The neurobiological substrates of dynamic cognitive reserve

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INTRODUCTION

Cognitive reserve (CR) is a theoretical framework used to explain the different individual resilience to neurodegeneration[1]. Two different underling mechanisms have been hypothesised, the neural reserve and the neural compensation that makes the brain better able to resist or compensate for brain damage[1]. Several previous studies investigated the effect of CR on brain resilience due to the lifestyle enrichment[1]. The most of the studies used static measures of CR[2,3], such as years of formal education[4,5] or occupational attainment that were no able to assess specifically the changes in the patients' cognition. In addition, these static measures are imprecise because they may relate to cognitive performance for reasons other than the reserve mechanisms[2]. For instance the same level of education or of occupational attainment does not reflect the same experience in all individuals[2]. Moreover, CR is modifiable throughout life and previous studies reported that high level of leisure cognitive, social and also physical activities performed during life reduced the risk of developing dementia[1,3-6]. More targeted studies investigated in patients with AD[2] and in healthy elderly[2] the CR measured in terms of changes in memory functions. All these previous studies quantified CR as residual variance of memory scores, accounted for demographical and brain damage variables. The residual method is in line with a definition of CR[2] as discrepancy between observed performance and expected level of performance. Therefore, individuals who perform better than predicted show positive residual score. It means that they have high CR. Conversely, subjects who perform worse than predicted show negative residual score and they have low CR. The residual variable (expressing the CR) differs from the observed score (in this case quantified as memory performance) because variance related to demographics, brain damage and cognitive efficiency was ruled out, in addition to error. To conceptualize CR in terms of residual variance of memory functions made the CR's concept more flexible and adaptable to cognitive changes. It involves a more dynamic concept of CR that better fit with the cognitive changes due to aging and neurodegeneration. However, some of these studies considered the brain pathology (in terms of white matter hyperintenisites, hippocampal or total intracranial volumes, etc.) as part of the composition of memory variance[2]. In our knowledge no previous study investigated the relationship between CR considered as residual variance of memory scores over time and regional grey matter volumes changes in AD patients at predementia stage. For this purpose we recruited a cohort of amnestic mild cognitive impairment due to AD patients and used the actual and previous memory performances as a measures of dynamic CR. Moreover, we investigated the potential association between the measure of dynamic CR and regional gray matter volume changes by using the voxel-based morphometry technique (VBM). Finally, we aimed at assessing the classification power in Converters and Non-Converters of the dynamic CR indexes.

MATERIAL AND METHODS

34 a-MCI

48 Healthy elderly (HE)

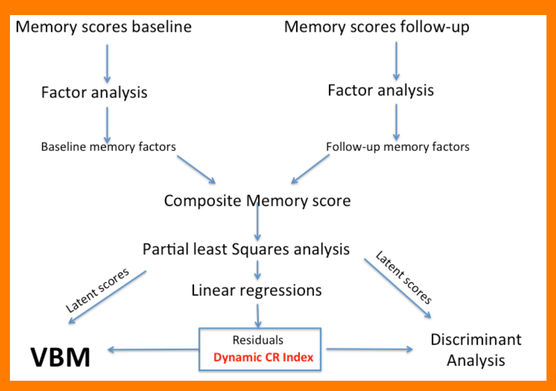
→ **Extensive neuropsychological assessment and 3T-MRI scans (T1-weighted images for Voxel-based morphometry analysis)**

Only episodic memory scores entered in the analyses. Specifically, 15-Word List Immediate recall (W-IR), 15-Word List Delayed recall (W-DR), 15-Word List Recognition Hit-Rates (W-HR), 15-Word List Recognition False (W-F), Short Story test Immediate (SS-IR) and Short Story test Delayed recall (SS-DR) scores entered as variable of interest in factor analyses.

