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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.

adopted, as follows: Aβ42 = > 500 ng/L; t-Tau = 0–350 ng/L; and p-Tau = 0–61 ng/L. Typical AD profile was considered the presence of both Aβ42 and t-Tau/p-Tau and atypical CSF profile for AD either the reduction of Aβ42 only or the increase of t-Tau/p-Tau with normal values of Aβ42.

On the basis of the neuropsychological presentation, the MCI sample was sub-grouped at the baseline visit into 22 amnestic single domain (a-MCI), 15 amnestic multidomain (md-MCI) and 8 non-amnestic single domain (na-MCI) (3 dysexecutive and 5 visuo-spatial) subjects. See Tables 1 and 2 for more details on the MCI sample.

The clinicians were blinded to [^{18}F]FDG-PET data (i.e., no information about either the distribution of FDG-uptake or the visual reading of SPM results, and no access to the scans themselves) during all the follow-up period, and the possible progression to dementia was classified according to current clinical criteria for each neurodegenerative dementia subtype (McKeith et al., 2005; Dubois et al., 2010; Gorno-Tempini et al., 2011; McKhann et al., 2011; Rascovsky et al., 2011; Armstrong et al., 2013).

All subjects and their informants/caregivers gave informed consent to the experimental procedure that had been approved by the local Ethical Committee.

2.2. [^{18}F]FDG-PET image acquisition and analysis

All [^{18}F]FDG-PET acquisitions were performed for diagnostic research purposes at the Nuclear Medicine Unit, San Raffaele Scientific Institute (Milan, Italy) following standardized procedures (Anchisi et al., 2005) within 6 months from the first baseline clinical visit. In particular, before radiopharmaceutical injection of [^{18}F]FDG (185–250 Mbq: usually, 5–8 mCi via a venous cannula), subjects were fasted for at least 6 h and measured blood glucose level threshold was <120 mg/dL. All images were acquired with a Discovery STE (GE Medical Systems, Milwaukee, WI) multi-ring PET tomography (PET-CT) system (time interval between injection and scan start = 45 min; scan duration = 15 min).

Images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm. Attenuation correction was based on CT scan. Specific software integrated in the scanner was used for scatter correction. Subjects' scans were obtained at resting state in a relaxed and comfortable position. All subjects gave written informed consent, following detailed explanation of the [^{18}F]FDG-PET procedure.

Image pre-processing and statistical analysis were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Single patient [^{18}F]FDG-PET scans were normalized according to the procedure

Table 2
Demographic data, clinical features and instrumental findings of each MCI patient. M = male; F = female; MMSE = Mini-Mental State Examination; a-MCI = amnestic single domain MCI; na-MCI = non-amnestic single domain MCI; md-MCI = amnestic multidomain MCI.

