Correlations between neuropsychological tests and structural brain magnetic resonance imaging in a cohort of patients with mild cognitive impairment

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Background

The current research is focused on early diagnosis of Alzheimer's disease (AD) also in the view of enrolment of patients in clinical trials to test disease-modifying therapies. Accordingly, several investigations were performed in order to detect sensitive and specific in vivo biomarkers able to well characterize patients at pre-dementia phase. Some of these biomarkers have shown a very good diagnostic performance as well as they were included in the recent diagnostic criteria for AD (1). Among the AD biomarkers, probably structural magnetic resonance imaging (sMRI) medial temporal lobe atrophy is the less studied. To this regard, the pathological changes and volume lowering of hippocampus and entorhinal cortex support the likelihood of AD pathophysiology and seem to correlate with the severity of cognitive impairment. More recent investigations also suggest an involvement of other brain structures in AD, for instance the striatum (composed of putamen, accumbens and caudate nucleus) (2).
From the clinical point of view, an important tool to improve the assessment of patients with cognitive impairment is represented by a complete neuropsychological evaluation including Mini Mental state examination (MMSE), ADAS-Cog (3) and several others. A computerized examination, named Cambridge automated neuropsychological test battery (CANTAB) (4), was also developed in order to improve the accuracy of the early diagnosis of neurodegenerative disorders. Its subtests explore different cognitive functions, like visual and spatial recognition, memory and learning, sustained attention, two-choice forced discrimination, and they show peculiar impairment traits in AD and amnestic mild cognitive impairment (a-MCI) patients, mainly in Paired Associates Learning (PAL) results . To the best of our knowledge, studies about correlation among MRI and neuropsychological tests, including CANTAB battery, are lacking.

Materials and methods

Patients' selection

We enrolled a cohort of 25 aMCI patients, referred to our Memory Clinic, between February 2013 and June 2013, according to the Workpackage 5 precepts, based upon the *PharmaCog Consortium* (within *European ADNI Protocol* context) agreement. Accordingly, all the patients were assessed every six months in a 2-year follow-up period. Criteria for the enrolment of patients were age between 55 and 90 years, memory loss complaints (which were confirmed by a relative), MMSE score of 24-30, overall Clinical Dementia Rating score of 0.5, 15-item Geriatric Depression Scale score of ≤5, modified Hachinski ischaemia score ≤4, score on the logical memory test of -1 SD from the age-adjusted mean and at least 5 years of education. Exclusion criteria were: enrolment in other clinical trial of experimental drugs, other significant neurological, psychiatric or systemic disease, the use of antidepressant drugs with anticholinergic side effects, antiparkinsonian medication, high dose of neuroleptics or chronic sedatives or hypnotics, and the use of narcotic analgesics. Written informed consent was obtained from all patients.

MRI acquisition and analysis

We used a 3 T Philips Achieva MRI scanner with a magnetization-prepared rapid gradient-echo (MP-RAGE) anatomical T1 scan. The segmentations were performed using FreeSurfer (5) analysis pipeline version 5.3, running on a Linux workstation (Ubuntu 15.10).

Neuropsychological assessment

All patients underwent neuropsychological assessments, consisting in an exhaustive battery exploring global functioning, memory, language, attention and visuo-spatial domains, and a selection of computerized tests from CANTAB. The *European ADNI platform* provided the test selection through a consensus of an international panel of researchers. The insertion of new cognitive measures represents an innovation aspect of the *European ADNI* with respect to the original ADNI protocol. In particular, the introduction of the computerized evaluation (CANTAB battery), among the other psychometric tests, has been proposed by the *PharmaCog Consortium*.

Statistical analysis

R software (3.1 version) was employed in order to achieve Spearman correlations between neuropsychological scores and MRI volumes at baseline. According to the literature, all the regional cerebral volumes were normalized by the estimated total intracranial volume (eTIV). We also performed a Principal Component Analysis (PCA), to reduce the dimensionality of MRI data. The Principal Components (PC) were then correlated with the neuropsychological data.

Aims

To assess the correlations at baseline between neuropsychological tests and magnetic resonance imaging (MRI) brain volumes obtained with FreeSurfer segmentation [3], as normalized according to estimated total intracranial volume (eTIV), in a cohort of well characterized patients with mild cognitive impairment (MCI).