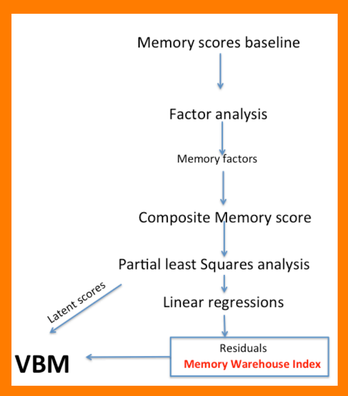
Demographic features of studied subjects

Baseline	a-MCI N=34	HE N=48
Mean (SD) age [years]*	70.9 (7.9)	69.2 (6.1)
Gender (F/M)[b]	19/15	20/24
Mean (SD) years of formal education*	10.5 (4.3)•	12.5 (3.7)
Mean (SD) MMSE score*	26.9 (2.0)•	28.9 (1.1)
Follow-up	**Converters N=15**	**Non-Converters N=19**
Mean (SD) age [years]*	73.6 (6.8)	72.9 (8.7)
Gender (F/M)[b]	12/3#	7/12
Mean (SD) years of formal education*	9.4 (4.2)	11.4 (4.4)
Mean (SD) MMSE score*	21.5 (5.4)#	28.0 (2.2)

Flow-chart of a-MCI to extract CR indexes



Flow-chart of HE to extract CR indexes



VBM correlational analyses

A one-sample T-test were employed to assess correlations between LT scores, d-CR, r-MW indexes and regional GM volumes in a-MCI patients and HE groups, respectively. Intracranial volume (obtained by adding up WM volume +GM volume + CSF volume) was entered in all analyses as covariate of no interest. Results were accepted as significant at p values<0.05 FWE corrected at cluster level.

RESULTS

Memory performances obtained by a-MCI compared with HE at baseline and by patients at follow-up

A) Baseline Domain	Test	a-MCI	HE
Verbal episodic long-term memory			
	W-IR	26.3 (7.1)*	40.4 (9.6)
	W-DR	3.1 (2.4)*	8.2 (2.3)
	W-HR	10.0 (3.0)*	13.4 (1.6)
	W-F	3.8 (3.7)*	1.6 (1.8)
	SS-IR	3.4 (1.8)*	5.6 (1.4)
	SS-DR	3.2 (2.5)*	5.5 (1.3)
B) Follow-up Domain	**Test**	**Converters**	**Non-Converters**
Verbal episodic long-term memory			
	W-IR	18.6 (6.6)#	32.3 (10.0)
	W-DR	1.3 (1.5)#	3.8 (2.9)
	W-HR	8.3 (5.3)	11.1 (2.7)
	W-F	9.4 (9.0)	3.4 (4.1)
	SS-IR	3.0 (2.7)	5.4 (1.3)
	SS-DR	1.0 (2.2)#	4.5 (2.3)

Results of factor analyses: total variance explained in a-MCI

Baseline

Factor	Initial Eigenvalues Total	% of Variance	% Cumulative	Extraction Sum of Squares Loadings# Total	% of Variance	% Cumulative	Rotate Extraction Sum of Squares Loadings* Total	% of Variance	% Cumulative
1	**2.51**	41.81	41.81	2.35	39.24	39.24	1.82	30.38	30.38
2	**1.46**	24.42	66.22	0.98	16.38	55.63	1.51	25.24	55.62
3	0.94	15.65	81.87						
4	0.66	10.99	92.87						
5	0.27	4.59	97.46						
6	0.15	2.54	100.00						

Follow-up

Factor	Initial Eigenvalues Total	% of Variance	% Cumulative	Extraction Sum of Squares Loadings# Total	% of Variance	% Cumulative	Rotate Extraction Sum of Squares Loadings* Total	% of Variance	% Cumulative
1	**3.31**	55.10	55.10	3.07	55.11	51.11	2.94	48.95	48.95
2	**1.30**	21.70	76.80	0.98	16.33	67.45	1.11	18.50	67.45
3	0.70	11.67	88.47						
4	0.38	6.33	94.80						
5	0.19	3.23	98.03						
6	0.12	1.97	100.00						

Extraction method: Maximum Likelihood; *Rotation method: Varimax with Kaiser Normalization

Results of factor analyses: total variance explained in HE

Total variance explained

Factor	Initial Eigenvalues Total	% of Variance	% Cumulative	Extraction Sum of Squares Loadings# Total	% of Variance	% Cumulative	Rotate Extraction Sum of Squares Loadings* Total	% of Variance	% Cumulative
1	**2.28**	38.00	38.00	1.82	30.34	30.34	1.85	30.92	30.92
2	**1.94**	32.30	70.30	1.85	30.86	61.21	1.82	30.29	61.21
3	0.74	12.44	82.74						
4	0.64	10.78	93.53						
5	0.26	4.37	97.90						
6	0.12	2.09	100.00						