Patient number	Gender	Age	Education	MMSE	Months from first symptoms to baseline	Diagnosis at the baseline	Time of follow-up	Diagnosis at the follow-up	PET pattern	CSF Abeta	CSF t-Tau	CSF p-Tau
#1	M	66	13	24	36	md-MCI	24	md-MCI	Negative	630	122	30
#2	F	75	13	27	24	a-MCI	36	a-MCI	Negative	557	148	41
#3	F	62	8	27	18	a-MCI	40	a-MCI	Negative	793	428	87
#4	F	74	8	29	12	a-MCI	32	a-MCI	Negative	750	233	51
#5	F	58	12	28	130	a-MCI	24	a-MCI	Negative	529	154	44
#6	F	60	8	27	24	a-MCI	18	a-MCI	Negative	701	220	62
#7	M	74	8	30	36	a-MCI	22	a-MCI	Negative	1237	277	84
#8	M	68	5	29	132	a-MCI	15	a-MCI	Negative	542	101	26
#9	F	69	8	26	26	md-MCI	27	md-MCI	Negative	–	–	–
#10	M	67	13	25	108	md-MCI	33	md-MCI	Negative	580	185	51
#11	M	77	13	27	60	a-MCI	27	a-MCI	Negative	847	379	84
#12	M	70	12	26	24	na-MCI	40	na-MCI	Negative	931	289	75
#13	F	69	13	28	38	a-MCI	28	a-MCI	Negative	493	242	61
#14	F	75	11	26	20	na-MCI	20	na-MCI	Negative	–	–	–
#15	F	79	11	28	36	a-MCI	26	AD	AD-like	754	557	163
#16	M	77	11	25	24	md-MCI	19	md-MCI	AD-like	453	313	82
#17	F	61	8	28	60	na-MCI	30	AD	AD-like	204	226	56
#18	F	71	5	28	24	a-MCI	60	AD	AD-like	243	370	24
#19	M	68	12	24	12	a-MCI	27	AD	AD-like	227	899	102
#20	F	66	15	26	24	na-MCI	22	AD	AD-like	–	–	–
#21	M	83	17	27	23	na-MCI	33	AD	AD-like	–	–	–
#22	M	66	8	29	12	a-MCI	24	AD	AD-like	424	200	61
#23	M	63	8	28	36	md-MCI	18	AD	AD-like	331	477	120
#24	F	62	8	24	25	md-MCI	32	AD	AD-like	253	347	84
#25	M	77	13	27	48	a-MCI	27	AD	AD-like	274	199	61
#26	F	79	12	26	26	na-MCI	32	md-MCI	AD-like	–	–	–
#27	M	73	8	28	36	a-MCI	31	md-MCI	AD-like	194	543	133
#28	F	72	12	28	24	a-MCI	20	a-MCI	AD-like	–	–	–
#29	M	73	8	23	24	md-MCI	26	AD	AD-like	–	–	–
#30	F	68	12	27	24	na-MCI	28	bvFTD	bvFTD-like	–	–	–
#31	M	73	6	27	36	md-MCI	36	bvFTD	bvFTD-like	924	275	54
#32	M	74	17	24	24	md-MCI	19	md-MCI	bvFTD-like	663	497	89
#33	M	70	10	28	48	md-MCI	33	bvFTD	bvFTD-like	491	241	71
#34	F	70	13	25	23	na-MCI	30	bvFTD	bvFTD-like	–	–	–
#35	F	63	8	23	19	md-MCI	29	sv-PPA	sv-PPA-like	557	132	37
#36	F	72	17	25	24	md-MCI	36	CBD	CBD-like	–	–	–
#37	M	72	17	24	36	md-MCI	23	DLB	DLB-like	336	676	132
#38	F	80	17	28	25	a-MCI	25	DLB	DLB-like	–	–	–
#39	F	74	13	29	60	a-MCI	38	AD	mTLD-like	407	531	107
#40	M	75	5	27	40	a-MCI	20	md-MCI	mTLD-like	429	163	41
#41	F	73	17	29	26	a-MCI	32	a-MCI	mTLD-like	372	373	28
#42	F	70	18	29	34	a-MCI	26	a-MCI	mTLD-like	422	176	43
#43	F	78	8	26	24	md-MCI	29	md-MCI	mTLD-like	232	418	80
#44	F	69	16	29	50	a-MCI	30	AD	mTLD-like	270	339	70
#45	F	64	8	28	24	a-MCI	36	a-MCI	mTLD-like	437	489	105