Results

At baseline, we observed several negative correlations between cerebral ventricle volumes and neuropsychological test scores, in particular *MMSE*, *AVLT (Auditory Verbal Learning Test) immediate* and *delayed*, *Category Fluency*, *Boston Naming Test (BNT)* and three CANTAB subtest: *PAL total errors*, *Spatial Recognition Memory (SRM)* and *Pattern Recognition Memory (PRM) immediate*. These volumes also showed positive correlations with *ADAS-Cog* (in this test, higher scores indicate worse performances). Moreover, *ADAS-Cog* scores showed negative correlations with left thalamus (r=-0,51-p<0,01), left hippocampus (r=-0,55-p<0,01), left amygdala (r=-0,47-p<0,05), left accumbens (r=-0,53-p<0,01) and right hippocampus (r=-0,57-p<0,01) volumes. Both the *immediate* and the *delayed recall* scores of *AVLT* positively correlated with left putamen (r=0,40-p<0,05 and r=0,42-p<0,05, respectively), left hippocampus (rs=0,42-p<0,05 and r=0,50-p<0,05), left amygdala (r=0,44-p<0,05 and r=0,48-p<0,05), left accumbens (r=0,40-p<0,05 and r=0,52-p<0,01) and corpus callosum (r=0,48-p<0,05 and r=0,52-p<0,01) volumes. *AVLT immediate* scores also had positive correlations with both right and left caudate nucleus (CN) volumes (right CN: r=0,46-p<0,05; left CN: r=0,42-p<0,05), while *AVLT delayed* scores showed positive correlations with right hippocampus (r=0,48-p<0,05) and right thalamus (r=0,41-p<0,05) volumes. Left accumbens volume also positively correlated with *Letter Fluency (PFL)* (r=0,45-p<0,05) and *BNT* (r=0,49-p<0,05) scores. Moreover, *BNT* scores had a positive correlation with corpus callosum volume (r=0,41-p<0,05). Furthermore, left putamen volume disclosed a positive correlation with *SRM* (a *CANTAB* subtest) score (r=0,51-p<0,01). Finally, the PCA showed the following results: three PC explained about 68% of data variability. In particular, PC1 positively correlated with thalamus, hippocampus, amygdala, cerebellum, accumbens and putamen volumes, then even with *AVLT* scores.

Table 1 – Demographics

Variable	Mean (Range) or n (%)
Age (years)	71 (64-74)
Sex (M)	10 (40%)
Educational level (years)	8 (5-13)

Table 2 – Standard neuropsychological assessment

Test	Mean	SD
MMSE	27.04	1.52
ADAS-Cog	21.22	7.82
Category Fluency	29.68	9.15
AVLT Immediate	31.20	7.29
AVLT Delayed	4.30	3.08
BNT	21.28	5.63
LM	26.86	4.92
Digit_span_fw	5.80	1.32
Digit_span_bw	4.04	1.27
Digit_Symb	29.48	11.08

Table 3 – Cambridge automated neuropsychological test battery

Domain	Test	Mean	SD
Working memory and executive functions	SWM - Errors	-0,38	1,09
	SWM - Strategy	-0,36	0,73
Attention	RVP - Choice reaction time	-2,13	1,61
	RTI - Simple reaction time	-0,59	1,27
	RTI - Choice reaction time	-0,77	1,43
Memory	DMS - All delayed	-1,19	1,54
	DMS - Simultaneous	-0,54	1,14
	DMS - Statistical probability of an error	-0,50	1,27
	SRM	-0,93	1,19
	PRM - Immediate	-0,60	1,41
	PRM - Delayed	-1,78	1,66
	PAL - Total errors	-1,15	1,94
	PAL - Errors in 6 shapes stage	-0,45	1,43