Extraction method: Maximum Likelihood; *Rotation method: Varimax with Kaiser Normalization

From the initial six verbal episodic memory scores entered in the analyses, two factors were extracted for baseline and others two factors were extracted for follow-up visit in a- MCI patients. In HE group .
In both cases the Goodness-of-fit test were not significant (for a-MCI Baseline: Chi-square 6.53, df=4, p=0.16; Follow-up: 7.74, df=4, p=0.10; and for HE: Chi-square=0.09, df=4, p=0.999) revealing that the extracted factors are a good description of the data

The C-MS was created by averaging the four extracted factors (Factor 1 and Factor 2) both for baseline and follow-up in a-MCI patients, and only for baseline in HE group. The C-MS were used in the Partial Least Squares analyses separately for patients and controls.

Partial Least Squares analysis in a-MCI

Panel A Latent factors	Independent variable (X) % of Variance	% Cumulative	Dependent variable (Y) % of Variance	% Cumulative	R^2
1	**0.36**	**0.36**	**0.36**	**0.36**	**0.34**
2	0.17	0.54	0.01	0.37	0.33
3	0.25	0.79	0.01	0.38	0.31
4	0.13	0.92	0.01	0.39	0.29
5	0.08	0.99	0.01	0.40	0.27
Panel B	**VIP index**	**B-matrix**	**Weight**	**Loadings**	
Gender	0.53	-0.09	-0.22	-0.26	
Age baseline	1.12	-0.01	-0.46	-0.51	
Education	0.40	-0.01	-0.16	-0.11	
Age follow-up	1.08	-0.01	-0.44	-0.51	
MMSE baseline	**1.36**	**0.06**	**0.55**	**0.48**	
MMSE follow-up	1.13	0.02	0.46	0.43	

Five latent variables (panel A) were extracted by PLS. The first latent variable (LT[1st]) explained the most of the variance of X and Y (36.0% in both cases) therefore it was retained for further analysis.
Moreover, the LT[1st] was significantly different (t=-2.87, df=32, p=0.007) in Converters (mean±SD: -0.74±1.1) compared to Non-Converters (mean±SD: 0.59±1.5).
The VIP index and the loadings (Panel B) revealed that the MMSE scores at baseline contributed for the mostly in the composition of LT[1st] variance. Therefore MMSE scores at baseline were regressed again from the LT[1st]. According to the Methods, the residual values of the LT[1st] was considered a proxy of dynamic CR (d-CR). However, no significant difference was found in the mean of d-CR index (t-0.66, df=32, p=0.51) between Converters (mean±SD: -0.03±0.2) and Non-Converters (mean±SD: 0.03±0.3).

Discriminant analysis

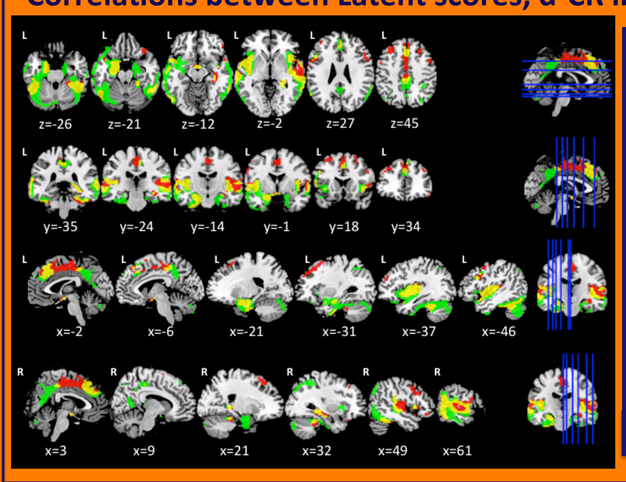
The LT[1st] resulted as the best predictors for patients' conversion to AD (Wilks's lambda= 0.79, F=8.24, p<0.007; 73.3% sensitivity; 63.2% specificity; 67.6% accuracy). Conversely, when only d-CR index was considered in the analysis, it showed a modest ability to correctly classify patients (53.3% sensitivity; 57.9% specificity; 55.9% accuracy).