implemented in the new standardized SPM5 [^{18}F]FDG dementia-specific template (Della Rosa et al., 2014) for spatial normalization of [^{18}F]FDG-PET scans. This is an optimized method that showed increased reliability and accuracy of estimated metabolic activity patterns compared to the standard [^{15}O]H_2O-PET template currently available for SPM normalization procedures. Indeed, it allows to better recognize relevant metabolic changes that may otherwise be obscured by spatial normalization. Each patient scan was tested for relative 'hypometabolism' by comparison with a normal reference [^{18}F]FDG-PET dataset ad hoc developed and validated (Perani et al., 2014). The dataset included a selection of [^{18}F]FDG-PET of healthy controls either from European Alzheimer Disease Consortium (EADC)-PET and from the San Raffaele Hospital normal database. Cognitive health was established in each EADC-PET center by means of a structured clinical and a neuropsychological battery as specified in a previous paper (Morbelli et al., 2012). The inter-scanner differences were accounted for by using a large number of subjects. Thiele and coworkers (Thiele et al., 2013), evaluating the impact of using healthy subjects from different PET scanners on the accuracy of voxel-based classification of [^{18}F]FDG-PET in AD diagnosis, found that a larger number of control cases correspond to higher accuracy. In particular, Thiele et al. showed that the accuracy of classification reached 91% when a larger set including images from a different PET scanner was considered. Noteworthy, a validation for different PET scan in [^{18}F]FDG assessment using SPM has been reported by our group (Gallivanone et al., 2014).

Age was included in the two sample T-test analysis as a covariate. Due to the lack of any significant difference in metabolic activity of male and female Alzheimer patients (Minoshima et al., 1997), gender was not controlled in the analysis. Proportional scaling was used to remove intersubject global variation in PET intensities, according to Signorini et al. (1999). Additionally, voxel-wise comparisons were made using a within-brain comparison-specific explicit [^{18}F]FDG mask (Ridgway et al., 2009) in order to remove emission counts outside of the brain and to restrict subsequent analyses to within-brain voxels (Spence et al., 2006). The "hypometabolic" SPM t-map was the basis for defining disease-specific patterns. The threshold was set at $p = 0.05$, FWE-corrected for multiple comparisons at the voxel level. Only clusters containing more than 100 voxels were deemed to be significant.

2.3. Statistical validation of [^{18}F]FDG-PET hypometabolic patterns for the classification and differentiation of MCI patients

All [^{18}F]FDG-PET scans were retrospectively evaluated and independently classified by two expert raters. Both raters were blinded to baseline clinical–neuropsychological data and to the diagnostic classification at the follow-up.Since each subject underwent a CT/PET scan, the raters were able to visually assess the brain atrophy.

