinical diagnosis of amnestic MCI due to AD [21] or AD dementia [22] were considered for inclusion in this study. These patients had been recruited from the memory clinics of the Royal Hallamshire Hospital (Sheffield, UK) and the nstitute of Clinical Medicine (Kuopio, Finland) as part of the EU-funded (Framework Programme 7) "Virtual Physiological Human – DementiA Research Enabled by IT" initiative (http://www.vph-dare.eu/) and had passed an initial screening in which major diagnostic exclusion criteria were ruled out, including a clinically significant history of mental illness and diagnostic elements suggesting potential diagnosis of pseudo-dementia.

Presence of depressive symptoms was evaluated with the Patient Health Questionnaire (PHQ-9) [23], a tool that has been shown to have good diagnostic properties in medical populations. A score of ≥ 5 was used as cut-off to distinguish depressed from non-depressed patients. Of the 145 patients meeting the study criteria, all those showing depression (n = 46) were included. A group of n = 46 non-depressed patients matched for major demographic variables

was also selected. Of the 92 patients, 2 datasets did not include MRI images and were thus discarded, giving a final sample of 90 patients (44 depressed/46 non-depressed, 50 MCI/40 dementia). A proportion of these patients also had CSF biomarkers assessments. The complete characterization of the cohort included in the analyses is reported in **Table 1**.

--- Please insert **Table 1** about here ---

This study was approved by the Yorkshire and Humber Regional Ethics Committee (Ref No: 12/YH/0474) for the Sheffield cohort and by the ethics committee of the Northern Savonia Hospital District for the Kuopio cohort. Written informed consent was obtained from each participant prior to enrollment.

2.2. VBM pre-processing

For each patient T1-weighted and Fluid-attenuated inversion recovery (FLAIR) scans were acquired at 3 T (Philips Ingenia). 3D T1-weighted images were set as follows: gradient echo, TR = 8.22 ms, TE = 3.8 ms, matrix 256 × 256, voxel size 0.94 × 0.94 × 1.1 mm^3, FOV = 240°. FLAIR images were instead recorded with the following specifications: voxel size: 0.56 mm^3, TR: 4.8 s; TE: 0.20 s; matrix size 448 × 448.

All analyses were carried out using Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Centre for Neuroimaging, London, UK) on MATLAB R2014a (Mathworks Inc., UK). T1-weighted images were pre-processed following a two-step VBM procedure: first they were reoriented to the bicommissural line and subsequently segmented in order to divide three brain tissues, i.e., gray matter, white matter and cerebrospinal fluid. Furthermore, maps of gray matter were normalized and modulated. Finally, they were smoothed with an 8 mm full-width at half maximum Gaussian kernel to maximize the signal and minimize artefacts.

FLAIR and T1-weighted scans were used to segment white matter lesions automatically using the Lesion Segmentation Tool toolbox for SPM [24]. White-matter lesion volume was quantified in milliliters and compared across groups to rule out major differences in hyperintensity burden.

Global macro-structural tissue-specific volumes were extracted for the calculation brain reserve using the "get_totals" command in Matlab (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).

2.3. Cognitive and other clinical variables

Three indices were created to assess different cognitive domains: episodic memory, semantic memory and executive function. Raw scores were initially transformed into *z* scores. Each index was then calculated averaging the *z* scores of specific neuropsychological tests. In detail, the episodic-memory index was constructed based on the delayed recall of the Logical Memory Test and two distinct verbal memory tests (assessing word learning and delayed recall) administered as part of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery [25]. The executive-function index comprised the Digit Span Test - Backwards and the Letter Fluency test. Finally, the semantic-memory index was based upon the Category Fluency test, the Similarities tests (as included in the WAIS battery) and the 15-item Boston Naming included in the CERAD battery.

Anxiety levels were assessed to characterize the sample more in detail by means of the Generalized Anxiety Disorder (GAD-7) [26].

Two proxy measures of reserve were used: level of education, quantified in years, for cognitive reserve and the parenchymal volume (normalized based on total intracranial volume) for brain reserve. Median values were calculated for each of these two measures in order to

split the patient cohort into subgroups of high or low reserve. The median cut-offs were 11 years of education for cognitive reserve and 0.67 for brain reserve.

