Cortical Changes in Incipient Alzheimer’s Disease

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Abstract. Mild cognitive impairment (MCI) is defined by memory impairment with no impact on daily activities. 10 to 15% of MCI convert to Alzheimer’s disease (AD) per year. While structural changes in the cortex of AD patients have been extensively investigated, fewer studies analyzed changes in the years preceding conversion. 46 MCI patients and 20 healthy controls underwent structural 1.0T-weighted high-resolution MR scans at baseline and after 1.4 (SD 0.3) years. All subjects were assessed yearly for up to 4 years with a comprehensive neuropsychological battery. Sixteen of the 46 patients converted to AD (cMCI) while 30 remained stable (sMCI). An accurate voxel-based statistical mesh-model technique (cortical pattern matching) with related region-of-interest analysis based on networks defined from a Brodmann area atlas (BAs) were used to map gray matter changes over time. At baseline, cMCI patients had 10 to 30% less cortical gray matter volume than healthy controls in regions known to be affected by AD pathology (entorhinal, temporoparietal, posterior cingulate, and orbitofrontal cortex, p = 0.0001). Over time, cMCI patients lost more gray matter than sMCI in all brain areas but mainly in the olfactory and in the polysynaptic hippocampal network (more than 8% gray matter loss, p < 0.024). sMCI patients had 10 to 20% less volume than controls in the posterior cingulate and orbitofrontal cortex (p < 0.008) although their progression over time was significantly slower than cMCI. AD patients in the MCI stage show greater gray matter loss in the olfactory and polysynaptic hippocampal network. These findings are in line with neuropathological knowledge.

Keywords: Alzheimer’s disease, cortical gray matter, early diagnosis, mild cognitive impairment, structural MRI

Supplementary data available online: http://www.j-alz.com/issues/22/vol22-4.html#supplementarydata06

INTRODUCTION

A great deal of attention has been focused on the prodromal stage of Alzheimer’s disease (AD), often referred to as mild cognitive impairment (MCI), which includes individuals with memory problems who do not meet criteria for dementia [1]. The current prevalence rate for MCI among 65 years old subjects is 12–18% [2]; annually, up to 15% of them progress to dementia [1]. Although many MCI subjects have cortical and hippocampal atrophy and on post-mortem the majority of them shows signs of AD pathology [3], many cases can remain stable or even revert to normal [2]. Several structural MRI studies indicate that gray matter loss in vulnerable brain regions, such as the hip-
pocampus and entorhinal cortex, are predictive of progression of MCI to AD, providing supporting evidence of the validity of MRI structural changes as markers of neurodegeneration [4].

Although the neurodegenerative changes that take place in patients who meet the diagnostic criteria for AD have been very well characterized by morphostructural studies [5], less is known on the changes in the earliest stages of the disease. In a longitudinal study with a population of MCI patients, Whitwell [6] found that matter atrophy involved primarily the medial temporal lobes and subsequently, it spread to more posterior regions and later on, in coincidence with the conversion from MCI to AD, involved the temporoparietal association cortex and the frontal lobes.

Another longitudinal study was conducted by Driscoll [7] who followed 138 normal individuals annually for up to 10 consecutive years. Eighteen of them were diagnosed with MCI over the course of the study and showed accelerated changes compared to normal controls in whole brain volume, ventricular cerebrospinal fluid, temporal gray matter, and orbitofrontal and temporal association cortices.

The aim of this study is to map gray matter differences that occur in the cortex of MCI patients within 1 and 4 years before conversion to AD. Our purpose is to gain an in vivo insight into the brain areas that are affected during the first stages of the disease. To our knowledge, this is the first study looking at gray matter differences in patients affected by MCI using cortical pattern matching (CPM), a computational brain imaging technique that enables volumetric changes of the cortical mantle to be mapped with millimetric spatial accuracy.