Partial Least Squares analysis in HE

Panel A Latent factors	Independent variable (X) % of Variance	% Cumulative	Dependent variable (Y) % of Variance	% Cumulative	R^2
1	**0.40**	**0.40**	**0.22**	**0.22**	**0.20**
2	0.17	0.57	0.01	0.23	0.19
3	0.27	0.85	0.01	0.23	0.18
4	0.15	1.00	0.001	0.23	0.16
Panel B	**VIP index**	**B-matrix**	**Weight**	**Loadings**	
Gender	0.70	0.20	0.35	0.32	
Age	0.92	-0.02	-0.46	-0.48	
Education	0.80	0.01	0.40	0.50	
MMSE	**1.42**	**0.19**	**0.71**	**0.65**	

In HE group four latent variables (panel A) were extracted by PLS analysis, and, also in this case, the LT[1st] explained the most of the variance (40% for X and 22% for Y, respectively). The VIP index and the loadings revealed that MMSE score contributed for the mostly in the composition of LT[1st]'s variance also for the HE group. Again MMSE scores was regressed from LT[1st] producing the residual LT[1st] value considered as r-MW. Finally, as stated in the Methods, residual LT[1st] and r-MW scores were used as variable of interest in the MRI analyses.

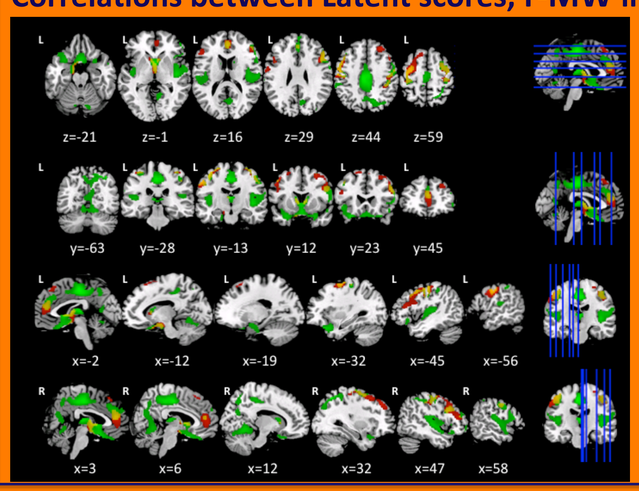
Correlations between Latent scores, d-CR index and regional GM volumes in a-MCI



The VBM correlation analysis in a-MCI revealed a significant direct association between LT[1st] scores and between d-CR index and regional GM volumes, respectively.
When considering LT[1st] scores as variable of interest (in green) we found significant correlations with GM volumes in widespread brain areas involving bilaterally anterior cingulate cortex (ACC, BA32), Posterior Cingulate Cortex (PCC, BA31) precuneus (BA7), hippocampus, perihinal, entorhinal and parahippocampal gyrus (BAs28, 35 and 34), insular cortex and extensively the cerebellum (mainly Crus-I, Lobule-VII).
When considering the d-CR index we found significant correlations with regional GM volumes in several brain areas. A part of these brain areas were the same observed in the previous analysis (the overlapped areas are shown in yellow in the Figure). Conversely, we found also a specific association (in red in Figure) mainly in the bilateral posterior middle part of the ACC (pm-ACC), in the superior frontal gyrus bilaterally (BA8), in the right orbitofrontal cortex (BA47), in the right superior temporal gyrus (BA22).

d-CR LT[1st] overlap

Correlations between Latent scores, r-MW index and regional GM volumes in HE



In HE group we found a significant positive association between LT[1st] scores (in green in Figure) and regional GM volumes involving mainly orbito-frontal cortex (BA47), ACC (BA32), PCC (BA31), precuneus (BA7), premotor cortex (BA6), insula, fornix and the thalamus bilaterally. We found also an association with the left amygdala and the hippocampus and with cerebellum (mainly the lobule VI bilaterally). When considering the r-MW index we found an overlap (in yellow in Figure) with the bilateral BA6, in the left amygdala, the bilateral thalamus, and finally in the bilateral ACC (BA32) and in the left orbito-frontal cortex (BA47). Conversely, we found specific association between r-MW index (in red) and GM volumes only in the left dorsolateral prefrontal cortex (BA46) and in the most medial part of the BA6 bilaterally