2.4. Statistical analysis

A 2×2 *ANCOVA* was run to investigate the voxel-based effect of the interaction between depression (present vs. absent) and each measure of reserve (high vs. low) on gray-matter maps. Age and hippocampal ratio were used as covariates. Hippocampal ratios, calculated as a fraction of hippocampal volume (including both left and right hippocampi) divided by total gray-matter volume, served to correct for neurodegenerative severity [27].
Similarly, 2×2 *ANCOVA*s were set up to investigate the effect of the interaction on the neuropsychological indices (age and hippocampal ratio were used as covariates in these models as well). This second set of analyses was carried out using IBM SPSS Statistics Version 24 (IBM, Chicago, IL, USA).

3. Results

3.1. VBM results

A significant main effect of depression was found in a bilateral cluster extending between cerebellar and parahippocampal cortices, with depressed patients showing smaller tissue volumes (**Table 2**). Concomitantly, a significant main effect of brain reserve was also found and this extended widely across most of the brain. No significant effect of the brain reserve-by-depression interaction was observed.

No significant results were found in association with the models that included cognitive reserve. A trend of smaller volume in cerebellar and temporal regions was found in depressed patients, along the same lines as the findings emerging from the analysis of brain reserve.

--- Please insert **Table 2** about here ---

3.2. Behavioral results

In the entire cohort scores on the PHQ-9 questionnaires were significantly correlated with the Executive-Functions index (*Spearman's rho* = -0.32; $p < 0.01$), showed a trend association with the Semantic-Memory index (*Spearman's rho* = -0.19; $p = 0.07$) and showed no significant associations with the Episodic-Memory index. BR and CR were instead positively associated with all three cognitive indices.

In the 2×2 *ANCOVA* models the interaction between brain reserve and depression was a significant predictor of executive cognitive performance ($p = 0.02$) (**Figure 1**). A main effect of brain reserve was observed for all cognitive indices ($p < 0.01$), with high brain reserve associated with better cognitive performance. Depressed patients obtained significantly lower scores on executive functioning than non-depressed patients ($p = < 0.01$).

Post hoc analyses were run to characterize the interaction more in detail. Among patients with low brain reserve no differences in cognitive performance were found between those with ($n = 22$) and without depression ($n = 23$). However, in patients with high brain reserve, depressed patients scored significantly worse than non-depressed ones on the indices of executive functioning ($p < 0.01$) and semantic memory ($p = 0.02$) (**Table 3**).

--- Please insert **Figure 1** and **Table 3** about here ---

No significant effects emerged from the model testing the interaction between cognitive reserve and depression.

3.3. Use of occupational attainment as part of the CR construct

Details on patients' lifetime occupations were available for 56 cases. To compute a more elaborate composite index of CR, the procedure described by Garibotto and colleagues [28] was followed to combine educational and occupational attainment in the form of an ordinal number ranging from 2 to 12. A median split was then carried out to separate patients with low and high CR and *post hoc* models were run to test the effect of this variable with the same methodology as that described in Section 2.4. No effect of the interaction emerged. This additional CR proxy was, however, associated with grey matter in the inferior frontal gyrus, lentiform nucleus and cerebellum, and was also associated with all three cognitive indices: episodic memory ($F = 6.801$, $p = 0.012$), semantic memory ($F = 28.179$, $p < 0.001$), and executive functions ($F = 14.466$, $p < 0.001$). Since however these results were only found in a sub-sample of the original cohort and did not extend to the entire group, their significance can only be interpreted as a trend.

4. Discussion

In this study we investigated the interplay between measures of reserve and depression, and how this interaction might modulate gray-matter loss and cognitive functioning in a cohort of patients diagnosed with MCI or mild dementia of the AD type.

Gray matter was not associated with cognitive reserve, neither when main effects nor when the interaction with depression symptomatology was studied. This is likely to be due to the fact that VBM, although significant results have been previously observed [19], is not sensitive enough to reveal the effect of cognitive reserve on the cerebral structure since this factor appears to be mainly related to the functional architecture of the brain [13].

Similarly, no interaction was found between levels of brain reserve and presence of depression. This negative finding may indicate that depressive symptoms may manifest as a consequence of AD pathology independently of the proportion of neural tissue possessed. Indeed, no differences in brain reserve were detected between depressed and non-depressed patients. Nonetheless, self-reported depression appeared to be associated with lower gray matter volume, in line with previous knowledge [29,30]. In particular, differences were found in a cluster comprising extensive portions of the cerebellum, brain region which appears to contribute to regulation of mood [31], and the parahippocampal gyrus, a region particularly affected by AD pathology [32,33] and late-life depression [34].

