

## CORRELATI BIOLOGICI E STRUMENTALI NELLA PROGRESSIONE DEL DETERIORAMENTO COGNITIVO. NEUROIMAGING: ANALISI MORFOMETRICA E FUNZIONALE

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### ABSTRACT

Several imaging markers, either structural, functional, or amyloid, could be used for monitoring the progression of the cognitive impairment, even in pre-symptomatic stages.

Structural magnetic resonance enables to study in vivo cerebral atrophy which is inevitably associated with neuronal loss. A number of different techniques, either automated (BBSI, VBM, cortical thickness measurement, cortical pattern matching) or manual (hippocampal and entorhinal cortex tracing) have been developed in order to assess and quantify atrophy over time.

As functional alterations precede structural changes, functional neuroimaging (PET, SPECT, fMRI and NIRS), providing in vivo activation indexes of the neurophysiological effects of AD, plays a key role in detecting cerebral longitudinal changes. As AD is neuropathologically characterised by extracellular amyloid plaques and intracellular neurofibrillary tangles, imaging Abeta plaques in living human brain with PIB-PET, FDDNP-PET or multiphoton microscopy may represent the favourite approach to monitor the disease progression.

**Parole chiave:** Decadimento cognitivo, progressione, neuroimaging

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The progression of cognitive impairment has been traditionally investigated through clinical and neuropsychological evaluations. However, monitoring the biological progression of the disease "in vivo", beyond symptomatic progression, plays a key role in studying the cognitive impairment.

Several imaging markers, either structural, functional, or amyloid, have been developed, providing a direct measure of the degree of disease modification induced by the "active" molecules.

In this paper we aim to review the main imaging techniques which could be used for monitoring the progression of the disease, even in pre-symptomatic stages.

### STRUCTURAL IMAGING

Alzheimer Disease (AD) is characterized by gradual cognitive decline and progressive cerebral atrophy. At autopsy, the histopathological disease hallmarks of amyloid plaques and neurofibrillary tangles are accompanied by widespread synaptic and neuronal loss. Macroscopic atrophy, which can be studied in vivo using computed tomography or magnetic resonance imaging, seems to be an inevitable concomitant of the cellular destruction, synaptic loss, and dendritic pruning of AD. Several magnetic resonance (MR)-based markers could be used to monitor the biological progression of the disease. **Brain Boundary Shift Integral (BBSI).** Fox et al recently developed BBSI technique to monitor rates of cerebral atrophy [1]. Briefly, each individual's follow-up scan is rigidly registered to its baseline scan, and the superimposed images are subtracted, in order to have the volume of the brain tissue lost or gained. Cerebral volume loss is then expressed as a percentage of initial total brain volume and annualized to give a rate of global atrophy.

Compared to region of interest (ROI) techniques used to measure atrophy, this automated BBSI technique does not require a-priori decisions about relevant ROI, has high repeatability and is insensitive to the operator. Furthermore, using serial scans of the same subjects, the eventual inter-individual variability is removed. On the other hand, it has the limit to investigate the whole brain, including white matter, in the evaluation of cerebral atrophy.

The rate of atrophy in a group of 18 AD patients was found to be significantly greater than in 31 controls (2.78% vs 0.24% per year). Moreover, the rate of global cerebral volume loss

was strongly correlated with cognitive decline given by MMSE score in 29 AD patients.

**Progressive hippocampal atrophy.** The hippocampus can be manually traced on contiguous slices in order to compute hippocampal volume. In expert hands, the reliability is high. Sensitivity and specificity in a cohort of 55 AD patients and 42 controls were 94% and 90%, respectively.

Small hippocampal volume was found to be predictive of subsequent conversion to AD in 80 patients with amnesic MCI independently of neuropsychological tests, apolipoprotein E genotype, and cerebrovascular comorbidity. Moreover, in a prospective study of 28 patients with AD, 43 with MCI, and 58 normal controls, the annualized percentage change in hippocampal volume decreased progressively from baseline cognitive status (AD>MCI>control), and, within the control and MCI groups, the rate of change in hippocampal volume correlated with the change in cognitive status over time (control-stable=1.73%; control-decliner=2.81%; MCI-stable=2.55%; MCI-decliner=3.69%) [2].

