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# Brain metabolic maps in Mild Cognitive Impairment predict heterogeneity of progression to dementia

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ABSTRACT

[18F]FDG-PET imaging has been recognized as a crucial diagnostic marker in Mild Cognitive Impairment (MCI), supporting the presence or the exclusion of Alzheimer's Disease (AD) pathology. A clinical heterogeneity, however, underlies MCI definition. In this study, we aimed to evaluate the predictive role of single-subject voxel-based maps of [18F]FDG distribution generated through statistical parametric mapping (SPM) in the progression to different dementia subtypes in a sample of 45 MCI. Their scans were compared to a large normal reference dataset developed and validated for comparison at single-subject level. Additionally, Aβ42 and Tau CSF values were available in 34 MCI subjects. Clinical follow-up (mean 28.5 ± 7.8 months) assessed subsequent progression to AD or non-AD dementias. The SPM analysis showed: 1) normal brain metabolism in 14 MCI cases, none of them progressing to dementia; 2) the typical temporo-parietal pattern suggestive for prodromal AD in 15 cases, 11 of them progressing to AD; 3) brain hypometabolism suggestive of frontotemporal lobar degeneration (FTLD) subtypes in 7 and dementia with Lewy bodies (DLB) in 2 subjects (all fulfilled FTLD or DLB clinical criteria at follow-up); and 4) 7 MCI cases showed a selective unilateral or bilateral temporo-medial hypometabolism without the typical AD pattern, and they all remained stable. In our sample, objective voxel-based analysis of [18F]FDG-PET scans showed high predictive prognostic value, by identifying either normal brain metabolism or hypometabolic patterns suggestive of different underlying pathologies, as confirmed by progression at follow-up. These data support the potential usefulness of this SPM [18F]FDG PET analysis in the early dementia diagnosis and for improving subject selection in clinical trials based on MCI definition.



## 1. Introduction

Mild Cognitive Impairment (MCI) is an umbrella term used to identify a transitional condition between normal cognitive functioning and dementia, in most cases Alzheimer's Disease (AD) (Albert et al., 2011). Cognitive impairment may be either isolated or involving multiple cognitive domains (Petersen et al., 2009; Kawashima et al., 2012). Up to 30% of subjects presents with the amnestic subtype. Compared to the estimated incidence of dementia in the normal elderly population (1–2% per year), the rate of progression in AD is much higher for the MCI subjects (10–15% per year) (Petersen et al., 2009). Longitudinal studies on MCI provided evidence for different possible progressions, ranging from the development of AD or non-AD dementias to the stabilization or even the reversion of cognitive impairments (Mitchell & Shiri-Feshki, 2009; Schroeter et al., 2009; Galluzzi et al., 2013). This clinical heterogeneity might reflect a variety of underlying neuropathological conditions (Petersen et al., 2009). In this view, MCI definition presents broad boundaries and goes much more beyond the so-called prodromal stage of AD (Dubois et al., 2010).

In clinical practice, even if the fulfillment of MCI condition is determined through clinical–neuropsychological judgment, a variable combination of instrumental tools may offer substantial information on the possible underlying pathology, allowing the recognition of prodromal AD cases or other causes of cognitive decline. In the last years, however, researchers mainly focused on the early diagnosis of the MCI caused by AD (or prodromal AD) rather than on the clinical

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characterization of MCI condition. The research criteria for MCI due to AD (Albert et al., 2011; Jack et al., 2011; Sperling et al., 2011) incorporated markers of Aβ42 protein deposition (i.e., cerebrospinal fluid (CSF) Aβ42 and [$^{11}$C]PiB-PET imaging) and markers of neurodegeneration (i.e., CSF, Tau, reduction of glucose metabolism in temporo-parietal cortex by [$^{18}$F]FDG-PET imaging, and hippocampal or medial temporal atrophy on MRI) (Herholz, 2010; McKhann et al., 2011; Jack, 2013). Similarly, the IWG criteria for prodromal AD require the positivity of biomarkers, in association with the presence of hippocampal-type memory dysfunction (Dubois et al., 2014).

[$^{18}$F]FDG-PET has been recognized as a crucial diagnostic marker in dementia since the early disease phases, predicting the possible progression to AD in MCI subjects (Anchisi et al., 2005; Chételat et al., 2005; Mosconi, 2005; Mosconi et al., 2008; Fouquet et al., 2009; Patterson II et al., 2010; Brück et al., 2013; Dukart et al., 2013; Hatashita & Yamasaki, 2013; Prestia et al., 2013), and allowing the exclusion of AD pathology (Silverman et al., 2008; Ossenkoppele et al., 2013). The typical AD metabolic pattern was shown even years before the disease onset, as proven in dominantly inherited AD (Bateman et al., 2012) and in familial sporadic cases (Mosconi et al., 2014).

In a memory clinic setting, molecular imaging has provided significant value over standard diagnostic work-up, influencing the final diagnosis (Sánchez-Juan et al., 2014). This is especially true when prior diagnostic confidence is low (Ossenkoppele et al., 2013). Although both amyloid-PET and [$^{18}$F]FDG-PET imaging might predict progression to AD in prodromal patients, FDG imaging provides extra information. By recognizing specific patterns of cerebral glucose hypometabolism, it can differentiate among major neurodegenerative diseases and dementia subtypes, according to the topographic distribution of metabolic changes (Teune et al., 2010; Perani, 2013).