Raters were first asked to specify whether the SPM-t map was normal or abnormal. Namely, a normal SPM-t map should not reveal any significant hypometabolic pattern at a FWE-corrected threshold, either at the voxel or the cluster level. Then, raters were asked to describe brain hypometabolism reporting the possible involvement of specific brain areas. Thus, they had to decide whether the hypometabolic pattern was suggestive of a specific neurodegenerative dementia subtype, according to a well-established literature (Salmon et al., 2003; Anchisi et al., 2005; Franceschi et al., 2005; Juh et al., 2005; McKeith et al., 2005; Herholz et al., 2010; Teune et al., 2010; Gorno-Tempini et al., 2011; Rascovsky et al., 2011; Crutch et al., 2012; Armstrong et al., 2013). Each patient scan thus received a label indicating whether it did not satisfy the criteria for the diagnosis of dementia (i.e., negative scan) or it was compatible with AD, dementia with Lewy-bodies (DLB) or FTLD subtypes.In particular, SPM-t maps were classified as AD-like pattern when they showed: a) bilateral temporo-parietal hypometabolism and/or involvement of precuneus/posterior cingulate cortex, namely the typical AD pattern (Herholz et al., 2002; Anchisi et al., 2005; Teune et al., 2010), b) asymmetric posterior perisylvian/parietal hypometabolism, which is the metabolic signature of atypical AD/logopenic variant of PPA (Gorno-Tempini et al., 2011), and c) temporo-parietal and occipital involvement, associated with hypometabolic foci in the frontal eye field regions, which characterizes the atypical AD/posterior cortical atrophy syndrome (Crutch et al., 2012; Cerami et al., 2015). Medial and lateral occipital cortex hypometabolism (McKeith et al., 2005; Teune et al., 2010), accompanying various degrees of temporo-parietal and frontal cortex dysfunction, was considered as suggestive of DLB-like pattern.In the FTLD spectrum, the following FTLD-like patterns were considered: a) prevalent involvement of the anterior cingulate cortex, ventromedial and/or dorsolateral frontal cortex, and orbito-frontal cortex as typical of the behavioral variant of frontotemporal dementia (bvFTD) (Salmon et al., 2003; Franceschi et al., 2005; Teune et al., 2010; Rascovsky et al., 2011); b) predominant temporal pole, anterolateral temporal cortex, either bilateral or unilateral, hypometabolism, as typical of the semantic variant of PPA (sv-PPA) (Gorno-Tempini et al., 2011); c) left fronto-insular hypometabolism in the case of non-fluent variant of PPA (nf-PPA) (Gorno-Tempini et al., 2011); d) asymmetric fronto-parietal hypometabolism with specific involvement of the parietal operculum as typical pattern of corticobasal degeneration (CBD) (Juh et al., 2005; Armstrong et al., 2013); and e) frontal–medial and frontal opercular hypometabolism with additional involvement of subcortical structures (thalamus and midbrain) as possible pattern of progressive supranuclear palsy (PSP) (Juh et al., 2005; Armstrong et al., 2013). An isolated hypometabolic pattern involving the medial temporal lobe (i.e., hippocampus, parahippocampal and entorhinal gyri) was also present in some MCI cases. Raters classified this medial temporal lobar dysfunction (mTLD)-like pattern separately (Marra et al., 2012; Whitwell et al., 2012).We calculated the inter-rater agreement level, and found comparable levels ($k = 0.895$), showing an "almost perfect agreement" between the two raters.In order to infer the probability of a single case of a having or not a specific targeted disease condition after a diagnostic test, we used the positive and negative "Post-test Probability" (i.e., the probability of developing or not developing a specific dementia subtype). Positive Post-test Probability should be intended as the probability of an individual of developing the condition of interest in the future and not of having the disease. The same, in the case of a negative test, applies to the Negative Post-test Probability.

3. Results

3.1. Single-subject voxel-based hypometabolic maps

Fourteen subjects (9 a-MCI, 3 md-MCI, 1 visuo-spatial na-MCI, and 1 dysexecutive na-MCI) showed normal brain metabolism. Fifteen cases (6 a-MCI, 5 md-MCI, and 4 na-MCI visuospatial) had an AD-like pattern. Twelve out of 15 subjects presented with a bilateral temporo-parietal hypometabolism, and/or precuneus/posterior cingulate cortex, while the remaining 3 showed a predominant left asymmetric hypometabolism mainly involving posterior perisylvian/parietal regions. Seven patients (5 md-MCI, 2 na-MCI dysexecutive) showed an FTLD-like pattern. Five of them presented the typical PET pattern of bvFTD, while the remaining two cases showed, respectively CBD and sv-PPA PET pattern. Two MCI patients (1 a-MCI and 1 md-MCI with memory and visuo-spatial impairments) presented a DLB-like pattern. See Fig. 1 for some examples of the AD-like, DLB-like, and FTLD-like PET patterns and Table 2 for details on clinical and instrumental findings of each subject.

The remaining seven MCI patients (1 md-MCI and 6 a-MCI) showed an mTLD-like pattern (Fig. 2A). Noteworthy, on visual inspection of CT or MRI scan, all these patients showed concomitant mild to severe medial temporal atrophy (see Fig. 2B).