Figure 1 – Results of PCA analysis

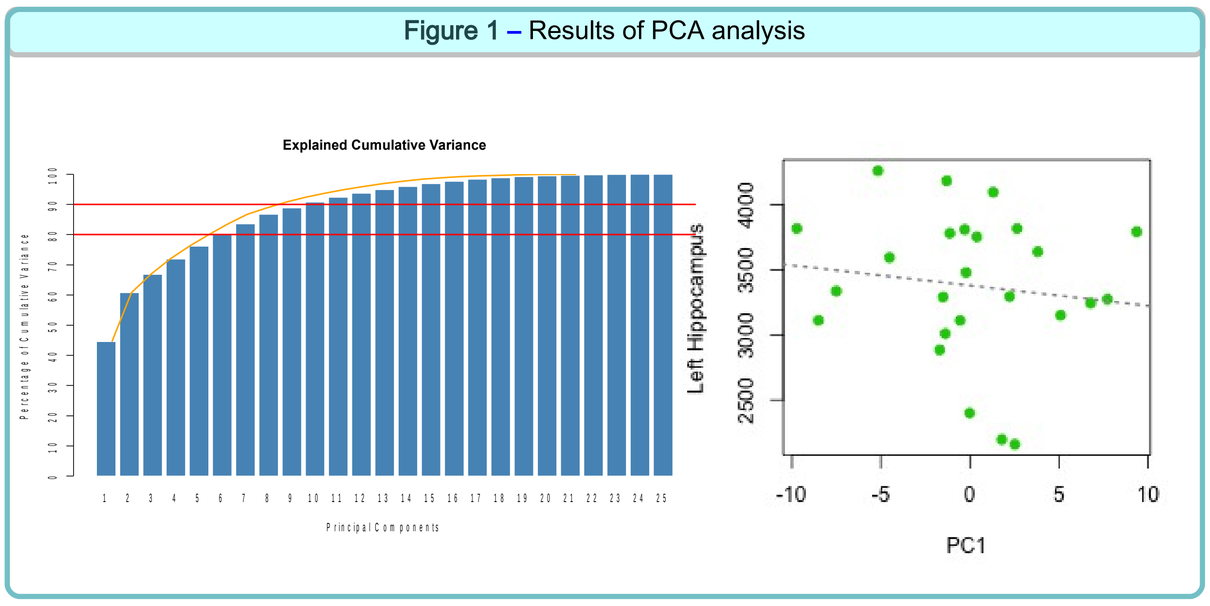
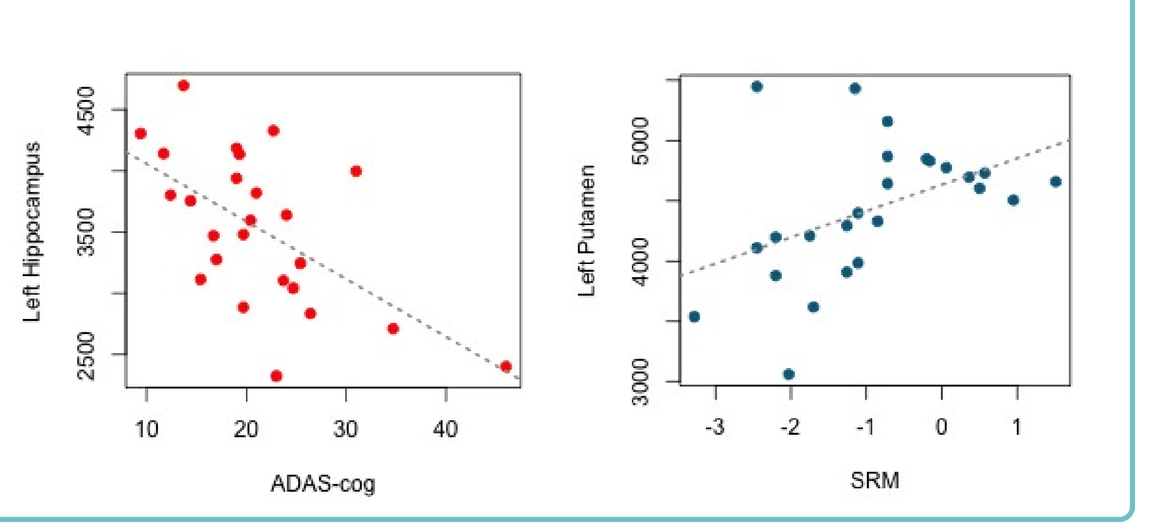


Figure 2 – Scatter-plots of neuropsychological assessments and MRI



Conclusions

We found consistent correlations at baseline between neuropsychological test scores and MRI volumes of basal ganglia, hippocampus and thalamus. These findings suggest a large involvement of these substructures in multiple cognitive domains. The correlations we found between ventricle volumes and numerous neuropsychological measures, can possibly disclose cognitive impairment aspects related to the general atrophy degree. Longitudinal observation of these parameters will add information about the parallelism of clinical and structural changes taking place in these subjects.

References

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