**Entorhinal cortex atrophy.** Several studies about AD showed that the entorhinal cortex (ERC) is particularly vulnerable to neurofibrillary tangle pathology and neuron loss. Furthermore, there is increasing evidence that the ERC is an early site for AD pathology, before the disease extends to the hippocampus and neocortex. AD was found to be associated with a greater rate of ERC atrophy than normal aging, and longitudinal ERC measurements were found to be better than cross-sectional measurements in separating AD from normal controls [3]. Serial measurements of the entorhinal cortex volume, performed manually tracing the structure on MR images, could be useful to monitor the disease progression.

**Cortical thickness.** Lerch et al. developed an automated method to measure cortical thickness on MR images [4]. Native MRIs are registered to stereotaxic space and classified into white matter, grey matter, and CSF. Deformable initial spherical models are fit to the white matter and pial surfaces, which are then used to measure cortical thickness in 3D throughout the brain.

Statistically significant widespread cortical atrophy, with a specific focus on the temporal lobe and limbic cortex, was found in 19 AD patients as compared with 17 normal controls [4]. The patterns of thinning co-locate well with the putative presence of microscopic pathological features (plaques and tangles), increasing confidence in these results.

The automated measurement of cortical thickness provides an objective, reproducible in vivo metric of disease progression and remission, often in contrast to the neurological examination.

**Cortical pattern matching.** Thompson et al. proposed a sensitive method to measure the topological variability of the cortex [5]. The approach is based on cortical flattening and sulcal matching, and enables to obtain for each group of subjects an average cortical model and measures of gray matter density which can be analyzed with statistical tools.

Thompson et al. longitudinally studied 12 AD patients and 14 elderly normal controls, and found that cortical atrophy occurred in a well-defined sequence as the disease progressed, from temporal and limbic cortices into frontal and occipital brain regions, mirroring the temporal sequence of beta-amyloid and neurofibrillary tangle accumulation observed at autopsy. Furthermore, local gray matter loss rates ( $5.3 \pm 2.3\%$

per year in AD versus  $0.9 \pm 0.9\%$  per year in controls) correlated extremely strongly with progressively declining cognitive status.

As it provides quantitative and dynamic visualization of cortical atrophy rates, cortical pattern matching could be used to better localize disease effects within cortex over time. Restricting the search space to the cortical sheet, it showed increased power than any measure based on volumes.

**Voxel-based morphometry.** MR images are registered to a global template, segmented to GM, WM and CSF and smoothed with a 8-12 mm filter. A t test is then performed on a voxel-wise basis between groups of subjects or within a group of subjects scanned at baseline and follow-up.

In a recent prospective study, Chetelat et al. studied 18 patients with MCI for 18 months [6]. Converters to probable AD (n=7) showed greater gray matter loss than non-converters (n=11) in the temporal neocortex, medial temporal lobe structures, posterior cingulate, and precuneus, bilaterally.

## FUNCTIONAL IMAGING

As functional alterations precede structural changes, functional neuroimaging plays a key role in detecting in vivo cerebral longitudinal changes in the earliest stages of AD.

**PET/SPECT.** FDG PET and SPECT provide sensitive, in vivo metabolic and perfusion indexes of the neurophysiological effects of AD, and can aid in determining the longitudinal progression of pathophysiological effects of AD even in the preclinical stages.

In the resting state, brain metabolism and perfusion are abnormally lower throughout the cortex in AD patients as compared with matched NL subjects, with a typical pattern of parieto-temporal and posterior cingulate cortex reduced function. Recently, we found that parahippocampal and inferior temporal hypoperfusion in amnesic MCI patients could be considered as a correlate of conversion to AD [7].