CSF evaluation, performed in 34/45 MCI patients, documented 1) typical AD values in 12 patients, 2) either low Aβ42 ($n = 5$) or elevated t-Tau and p-Tau ($n = 7$) in 12 patients, and 3) normal CSF biomarkers value in the remaining 10. None of the subjects with normal CSF values presented an AD-like pattern and none of the MCI cases with negative SPM-t map, for which CSF was available (12/14 cases),

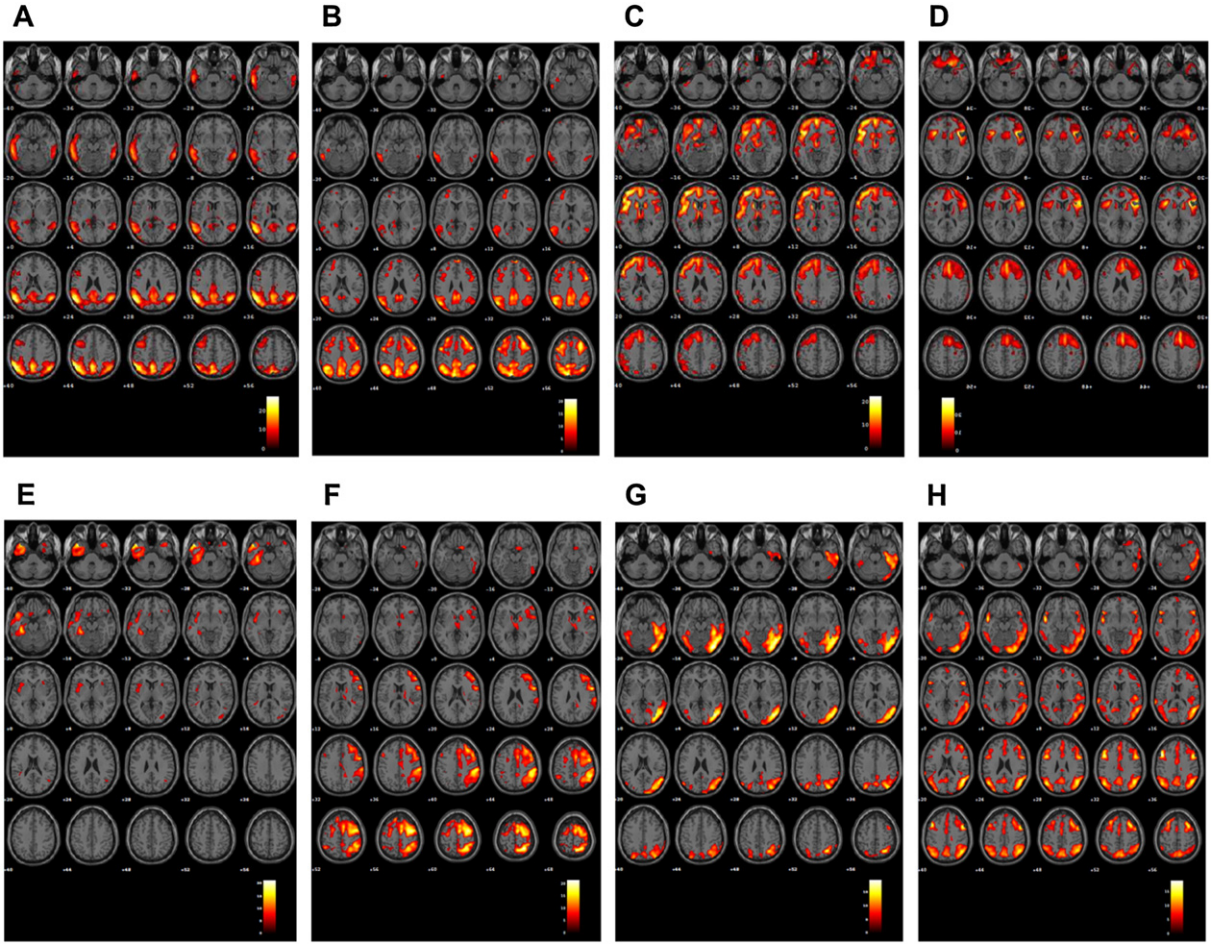

Fig. 1. The SPM-t maps of hypometabolism of eight MCI cases, as example: PET patterns corresponding to Alzheimer's disease (A, B), behavioral variant of frontotemporal dementia (C, D), semantic variant of primary progressive aphasia (E), corticobasal degeneration (F), dementia with Lewy bodies (G, H). Yellow/red scales shown in SPM maps are regions which are hypometabolic in MCI patient in comparison to the normal control database (see text for details).