MATERIALS AND METHODS

Study subjects and assessment

The Translational Outpatient Memory Clinic (TOMC) of the Scientific Institute for the Research and Care of Alzheimer’s Disease (Istituto di Ricovero e Cur a a Carattere Scientifico [IRCCS] Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy) is an outpatient facility with a multidisciplinary team of neurologists, geriatricians, neuropsychologists, neuroscientists well-versed in image analysis, biologists, neurophysiologists, and geneticists (see [8] for a description of the TOMC); between April 2002 and December 2005, 145 patients came to the attention of TOMC for a clinical evaluation. 45 of them were diagnosed with MCI, based on the current research diagnostic criteria [1] and have been included in a prospective project on the natural history of MCI (Mild Cognitive Impairment in Brescia – MCIBs) [9]. The inclusion criteria were a disease onset after 60 years of age, a clinical follow up equal to or greater than 12 months and 2 MRI scans collected at baseline (t0) and after 1.4 ± 0.3 years (t1).

All patients underwent a clinical evaluation including laboratory exams, physical and neurological examination, neuropsychological assessment, and MR scan. History was taken with a structured interview from patients’ relatives (typically spouses). Laboratory exams included genomic DNA extraction with APOE genotyping according to standard procedures. White matter damage was ascertained computing global score on Wahlud visual scale [10] for each participant.

Neuropsychological assessment

Neuropsychological assessment was performed by a psychologist at each follow-up visit and included: (i) global cognitive functioning, (ii) phonological and semantic verbal fluency as well as language comprehension; (iii) visuospatial and constructional abilities; (iv) frontal-executive functions; and (v) learning and memory [11]. The instrumental activities of daily living (IADL) questionnaire [12] was also administered to investigate the impact of cognitive decline on patients activities.

MR acquisition

MR scans were acquired with a Philips Gyroscan 1.0 T scanner at the Neuroradiology Unit of the Città di Brescia hospital. High-resolution gradient echo sagittal 3D sequences (TR = 20 ms, TE = 5 ms, flip angle 30°, field of view = 220 mm, acquisition matrix = 256x256 and slice thickness = 1.3 mm) were acquired. Gray matter was studied with the cortical pattern matching algorithm developed at the Laboratory of Neuroimaging (LONI) of the University of California, Los Angeles [5].

The 3D images were reoriented along the AC-PC line and voxels below the cerebellum were removed with the MRLcro software (http://www.cabiatl.com/mricro/mrlcro/mrlcro.html) in order to improve extraction of the cerebral cortex in areas adjacent to the cerebel- lum. The anterior commissure was manually set as the origin of the spatial coordinates for an anatomical normalization algorithm implemented in the Statistical
Parametric Mapping (SPM99) software package (http://www.fil.ion.ucl.ac.uk/spm/). A 12-parameter affine transformation was used to normalize each image to a customized template in stereotaxic space, created from the MRI scans of 40 control subjects.

Cortical pattern matching

Individual brain masks for each hemisphere were extracted from normalized images with the automatic software Brainsuite (http://brainsuite.usc.edu), visually inspected and manually corrected with Display, a three dimensional visualization program (http://packages.bic.mni.mcgill.ca/gz/) that allows the manual correction of errors in regions of interest (or ‘masks’) differentiating brain and non-brain tissues. The resulting masks were then applied to normalized images to obtain ‘skull-stripped’ images of each hemisphere. After automated 3D hemispheric reconstruction using an intensity threshold that best differentiated gray matter from extracerebral cerebrospinal fluid [13], a total of 39 sulcal lines for each hemisphere were manually traced (17 sulci on the lateral surface, 12 sulci on the medial surface and 10 lines drawn to outline interhemispheric gyral limits of each hemisphere) by a single tracer (A.P.) on the cortical surfaces, following a detailed and extensively validated protocol (http://www.loni.ucla.edu/~khayashi/Public/medial_surface/, http://www.loni.ucla.edu/~esowell/new.sulcvar.html) for each subject. The reliability of manual outlining was assessed prior to experimental subject tracing with a standard protocol requiring the same rater to trace all lateral and medial sulci of six test brains [14]. At the end of the reliability phase, the mean 3D difference of tracer from the gold standard [14] was < 3 mm everywhere for medial and lateral sulci. Individual sulcal maps were averaged to create a common average sulcal map for all subjects in the study [15]. The individual cortical surfaces were parameterized, flattened, and warped. Image voxels were classified using a partial volume classifier algorithm [16].