r-MW LT[1st] overlap

DISCUSSION

In the present study we investigated the neural substrates underlying different levels of CR assessed by dynamic measures. We created indexes of dynamic CR from available verbal episodic memory scores performing a series of factorial and regression analyses. These indexes were used to investigate potential association with GM volumes by VBM. We observed a high correlation between the factors extracted using the factor analyses and the immediate and the delayed recall scores, both in patients and in HE groups. We speculated that the factors extracted, and the derived composite memory score (C-MS), may be considered a synthetic representation of the observed variables (the episodic memory scores). Therefore, we using the PLS to extract the LT scores underlying the C-MS, ruling out potentially confounding factors. Specifically, we obtained that the first LT (the LT[1st]) explained the most of the variance, reflecting the maximum common variance of the episodic memory factors (measured as C-MS), ruling out demographic variables and general cognitive efficiency. Both in a-MCI and HE groups the PLS analysis showed that the MMSE scores contributed significantly in the composition of LT[1st] scores (as measured by the VIP index). This means that the variance of the C-MS included, at least in part, the variance due to the level of general cognitive efficiency. In the present case, the CR considered in terms of latent variable, derived from the C-MS, is conceptualised as variance formed both by episodic memory and by the general cognition scores. Therefore, the CR index did not express uniquely the changes in memory performances but the general cognitive changes occurring during 36 months. As a consequence, to obtain a CR index expressing changes in the variance of the episodic memory only, general cognitive efficiency scores were regressed again from LT[1st] scores. The d-CR index obtained was considered as a "pure" measure of dynamic changes in episodic memory.
The present study showed that LT[1st] and d-CR scores were not equivalent to express the CR. It is remarkable that when considering the CR's scores (LT[1st] and d-CR scores) in a-MCI patients divided according their clinical profile in Converters and Non-Converters we observed significant difference only for the LT[1st] scores. Indeed, Converters showed significantly negative LT[1st] scores compared to Non-Converters that showed positive LT[1st] scores. We hypothesised that only in Converters group, when memory performance worsening, the relative weight of the level of general cognitive efficiency (as measured by the MMSE scores) significantly increase in explaining the total variance of the C-MS. Conversely, we did not observe this trend when comparing Converters and Non-Converters in the d-CR score. In other words, when memory performance worse the ability to use in synergy the other cognitive functions, different from memory, permits to withstand cognitive decline. Moreover, LT[1st] scores were the best predictors for patients' conversion to AD in the discriminant analysis. Conversely, d-CR index showed only a modest ability to correctly classify patients. When considering the neuroimaging analyses in a-MCI, LT[1st] and d-CR scores showed correlations with GM volumes both in the common and in the specific brain areas. We speculated that the common brain areas we observed are likely involved both in the memory and in the more general cognitive efficiency processes. Conversely specific correlations might be expression of compensative mechanisms, confirming that the a-MCI patients with high CR cope better with neurodegenerative process[7]. Also in the HE group there were areas of overlapping between LT[1st] and r-MW scores with GM volumes.
Some of these areas were the same observed also in the a-MCI patients (BAs7, 31, 32, 47, cerebellum) but others, such as thalamus and insula bilaterally, were found associated with CR scores only in the HE group. A previous study showed these brain regions altered in healthy elderly accordingly with their CR level (Stern et al., 2005) suggesting the existence of a compensatory network that is used to maintain function in the face of age-related physiological changes. In conclusion this study showed that CR measured as decomposition of memory variance include also more general cognitive abilities. Therefore the integrity of memory function is not sufficient to withstand neurodegeneration. The ability to use synergistically the different cognitive functions is protective against the conversion to AD. Using CR's measures limited to assess only memory function is likely less sensitive to detect the cognitive decline and to predict patients' conversion.

References: [1]Barulli D, Stern Y. Trends Cogn Sci . 2013 17, 502-509; [2]Reed BR, et al. Brain. 2010 Aug;133(Pt 8):2196-209; [3] Zahodne LB, et al., Neuropsychologia. 2015 Oct;77:260-6; [4] Serra L, et al. Rejuvenation Res 2011 14, 143-151; [5]Serra L, et al., Neurobiol Aging 2015 36, 592-600;[6] Bozzali M, et al. J Alzheimers Dis 2015 44, 243-250; [7]Serra et al. J Alzheimers Dis 2016 in press.