presented low Aβ42 values. Noteworthy, all subjects with mTLD-like pattern showed low Aβ42 values (seeTable 2for details on single cases). At the clinical follow-up (mean 28.5 ± 7.8 months), 11/15 cases with AD-like pattern and 2/8 subjects with mTLD-like pattern converted to AD; none of the cases with negative SPM-t map progressed to dementia. Both subjects with DLB-like pattern developed within 6 months from the baseline further cognitive decline, with fluctuating cognition and/or hallucination, extrapyramidal signs and loss of functionality. Thus, at the follow-up they were classified as probable DLB, fulfilling the McKeith criteria (McKeith et al., 2005). Four up to five subjects with bvFTD-like pattern and predominant executive dysfunctions at the neuropsychological assessment developed frank behavioral disorders (i.e., apathy and disinhibition, loss of empathy and inappropriate behaviors) with relevant loss of functionality during the clinical follow-up. Their cognitive decline with predominant impairment of frontal and temporal functions was accompanied with a relative perseveration of memory and visuo-spatial abilities. Therefore, they fulfilled the criteria for probable bvFTD (Rascovsky et al., 2011). After 18 months from the baseline visit, the MCI with dysexecutive syndrome and naming impairment and a CBD-like pattern developed asymmetric limb ideomotor apraxia and extrapyramidal signs. For this reason, according to the current criteria (Armstrong et al., 2013), she was classified at the follow-up as CBD. Finally, within the first year of clinical follow-up, the subject with long-term memory and naming impairments at the neuropsychological evaluation, showing an sv-PPA-like pattern, converted to a frank fluent aphasic syndrome (anomia, semantic disorders, and spared repetition), compatible with the sv-PPA subtype (Gorno-Tempini et al., 2011). SeeTable 2for a summary of [^{18}F]FDG-PET patterns and clinical follow-up.

3.2. Statistical validation of [^{18}F]FDG-PET hypometabolic patterns for the classification and differentiation of MCI patients

An exact binomial sign test indicated that the [^{18}F]FDG-PET significantly classified 79% of all MCI patients, more often than would be expected by chance (50%) ($p = 0.0025$). Five MCI subjects were positive for a neurodegenerative disease according to SPM-t maps (4 AD-like and 1 bvFTD-like patterns) but still diagnosed as negative for dementia (not progressed) at clinical follow-up. No significant difference ($p = 0.202$) in the follow-up time was found between the non-progressing sample (mean = 24.2 ± 6.7 months) and the MCI subjects which progressed to AD at follow-up (mean = 29.7 ± 8.7 months).

Within the MCI subjects diagnosed with a specific dementia subtype at clinical follow-up (i.e., AD, DLB or FTLD subtypes) ($n = 24$), the Positive Post-test Probability was 100%. This value indicates the probability of progression to the targeted dementia subtype in the single subject after the evidence of hypometabolism in the [^{18}F]FDG-PET SPM-t maps. MCI patients showing negative [^{18}F]FDG-PET SPM-t maps ($n = 14$), classified as negative, did not present progression to dementia at clinical follow-up, hence leading to Negative Post-Test Probability of 100%, as well.