To perform cortical analyses on t1 images, each scan was realigned to its t0 reference with SPM99 before cortical extraction and resliced. Time1 (t1) images were then warped to the t0 common average sulcal map, parameterized, flattened and classified using the same classifier algorithm [16].

Gray matter volumes were extracted and mapped onto the corresponding parametric hemispheric model in exact spatial correspondence. Grey matter density, a commonly used measure of regional gray matter volume [17–19], was computed at each cortical point as the proportion of tissue classified as gray matter in a sphere centered at that point, with a radius of 15 mm, and then averaged within each group to obtain the mean gray matter density.

Maps of the difference of gray matter were computed based on the ratio, at each cortical point, between the mean gray matter density value at that point in each patient group (sMCI and cMCI at t0) and the mean gray matter density in the control group. This ratio allows maps of the relative deficit in gray matter to be visualized, as a proportion, or percentage, of the normal values seen in healthy controls. Moreover, maps of gray matter loss in cMCI and sMCI patients between t0 and t1 conditions were produced, computing the gray matter density value at each cortical point in each patient pertaining to one group at the baseline condition and the gray matter density value of the same patient at the t1 condition.

A deformable Brodmann area atlas [20] was applied to the left and right hemisphere average models and values of mean gray matter volume were computed from all vertices comprising a given Brodmann area (BA). For the Region-of-interest-based analysis, 5 brain networks were identified (the polysynaptic hippocampal, the olfactory, the direct hippocampal, the sensorimotor and the visual pathway) comprising all the BAs having a functional and a structural link to each other, as previously described (Fig. 1) [17,21] with mean values of gray matter volumes computed for each of the selected networks.

During the 4 year follow up period, 16 MCI (cMCI) converted to AD according to NINCDS ADRDA criteria [22], while 30 MCI remained stable (sMCI). 20 cognitively and age matched healthy controls were selected from those enrolled in a previous study [17] and underwent multidimensional assessment including clinical, neurological and neuropsychological evaluations.

Written informed consent was obtained from patients and controls prior to their inclusion in the study. No compensation was provided for study participation. The study was approved by the local ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Statistical analysis

CPM analyses were carried out assessing the relationship between gray matter density and diagnosis to identify cortical gray matter difference respectively in
cMCI and sMCI compared to healthy elderly controls (HE) and computing gray matter loss in cMCI and sMCI patients between t0 and t1 conditions. Cross-sectional (p-maps for two samples t-test) and longitudinal maps for the paired subjects (p maps for paired t-test) indicating the percentage of reduction and uncorrected p-maps of significance were created. A surface point significance threshold of $p < 0.05$ was used to visualize the regional specificity of gray matter changes in the cortex. Set-level correction for multiple comparisons was carried out by permutation testing at threshold of $p = 0.05$. This analysis assesses the fraction of the cortical surface area with statistics exceeding the given threshold and compares it with a null distribution constructed empirically by randomly assigning subjects to groups for cross-sectional maps; for longitudinal maps it flips the sign of each data entry a random number of times and collects the suprathreshold results for a variety of thresholds, in the cortical surface area [23]. A direct comparison between cMCI and sMCI was addressed both at t0 and t1 conditions.

The effect of the gender distribution was examined by performing a CPM analysis for each group (males versus females healthy elderly controls and males versus females patients pooling cMCI and sMCI together) in men and women separately. The possible confounding effect of age was examined by excluding seven sMCI and one cMCI patients whose ages at onset were below 65 years of age from our samples and then re-running the principal CPM analyses on the remaining patients (see Supplementary Table 1 for baseline sociodemographic, cognitive, and genetic features of the excluded MCI patients; available online: http://www.j-alz.com/issues/22/vol22-4.html#supplementarydata06).