From the analyses of cognitive domains in the entire cohort, instead, an interaction between brain reserve and depressive symptoms emerged for executive function performance. *Post hoc* analyses revealed that when patients were split based on their brain-reserve level, depression affected those with high brain reserve since in this sub-cohort depressed patients performed significantly worse on the executive-function index. Indeed, depressive symptoms in healthy older adults and patients with AD are known to be associated with an impairment in executive functions [7,35]. In fact, in our sample the presence of self-reported depressive symptoms was associated with worse executive performance, while a significant main effect of brain reserve was found predictive of performance on all the three cognitive domains.

These findings show that, although no modulating effects of brain reserve could be

highlighted at the macro-structural neural level in relation to depression, cognitive performance of patients with mood alterations is positively influenced by such variable. Cognitive reserve showed instead neither a significant interaction with depressive symptoms nor a main effect on cognitive performance. This may be due to the fact that brain reserve may significantly explain variability in cognitive abilities of people affected by AD presenting with various degrees of depressed mood better than cognitive reserve. Indeed, depression in AD may, to some extent, be consequential to neurodegenerative changes rather than completely due to patients' awareness of their condition [36]. Thus, possessing more brain tissue may modulate the detrimental impact that depression may have on AD-related cognitive decline.

This study is not free from limitations. Although the PHQ-9 is a useful screening instrument that provides a comprehensive summary of the patients' symptoms in a way that is of easy application in secondary and tertiary care units, cut-off values may need adaptation for use with people with cognitive impairment [37]. Therefore, more thorough evaluations are needed to reach a proper clinical diagnosis of depression. In fact, an inspection of individual PHQ-9 items of available scoresheets revealed that the main symptoms reported were insomnia, loss of energy and concentration difficulties. Vice versa, depressed mood or anhedonia, at the basis of a diagnosis of depression according to DSM-5 criteria, were reported by very few patients. However, the aim of this study was to investigate depressive symptoms, rather than major depressive disorder of clinical relevance. At the centre of the experimental hypothesis was the interactive mechanistic link between reserve and depression. A validated clinical cut-off (i.e. PHQ-9 score $\geq$ 10) may be more indicated for studies focusing on clinical depression. In fact, patients who reported high levels of depressive symptoms had no history of depression and were not treated with antidepressants. Furthermore, the patients' symptoms might in part originate from increased awareness of their

cognitive and functional difficulties, which is supported by increased volumetric integrity compared to non-depressed patients. Moreover, another limitation could be the use of a single proxy for cognitive reserve. A composite index that takes into account additional socio-behavioral measures, might be more sensitive to capturing the protective effects of this construct. Finally, we also acknowledge that there was no voxel-by-voxel neuropathological information coming from *in vivo* molecular imaging of amyloid and tau depositions. Such piece of evidence would have been extremely informative to interpret the link between grey-matter volume and the effect of our two predictors (depression and reserve). Future prospective studies are needed to address this shortcoming.

5. Conclusion

These findings suggest that brain reserve modulates the statistical association between depression and neurodegenerative processes in patients with MCI and dementia of the AD type. Further investigations are needed to clarify the modulatory role played by cognitive reserve in this clinical population. Further neuroimaging studies may help disentangle the influence of these resilience factors, especially using a combination of functional and structural MRI, and may provide useful information to treatment research.

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Figure Caption

Figure 1 Results of the analysis on the interaction between brain reserve and depression on cognitive performance.

Table 1. Demographic and neurostructural characteristics of the cohort

Descriptive Variable	**Depressed**	**Non-depressed**	***p***
Diagnosis (MCI/AD)	23/21	27/19	0.54
Age (years)	66.57 (9.93)	67.72 (10.09)	0.59
Gender (f/m)	21/23	20/26	0.69
GAD-7	8.20 (5.71)	1.98 (1.86)	< 0.01
Brain Reserve	0.68 (0.08)	0.68 (0.08)	0.81
Cognitive Reserve (Education years)	11.11 (3.22)	12.07 (3.52)	0.18
Hippocampal Ratio	1.27e-02 (8.52e-04)	1.26e-02(7.96e-04)	0.43
White Matter Hyperintensities (ml)	5.52 (7.81)	8.51 (11.52)	0.16

Counts are reported for dychotomical variables (i.e., diagnosis and gender. Means and standard deviations are indicated for all other variables. Differences in diagnosis and gender proportions were tested with a *chi-squared* test. All remaining variables were analysed with independent-sample *t* tests.