Compared to amyloid-PET that provides a basic dichotomous information (AD vs. non-AD pathology), [$^{18}$F]FDG-PET imaging can be particularly useful in predicting the differential progression of MCI condition. It is extremely useful for the early differential diagnosis in dementia conditions as it is closely related to severity, progression and type of cognitive impairment. Medial temporal and parietal hypometabolism on [$^{18}$F]FDG-PET imaging may also predict clinical progression of elderly normal into mild cognitive impaired subjects (Ewers et al., 2014). Moreover, combining [$^{18}$F]FDG-PET information with clinical–neuropsychological data is also of particular utility for prognostic purposes in MCI subjects (Perani, 2008, 2013; Pagani et al., 2010). In addition, as recently showed by Rabinovici et al. (2011), the adoption of semi-quantitative measurements of [$^{18}$F]FDG-PET scan can increase specificity (from 84% to 98%) in the differential diagnosis between AD and non-AD dementias, namely frontotemporal lobar degeneration (FTLD) in the above-mentioned study.

In this study, we assessed the role of [$^{18}$F]FDG-PET imaging in the diagnostic flow chart of MCI subjects, evaluating the consistency of hypometabolic patterns at baseline in terms not only to correct prediction of possible progression to AD, but also to non-AD dementia subtypes on the basis of clinical classification at follow-up. In order to obtain higher diagnostic accuracy, we measured [$^{18}$F]FDG-PET scans with an objective voxel-based Statistical Parametrical Mapping (SPM) procedure (Della Rosa et al., 2014) and used a large.

## 2. Materials and methods

### 2.1. Subjects

Forty-five MCI subjects (19 men, 26 women; mean age = 70.5 years and standard-deviation [SD] = 5.7; CDR = 0.5) were included in the study (Table 1). They were recruited at the San Raffaele Scientific Institute (Milan, Italy), referring with memory or other mild cognitive disorders, and evaluated by a team of experienced behavioral neurologists and neuropsychologists with a structured clinical interview, a full neurological examination, and a standard neuropsychological battery. MCI condition was defined as the presence of objective impairment at neuropsychological evaluation in memory or other cognitive domains in the absence of functional impairment and no dementia (Petersen et al., 2009; Albert et al., 2011). All patients underwent clinical and neuropsychological follow-up visits every 6 months in order to evaluate possible decline. The neuropsychological battery included measures of short- and long-term verbal–auditory and visuo-spatial memory, executive functions, language domain and visuo-spatial abilities, as well as a neurobehavioral assessment. In particular, global cognitive functioning (Mini-Mental State Examination), memory and executive functions (Rey Auditory Verbal Learning Test; Rey's Figure Recall Test; Verbal and Visual Digit Span Task; Attentive Matrices; Raven's Progressive Matrices) (seeLezak, 2000for details), language abilities (Phonological and Semantic Fluency; Token test (De Renzi & Vignolo, 1962); Aachener Aphasie Test (AAT) (Luzzatti et al., 1994) or "Batteria per l'analisi dei deficit afasici" (BADA) (Miceli et al., 1994) subtests), and visuo-perceptual and visuo-spatial abilities (Rey's figure copy test) (seeLezak, 2000) were assessed in each patient. Specific tasks (e.g. Pyramids and Palm-tree Task (Gamboz et al., 2009); Visual Object and Space Perception Battery (VOSP) (Warrington & James, 1991) subtests) were administered only in specific cases. Neuropsychiatric Inventory (Cummings et al., 1994) and Frontal Behavioral Inventory (Kertesz et al., 1997; Alberici et al., 2007) were administered to caregivers in order to exclude significant behavioral symptoms. No case showed significant positive (e.g. aggressiveness, disinhibition or psychotic disorders) or negative (e.g. loss of empathy or sympathy) behavioral changes. Mild to moderate anxiety and apathy were reported in some cases. No subject presented with extrapyramidal signs, apraxia or aphasia at the neurological examination; and few subjects complained of anomia. None reported sleep disorders.

In 34 out of 45 subjects, CSF Aβ42, total Tau (t-Tau) and phosphorylated Tau (p-Tau) values were obtained by lumbar puncture during the hospitalization. After centrifugation, CSF samples were stored at −80 °C until the analysis. Then, measurements of Aβ42, t-Tau and p-Tau were performed in the local laboratory by technicians blinded to the clinical diagnosis, using a commercially available ELISA kits (Innogenetics®, Gent, Belgium), according to the manufacturer's instructions. Cut-off values for AD reported in the literature (Tapiola et al., 2009) were

**Table 1**
Clinical and demographical features of patients' sample.

| | All | a-MCI | na-MCI | md-MCI | Statistics |
|---|---|---|---|---|---|
| Patients (male) | 45 (19) | 22 (7) | 8 (2) | 15 (10) | – |
| Age in years (mean ± SD) | 70.6 ± 5.7 | 70.8 ± 5.9 | 71.5 ± 7.1 | 69.8 ± 4.9 | NS |
| Education in years (mean ± SD) | 11.1 ± 3.7 | 11.2 ± 3.8 | 11.6 ± 3.7 | 10.9 ± 3.7 | NS |
| Months from symptoms onset to baseline visit (mean ± SD) | 36.4 ± 26.4 | 41.5 ± 31.8 | 28 ± 13 | 33.4 ± 22.4 | NS |
| Follow-up in months (mean ± SD) | 28.5 ± 7.8 | 28.9 ± 9.5 | 29.3 ± 6.3 | 27.4 ± 5.9 | NS |
| MMSE raw score (mean ± SD) | 26.7 ± 1.9 | 28.1 ± 0.8 | 26.3 ± 0.9 | 25.1 ± 1.6 | p = 0.0000 * |

a-MCI = amnestic single domain MCI; na-MCI = non-amnestic single domain MCI; md-MCI = amnestic multidomain MCI;MMSE = Mini-Mental State Examination; * = a-MCI > na-MCI; a-MCI > md-MCI; na-MCI > md-MCI.