Significant differences in sociodemographic, cognitive, genetic, neuropsychological and morphostructural features between groups of subjects or between conditions (t0 vs t1) for each diagnostic group taken separately were computed on raw volumes using one or two-way ANOVA (with Tukey’s post-hoc comparisons) for continuous and chi square test for dichotomous variables. Wilson’s method was used to calculate confidence intervals for proportions.

### RESULTS
Table 1 shows that patients and controls were generally in their 70s, with their mean educational level being between primary and middle school. Their global cognitive performance and the prevalence of younger subjects as well as the homo and heterozygous carriers of ApoE ε4 were as expected, based on the diagnostic categories. Gender was unbalanced, with lowest prevalence of females in the cMCI group, while the distribution was similar in the sMCI and in the healthy elders. White matter damage was minimal and equally present between the two groups.
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Table 1
The baseline sociodemographic, cognitive and genetic features of patients with mild cognitive impairment who converted within 4 years (cMCI) or remained stable (sMCI), and healthy elders

<table>
<thead>
<tr>
<th></th>
<th>cMCI (N = 16)</th>
<th>sMCI (N = 30)</th>
<th>Healthy elders (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.8 ± 5.4</td>
<td>66.8 ± 7.7</td>
<td>72.5 ± 7.6</td>
</tr>
<tr>
<td>Gender, female (%)</td>
<td>6 (37%)</td>
<td>23 (77%)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Education, years</td>
<td>7.5 ± 4.1</td>
<td>7.4 ± 3.7</td>
<td>8.8 ± 4.2</td>
</tr>
<tr>
<td>Mini Mental State</td>
<td>26.0 ± 2.5</td>
<td>27.7 ± 2.3</td>
<td>29.1 ± 0.9</td>
</tr>
<tr>
<td>Exam [range]</td>
<td>[24–29]</td>
<td>[25–30]</td>
<td>[27–30]</td>
</tr>
<tr>
<td>ApoE ε4 carriers, n (%)</td>
<td>9/16 (56%)</td>
<td>10/28 (36%)</td>
<td>4/15 (27%)</td>
</tr>
<tr>
<td>ε4 homozygous</td>
<td>3/9 (33%)</td>
<td>1/10 (10%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Wahlund global score*</td>
<td>4.5 ± 3.7</td>
<td>3.7 ± 3.6</td>
<td>2.7 ± 4.3</td>
</tr>
</tbody>
</table>

Values indicate mean ± SD.
No or same markers denote no differences and different markers denote significant differences on one-way ANOVA (with Tukey’s post-hoc comparisons for continuous and chi square for dichotomous variables).
*Missing data for 1 cMCI patient.

Fig. 2. Map of the difference of gray matter at baseline of 16 converted and 30 stable MCI patients compared with 20 healthy elderly persons. Corrected set level significance on permutation test is reported on top of each hemisphere.
Neuropsychological performance revealed increasing cognitive impairment from t0 to t1 (Table 2) for the cMCI group only. However, delayed visuospatial memory, language production and frontal executive tests were more sensitive to stress changes and differences between patient groups as time proceeded (p of the interaction between group and time < 0.047). Just one out of 30 sMCI patients had lost 2 or more daily living functions at baseline and that remained so up to t1.

Figure 2 shows that compared to HE, cMCI subjects featured cortical gray matter loss, at baseline (t0) up to 20–35% in the posterior cingulate/retrosplenial, subgenual/orbitofrontal cortices, and less widespread loss of up to 15–20% in the temporoparietal regions (p = 0.0001 on permutation testing for both left and right hemispheres). Compared to HE, sMCI featured on average 10 to 20% posterior cingulate and orbitofrontal cortex gray matter loss, with less marked loss in the medial temporal (lower than 10%) regions (p < 0.008).

Figure 3 shows the gray matter loss for the two groups of MCI patients between t0 and t1 conditions; while there was a general gray matter decline for both groups as time progressed, cMCI were losing 12 and up to 18% more gray matter than sMCI in the posterior cingulate/retrosplenial and frontal, medial temporal and temporal polar cortices (p = 0.0001 on permutation testing for both hemispheres). The sMCI longitudinal group’s gray matter loss was confined to a maximum of 12% in the orbitofrontal and temporal poles (p = 0.001 on permutation testing for both hemispheres).