**fMRI.** There are few longitudinal studies using functional MRI in AD. Several studies found diverged activation in high AD-risk and low AD-risk groups, suggesting that fMRI may report on the presence and progression of neuropathology in presymptomatic AD. Additional studies are needed to better understand how fMRI findings may be used as a potential biomarker for preclinical AD.

**NIRS.** Near Infrared Spectroscopy (NIRS) is an optical method that allows non-invasive in vivo monitoring of concentration in oxygenated and deoxygenated hemoglobins (Hbs) in cortical areas. AD and MCI patients were shown to have reduced concentrations of haemoglobin during brain activation in comparison with normal controls. NIRS sensitivity and specificity for the diagnosis of AD or MCI are comparable with those obtained from neuroimaging studies. With the advantages of non-invasiveness, low cost and being small and portable, NIRS could be used to monitor the disease progression [8].

## AMYLOID IMAGING

AD is neuropathologically characterised by extracellular amyloid plaques and intracellular neurofibrillary tangles, which are associated with progressive neuronal loss. As pathological processes occur at the cellular level, amyloid imaging biomarkers may represent the favourite ones to monitor the dis-

case progression.

**PIB.** Research is indeed very active into molecules labelled with radioactive isotopes that might enter the brain, bind selectively to  $\beta$ -amyloid, and be visualised with PET scanners, enabling in vivo quantification of amyloid plaque load in AD. The compound at the most advanced stage of validation is the Pittsburgh compound B (PIB), a carbon-11-labelled benzothiazole derivative, which was shown to correlate with two of the more traditional Alzheimer's markers,  $\beta$ -amyloid in the cerebral spinal fluid and progressive brain atrophy [9], suggesting that the presence of beta amyloid as detected with <sup>11</sup>C-PIB PET is associated with neuronal destruction over time.

This provides support for amyloid deposition playing a primary role in the pathogenesis of AD. Furthermore, such non-invasive detection and in vivo measurement of senile plaques could be a potential diagnostic test for early or presymptomatic detection of AD patients.

**FDDNP.** Another promising radioligand applicable to imaging A $\beta$  plaques in living human brain with PET is [(18)F]FDDNP. Recently, Small et al. [10] investigated FDDNP-PET bindings in 25 AD, 28 MCI patients and 30 healthy controls and found that FDDNP-PET binding can differentiate MCI from AD patients and normal controls better than did metabolism on FDG-PET or volume on MRI.

**Multiphoton microscopy.** Multiphoton microscopy is an optical imaging technique that uses near infrared light that is benign to living tissue and penetrates more deeply than visible or UV light, permitting high-resolution imaging of microscopic structures deep within the cortex over time. Since now, multiphoton microscopy has been used for transcranial imag-

ing of the brains of living transgenic mouse models of Alzheimer's disease. Direct detection of senile plaques in these mice has allowed the characterization of the natural history of individual senile plaques, and the evaluation of plaque clearance during immunotherapy, rendering multiphoton microscopy a promising technique to study AD in humans, too.

**Table 1.** Imaging techniques which could be used for monitoring the progression of the disease

		<b>Post-processing tool</b>	<b>Human intervention</b>
<b>Structural imaging</b>	MR	BBSI	Automated
	MR	Progressive hippocampal atrophy	Manual tracing
	MR	Entorhinal cortex atrophy	Manual tracing
	MR	Cortical thickness	Automated
	MR	Cortical pattern matching	Semi-automated
	MR	VBM	Automated
<b>Functional imaging</b>	PET/SPECT	Regions of interest, VBM	Manual, semi-automated or automated
	fMRI	Regions of interest	Manual, semi-automated or automated
	NIRS	Regions of interest	Manual
<b>Amyloid imaging</b>	PIB-PET	Regions of interest	Manual
	FDDNP-PET	Regions of interest	Manual
	Multiphoton microscopy	visual rating	Manual

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