4. Discussion

MCI is a heterogeneous condition due to various pathological substrates and characterized by different outcomes (Yaffe et al., 2006; Fisher et al., 2007; Ganguli et al., 2011). Longitudinal studies on MCI

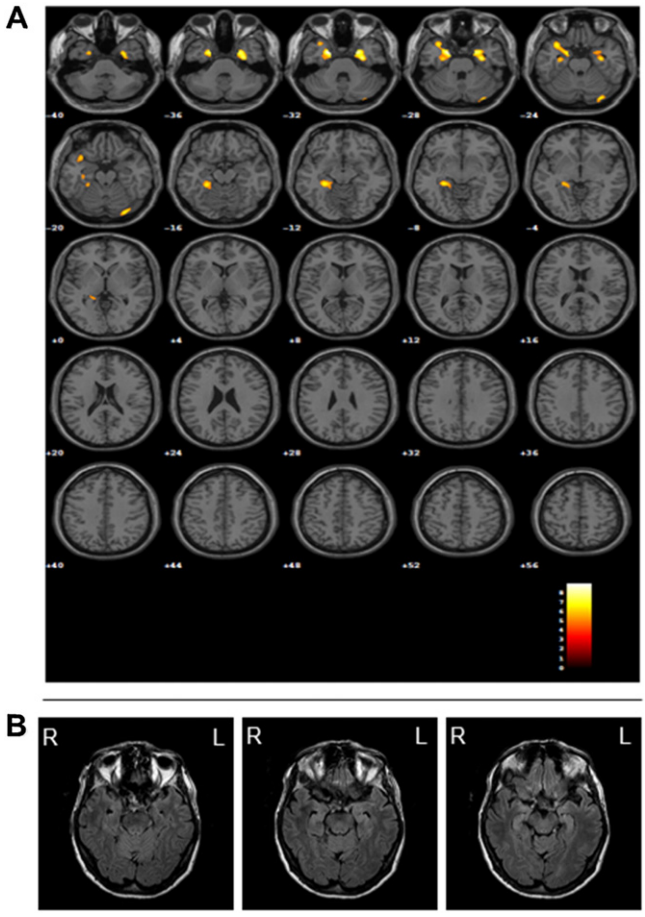

Fig. 2. The SPM-t map of hypometabolism of an amnestic single domain MCI with mTLD-pattern displayed on axial view of an MRI standardized structural scan showing a selective temporo-mesial hypometabolic pattern (A). Axial T1-weighted MRI images showing mild-moderate selective temporo-mesial atrophy more pronounced on the left side (B). L = left; R = right.

patients provided evidence for different possible progressions, ranging from progression to AD or non-AD dementia, to the stabilization or even to the normalization of cognitive impairment (Mitchell & Shiri-Feshki, 2009; Han et al., 2012; Galluzzi et al., 2013). Although the outcome is apparently not consistently related to the clinical subtype of MCI (Han et al., 2012), the amnestic may be more predictive of incident dementia, particularly of AD, than the non-amnestic subtype (Petersen et al., 2009; Ward et al., 2012). Subjects with non-amnestic md-MCI appear more likely to convert to a non-AD dementia (Busse et al., 2006), and those with non-amnestic MCI may progress to frontotemporal dementia (Yaffe et al., 2006). Moreover, md-MCI, particularly amnestic, has been proved to be the subtype that reverts to normal cognition less frequently (Han et al., 2012).

In this study, using objective voxel-based analysis of [^{18}F]FDG-PET scan, we provided evidence of distinct patterns of hypometabolism underlying the MCI condition at the onset. The different patterns predict the progression of specific cognitive deterioration at the clinical follow-up corresponding to different neurodegenerative substrates. In agreement with previous [^{18}F]FDG-PET findings (Mosconi et al., 2008), we showed heterogeneous hypometabolic profiles among MCI subjects. Moreover, the typical AD [^{18}F]FDG-PET pattern mostly characterized the group of md-MCI.

At the clinical follow-up, seven MCI patients of our sample fulfilled the criteria for FTLD subtypes and two for DLB confirming that MCI condition includes patients at risk for progression to non-AD dementias.