Table 3 shows the average volume percent differences between t0 and t1 conditions for each group separately. ROI are defined in terms of networks of functional and structural linked BAs. As expected, the atrophy pattern is similar to that outlined in Fig. 3 although
Table 2
Baseline (t0) and follow-up (t1) neuropsychological features of converted (cMCI) and stable (sMCI) patients

<table>
<thead>
<tr>
<th></th>
<th>cMCI (n = 16)</th>
<th>sMCI (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t0</td>
<td>t1</td>
</tr>
<tr>
<td>Rey’s List Immed. Recall</td>
<td>29.1 ± 7.1</td>
<td>29.0 ± 9.1</td>
</tr>
<tr>
<td>Rey’s List Delayed Recall</td>
<td>4.8 ± 5.5</td>
<td>3.6 ± 3.9</td>
</tr>
<tr>
<td>Rey’s Figure Recall</td>
<td>7.2 ± 4.4</td>
<td>5.9 ± 5.5</td>
</tr>
<tr>
<td>Token</td>
<td>31.7 ± 2.5</td>
<td>31.3 ± 2.3</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>29.4 ± 17.4</td>
<td>23.3 ± 7.4</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>25.5 ± 5.4</td>
<td>24.3 ± 7.3</td>
</tr>
<tr>
<td>Frontal-exec. Clock drawing</td>
<td>1.9 ± 1.3</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>Visuospatial Rey’s Figure Copy</td>
<td>29.2 ± 5.1</td>
<td>27.6 ± 6.1</td>
</tr>
<tr>
<td>IADL Patients who lost 2+ functions (%)</td>
<td>3/16 (19%)</td>
<td>4/16 (25%)</td>
</tr>
</tbody>
</table>

Values indicate mean ± SD. Bold letters indicate where the interaction between group (cMCI and sMCI) and time (t0 and t1) is significant at p < 0.05. Δ (± 95% C.I) refers to the percentage difference between baseline and t1 mean neuropsychological scores (± 95% confidence intervals) for each group separately.

Table 3
Region-of-interest-based analysis of gray matter volumes. Values reported below are mean values of gray matter volumes computed throughout all voxels comprising given network of BAs

<table>
<thead>
<tr>
<th>Networks</th>
<th>Healthy Elderly (HE) vs T1 vs T0 vs T1 vs T0HE</th>
<th>cMCI patients</th>
<th>sMCI patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HE vs T1 vs T0 (±95% C.I)</td>
<td>t0</td>
<td>t1</td>
</tr>
<tr>
<td>Polysynaptic pathway</td>
<td>10,061 ± 1,448</td>
<td>14,301 ± 1,622</td>
<td>0.005</td>
</tr>
<tr>
<td>Hippocampal pathway</td>
<td>15,354 ± 1,541</td>
<td>13,669 ± 1,460</td>
<td>0.004</td>
</tr>
<tr>
<td>Olfactory</td>
<td>5,771 ± 415</td>
<td>4,878 ± 608</td>
<td>0.0001</td>
</tr>
<tr>
<td>Direct</td>
<td>38,248 ± 2,956</td>
<td>35,851 ± 3,547</td>
<td>0.177</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>37,676 ± 4,010</td>
<td>35,202 ± 3,048</td>
<td>0.158</td>
</tr>
<tr>
<td>Visual</td>
<td>5,661 ± 439</td>
<td>5,163 ± 564</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>5,974 ± 544</td>
<td>5,277 ± 466</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td>7,199 ± 618</td>
<td>6,555 ± 567</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>6,914 ± 744</td>
<td>6,184 ± 447</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are mm³ mean ± SD. Δ denotes the percent difference between gray matter concentrations for each condition; BA Brodmann’s area, L left, R right. C.I.: 95% confidence intervals around Δ % difference
Bold letters indicate gray matter volumes where the interaction between the variables group (cMCI and sMCI) and time (t0 and t1) is significant at p < 0.05.
the values, being area averages, are always lower. At baseline, each group featured less gray matter compared to the healthy elderly group. The most affected areas were the polysynaptic hippocampal pathway and the olfactory networks \( p < 0.046 \). Other networks, such as the sensorimotor and the visual network seemed to be involved just in the cMCI group \( p < 0.041 \). A loss of gray matter was not detected in the direct hippocampal pathway of MCI patients compared to controls. At t1, both groups were losing a significant amount of gray matter in all the selected networks \( p < 0.01 \), but the olfactory one appeared to be involved more quickly as the interaction between group and time condition is significant \( p = 0.029 \) for the left hemisphere; see Supplementary Fig. 1 for the point by point interaction significance map). In the cMCI group the average gray matter loss transitioning from the t0 to t1 condition in this brain area was 9% while it was 3% for the sMCI group. Loss in other networks over time was, for each group, around 5 to 10%.