Figure 1

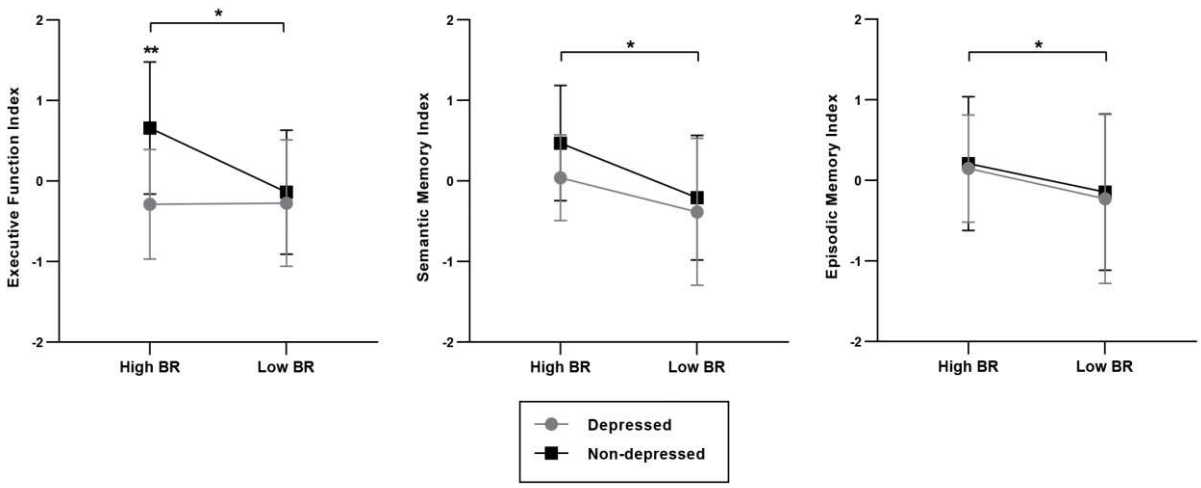

Table 2. Main effect of depression on gray matter volume (Non-Depressed > Depressed)

Cluster extent	Side	Brain region	*t* value	MNI coordinates		
				x	y	z
11955	R	Pyramis	3.12	32	-80	-42
	L	Culmen	3.03	-15	-42	-16

R	Dentate nucleus	2.99	12	-54	-34
R	Inferior semi-lunar lobule	2.86	28	-72	-56
R	Inferior semi-lunar lobule	2.70	22	-80	-50
R	Culmen	2.65	18	-33	-14
R	Culmen	2.63	18	-62	-15
R	Parahippocampal gyrus	2.58	12	-42	-3
R	Declive	2.49	26	-72	-27
L	Declive	2.47	-24	-75	-26
R	Declive	2.45	36	-78	-28
L	Vermis	2.35	0	-70	-33
R	Tonsil	2.25	9	-46	-48
R	Tonsil	2.24	42	-42	-46
L	Culmen	2.23	0	-50	-15
L	Tonsil	2.21	-2	-56	-42

$p < 0.05$ FWE

Table 3 *Post hoc* analyses comparing depressed patients with high vs. low brain reserve and non-depressed patients with high vs. low brain reserve. The cognitive indices are the result of *z*-score transformation. Mean and standard deviation are included in each cell.

Cognitive Variable	Depressed	Non-Depressed	*F*	*p*
Patients with High Brain Reserve				
Episodic-Memory Index	0.15 (0.67)	0.21 (0.83)	1.00	0.76
Semantic-Memory Index	0.04 (0.53)	0.47 (0.71)	5.85	0.02*
Executive-Functions Index	-0.29 (0.68)	0.66 (0.82)	16.36	< 0.001**
Patients with Low Brain Reserve				
Episodic-Memory Index	-0.23 (1.05)	-0.14 (0.97)	0.23	0.63
Semantic-Memory Index	-0.38 (0.91)	-0.21 (0.77)	0.53	0.47
Executive-Function Index	-0.27 (0.78)	-0.14 (0.77)	0.44	0.51