Thus, within our sample, statistical analysis revealed that subjects with specific pattern at the objective voxel-based analysis of [^{18}F]FDG-PET imaging have a high probability of developing specific dementia subtypes, proving further evidence that semi-quantitative analysis of [^{18}F]FDG-PET imaging has high accuracy in the early identification of disease-specific patterns that will progress to different dementia conditions (Rabinovici et al., 2011). Our data also showed that subjects with negative hypometabolic pattern do not progress to dementia at the clinical follow-up. This finding supports the high specificity of objective voxel-based analysis of [^{18}F]FDG-PET scan and its role as exclusionary test (Silverman et al., 2008; Ossenkoppele et al., 2013). Normal [^{18}F]FDG uptake in MCI indicates a low chance of progression within 2 years, even in presence of significant memory impairment on neuropsychological testing, as already reported by our group (Anchisi et al., 2005).

The five MCI subjects with positive [^{18}F]FDG PET that did not progress to dementia in the follow-up time cannot be regarded as false positives. The positivity of [^{18}F]FDG-PET imaging suggests the presence of disease in terms of hypometabolism even in the absence of dementia. In these cases, higher educational and/or occupational level may be proxies for brain functional reserve, reducing the severity and delaying the clinical expression of the underlying pathology, as previously showed by our group (Garibotto et al., 2008). Nevertheless, a longer follow-up is needed to evaluate possible progression of cognitive decline.

Some MCI subjects showed selective medial–temporal dysfunction without the typical AD hypometabolism in the temporo-parietal, precuneus/posterior cingulate cortex. On structural imaging, they showed a concomitant severe atrophy in the same areas. Both these findings suggest the recently identified pathological limbic-predominant subtype of AD (Marra et al., 2012; Whitwell et al., 2012), which is clinically characterized by a prevalent amnestic syndrome, a greater involvement of limbic structures on imaging and higher neurofibrillary tangle counts in the hippocampus compared to the cortex (Whitwell et al., 2012). In agreement with this view, the subjects in this group presented low CSF Aβ42 values, suggesting an underlying AD pathology. In line with previous findings of a slow rate of progression in subjects with selective focal medial temporal lobe dysfunction (Marra et al., 2012), our cases showed a more favorable prognosis notwithstanding a long disease duration (range 3–8 years), and they did not progress to dementia at the time of follow-up.

Our results show also that CSF findings mostly agreed with [^{18}F]FDG-PET imaging in the evaluation of single cases. The majority ($n = 9$) of subjects with AD-like PET pattern for which a CSF study was available (10/15 cases) showed low CSF Aβ42 values. None of the investigated subjects with negative or non-AD SPM-t maps presented a typical CSF AD pattern. Further studies are, however, needed to establish the agreement rate between automated voxel-based single-case analysis of [^{18}F]FDG-PET imaging and CSF Aβ42 and Tau values.

5. Conclusion

Most clinicians estimate the prognosis of MCI on the basis of the combination of the clinical–neuropsychological features and the results of structural imaging. The information collected within this scenario is often insufficient to early diagnose dementia with acceptable confidence, and only longitudinal follow-up might confirm the diagnostic hypothesis. The use of a second-level diagnostic tool, such as the topographic biomarker as obtained by [^{18}F]FDG-PET imaging supported by a voxel-based analysis, allowing the recognition of brain dysfunctional changes typical of AD or non-AD pathology at the single-subject level, might improve early diagnosis and prognosis in MCI condition avoiding multiple examinations over months and years, which may lead to unnecessary delay in proper management and therapeutic interventions.

The present findings support the current position that MCI can no longer be assumed to be a transitional state between normal aging and AD (Dubois et al., 2010; Albert et al., 2011). While including different subtypes of clinical disorders, there are individuals even in the

preclinical phase that may be on a pathway to non-amyloid-based neurodegeneration (Jack et al., 2013; Klunk & Perani, 2013), and amyloid deposition might be relatively unimportant in these subjects who could develop non-AD dementia. The correct identification of the different MCI subtypes and their possible AD or non-AD pathological substrate will be essential also for the implementation of appropriate therapeutic interventions and for realistic expectations for slowing or stopping the clinical decline.

Conflicts of interest

All authors have no financial conflict of interests.

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