The effect of gender was controlled by computing gray matter volumes in the networks listed in Table 3 at t0 condition, separately for men and women in older healthy controls and MCI patients pooled together. Only the comparisons for the sensorimotor network was significant by the Mann-Whitney U-test in the patients group between males and females \( p = 0.001 \), indicating that gender was not a confounder of the findings of this study. The second CPM analysis was performed to control “age at onset” effect. Excluding one cMCI and seven sMCI patients whose ages at onset were less than 65 years from the sample revealed the same pattern of cortical gray matter deficit observed in the principal analyses \( p = 0.001 \) on permutation testing for both left and right hemispheres in HE vs cMCI comparison; \( p = 0.003 \) for the left and \( p = 0.007 \) for the right hemispheres in HE versus sMCI comparison (Supplementary Fig. 2).

A third CPM analysis was performed to directly compare cMCI and sMCI at both t0 and t1 conditions. The results revealed the same pattern of cortical gray matter deficit indicated by the principal analyses \( p = 0.05 \) on permutation testing for both left and right hemispheres in sMCI vs cMCI comparison at t0 condition; \( p = 0.0002 \) for the left and \( p = 0.0001 \) for the right hemispheres in sMCI versus cMCI comparison at t1 condition) (Supplementary Fig. 3).

**DISCUSSION**

Using an advanced, accurate, and reliable computational anatomy technique, gray matter volume loss of stable and converted MCI patients have been compared at t0 to that of healthy elderly controls and also longitudinally between t0 and t1 and several key conclusions can be drawn. Firstly, in accordance to prior findings, at baseline \( (t0) \) the overall pattern of structural MRI changes in cMCI, was similar to the one of patients affected by AD [24], but with a lower severity. Compared to healthy elderly subjects, cMCI patients featured cortical gray matter loss up to 35% in the posterior cingulate/retrosplenial, subgenual/orbitofrontal cortices, and less widespread loss of up to 15–20% in the temporoparietal regions. These data agree with the well-documented progression of this pathology in the brain [25]. Also, the MCIs who remained stable, at t0 and t1 displayed a pattern of significant atrophy compared to controls. This pattern overlaps the cMCI pattern, but at a lesser degree. This finding is in agreement with other voxel based morphometry (VBM) [26] studies and can be explained by the relatively short follow-up, which may have prevented the detection of patients on their way to develop AD within this group. This interpretation is in line with data from Whitwell and colleagues [6] showing that MCI patients who remained stable for 8 years do not have appreciable GM atrophy compared to controls.

In both patient groups, a global pattern of atrophy can be detected for all analyzed neural networks, as time proceeds from t0 to t1. These findings could reflect normal aging processes as well as potential pathological processes that may be related to conversion to AD. Previous cross-sectional and longitudinal whole brain studies of normal aging showed most significant gray matter loss in frontal and parietal areas as compared to the temporal and occipital lobes [27]. The gray matter loss in the temporal lobe and in the orbitofrontal cortex (the network that we defined as “olfactory” and comprising BA 11 – prefrontal orbital cortex – and BA 25 – subgenual cortex) may be more specifically associated with the MCI status, reflecting pathological processes present in both stable and cMCI. In support of this interpretation, neuropathological [28] and longitudinal MRI studies indicate early and marked alterations in the temporal lobes of subjects at-risk of developing AD, including MCI [29], very old subjects [30], ApoE4 carriers [31], and asymptomatic subjects with familial AD [32]. Atrophy of the subgenual/orbitofrontal cortex, involved in the perception of smell [33], have been found repeatedly in patients with MCI and overt AD [26], while smell discrimination seems to be reduced early during the course of the disease [34]. Pathologic data indicate that this area is
heavily affected by tangle and amyloid pathology [35]. Interestingly, atrophy in the orbitofrontal cortex of AD patients has been found to be more severe in men than in women [36]. This is consistent with a greater prevalence of men in cMCI compared to sMCI and healthy elderly controls in our study.

The results of our study indicated a significant interaction between diagnostic group (cMCI or sMCI) and time condition (t0 or t1) with a greater loss of grey matter in the left olfactory network together with a trend for the polysynaptic hippocampal pathway ($p < 0.09$ for both hemispheres). These results seem to indicate these two neural networks to be the most important areas in predicting the transition from MCI to AD. Recent studies analyzing brain areas predictive of conversion to AD reported an accelerating atrophy in those networks in patients affected by MCI. [37], identifying the cingulate gyrus and the orbitofrontal cortex as the most predictive brain areas of conversion.

Whereas the posterior cingulate/retrosplenial cortex is the target of efferent fibers coming directly from the polysynaptic hippocampal pathway [17], the orbitofrontal cortex undergoes widespread damage in AD due to the neurofibrillary tangle pathology [38] that could be heavily related to some of the non-memory-related behavioral changes observed in this disorder [39].

The neuropsychological tests for which scores at t1 condition were significantly worse than t0 in cMCI compared to sMCI were highly related to executive functions such as the clock drawing or verbal fluency tests, while some others were more related to memory performances highly dependent on the hippocampus. Visuospatial memory is one of the first domains to be impaired in individuals affected by MCI [40] and is highly related to medial temporal lobe function, as well as anterior cingulate, and prefrontal cortex. Nishi and colleagues [41] examined the correlation between visual delayed recall of the Rey figure test and glucose hypometabolism using FDG-PET, finding a positive correlation between the deficit in visual delayed recall and a bilateral posterior cingulated hypometabolism in the brain of individuals affected by MCI. These findings are in accordance with our results that show a loss of gray matter in the posterior cingulated cortex and medial temporal lobes of patients affected by cMCI over the t0 to t1 time domain.

Not surprising was the decline in letter and category fluency and clock drawing in cMCI patients. Longitudinal studies investigating the performances of MCI patients on letter and category fluency indicate a progressive decline [42]. Those tests together with clock drawing impose significant demand on executive processes, which are highly related to the integrity of the frontal lobe, thus the greater loss over time of frontal gray matter volume in the cMCI group compared to sMCI can explain the decline of verbal fluency and clock drawing in this group.

This study has several limitations. Our sample size is low and gender was not equally distributed between the groups. Moreover, the possible contribution of age on the observed patterns of regional cortical atrophy should be taken into account, given that all investigated neural networks slowly decline with normal aging [7], greater atrophy occurs in young individuals affected by AD [18] and the slightly younger age of our sMCI group. Since age is the major risk factor for AD [26] we were not surprised by the age differences’ influence between the cMCI and sMCI. Although we statistically controlled for the effects of age and gender, we cannot exclude the age differences influence in the group comparisons.

The image acquisition protocol and post-processing methods used are not directly comparable with other similar reports, although their reproducibility and stability over time seems to be good [43]. The impact of medications was not assessed in the present study.

With several promising disease-modifying candidate treatments under development, being able to discern subtle structural cortical changes over time between MCI condition and the immediately succeeding cognitive state of mild AD with anatomical precision, raises hopes for our ability to identify structural disease-modifying effects.

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