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FDG-PET and CSF biomarker accuracy in prediction of conversion to different dementias in a large multicentre MCI cohort

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ABSTRACT

Background/aims: In this multicentre study in clinical settings, we assessed the accuracy of optimized procedures for FDG-PET brain metabolism and CSF classifications in predicting or excluding the conversion to Alzheimer's disease (AD) dementia and non-AD dementias.

Methods: We included 80 MCI subjects with neurological and neuropsychological assessments, FDG-PET scan and CSF measures at entry, all with clinical follow-up. FDG-PET data were analysed with a validated voxel-based SPM method. Resulting single-subject SPM maps were classified by five imaging experts according to the disease-specific patterns, as "typical-AD", "atypical-AD" (i.e. posterior cortical atrophy, asymmetric logopenic AD variant, frontal-AD variant), "non-AD" (i.e. behavioural variant FTD, corticobasal degeneration, semantic variant FTD; dementia with Lewy bodies) or "negative" patterns. To perform the statistical analyses, the individual patterns were grouped either as "AD dementia vs. non-AD dementia (all diseases)" or as "FTD vs. non-FTD (all diseases)". Aβ42, total and phosphorylated Tau CSF-levels were classified dichotomously, and using the Erlangen Score algorithm. Multivariate logistic models tested the prognostic accuracy of FDG-PET-SPM and CSF dichotomous classifications. Accuracy of Erlangen score and Erlangen Score aided by FDG-PET SPM classification was evaluated.

Results: The multivariate logistic model identified FDG-PET "AD" SPM classification (Expβ = 19.35, 95% C.I. 4.8–77.8, $p < 0.001$) and CSF Aβ42 (Expβ = 6.5, 95% C.I. 1.64–25.43, $p < 0.05$) as the best predictors of conversion from MCI to AD dementia. The "FTD" SPM pattern significantly predicted conversion to FTD dementias at follow-up (Expβ = 14, 95% C.I. 3.1–63, $p < 0.001$). Overall, FDG-PET-SPM classification was the most accurate biomarker, able to correctly differentiate either the MCI subjects who converted to AD or FTD dementias, and those who remained stable or reverted to normal cognition (Expβ = 17.9, 95% C.I. 4.55–70.46, $p < 0.001$).

Conclusions: Our results support the relevant role of FDG-PET-SPM classification in predicting progression to different dementia conditions in prodromal MCI phase, and in the exclusion of progression, outperforming CSF biomarkers.

Abbreviations: aMCI, single-domain amnestic mild cognitive impairment; AD, Alzheimer's disease; AUC, area under curve; bvFTD, behavioral variant of frontotemporal dementia; CBD, corticobasal degeneration; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; EANM, European Association of Nuclear Medicine; FDG, fluorodeoxyglucose; FTD, frontotemporal dementia; LR+, positive likelihood ratio; LR-, negative likelihood ratio; md aMCI, multi-domain amnestic mild cognitive impairment; md naMCI, multi-domain non-amnestic mild cognitive impairment; MCI, mild cognitive impairment; naMCI, single-domain non-amnestic mild cognitive impairment; p-tau, phosphorylated tau; PET, positron emission tomography; PSP, progressive supranuclear palsy; t-tau, total tau

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1. Introduction

Alzheimer's disease (AD) dementia and other neurodegenerative dementias are preceded by a prodromal phase, namely mild cognitive impairment (MCI), characterized by subtle clinical-neuropsychological changes (Petersen et al., 2009), which are related to synaptic dysfunction and long-lasting pathological deposition of toxic proteins in the brain (Pievani et al., 2014). MCI is characterized by objective neuropsychological deficits in one or more cognitive domains without functional impairment in everyday life activities (Petersen et al., 2009). Clinical longitudinal studies on MCI subjects provided evidence for different clinical outcomes, including conversion to AD or non-AD dementias, to stabilization of cognitive profile, or even reversion to normal cognition (Mitchell and Shiri-Feshki, 2009; Petersen et al., 2009). In the prodromal phase, the clinical-neuropsychological assessment has limited accuracy for the prediction of conversion to AD dementia (Löppönen et al., 2003; Storandt and Morris, 2010). To overcome this limit, diagnostic biomarkers such as neuroimaging (i.e., MRI, FDG-PET and amyloid-PET) and cerebrospinal fluid-CSF (i.e., Aβ42, total (t-Tau) and phosphorylated (p-Tau) Tau measures) have been included in the current research criteria for "MCI due to AD" (Albert et al., 2011). Among these biomarkers, the FDG-PET patterns of hypometabolism seem to be particularly accurate in predicting conversion from MCI to dementia, when compared to other biomarkers (Anchisi et al., 2005; Bloudek et al., 2011; Dukart et al., 2015; Fellgiebel et al., 2007; Landau et al., 2010; Perani et al., 2016; Prestia et al., 2013a; Robb et al., 2017; Shaffer et al., 2013; Yuan et al., 2009). Notably, a recent meta-analysis on a large sample of MCI (N = 97) has shown that adding FDG-PET imaging information to clinical data provides a better prediction of conversion from MCI to dementia in comparison with clinical data alone, with misclassification rate dropping from 41.3% (clinical data alone) to 27.2% (combined clinical and FDG-PET data) (Shaffer et al., 2013). This study also showed that adding CSF and MRI data does not significantly improve clinical diagnosis.

However, the most recent Cochrane review on the use of FDG-PET for the early diagnosis of AD dementia and other dementias in people with MCI, concluded that there is no enough evidence to support the use of FDG-PET in clinical routine, mainly due to a lack of standardized and validated data analysis procedures (Smailagic et al., 2015). Another paper by the European Association of Nuclear Medicine (EANM) stated that even if a clear variability in diagnostic performance of FDG-PET is reported in the literature, it is not attributable to the method itself, but rather to a number of factors such as study design, definitions of MCI and data analysis procedures (Morbelli et al., 2015). Thus, the lack of validated and standardized methods for semi- or quantitative measures to assess FDG-PET biomarker performance in different clinical settings seems to be the most important factor in producing the discrepancies in the reported accuracy (see (Frisoni et al., 2013, 2017; Garibotto et al., 2017; Perani, 2014; Prestia et al., 2013b)) and a consequent mismatch in the proposed diagnostic algorithms (Albert et al., 2011; Dubois et al., 2014; McKhann et al., 2011a). The use of validated semi-quantitative methods and standardized operating procedures for the correct use of neuroimaging biomarkers in research and clinical settings is indeed strongly recommended by the international scientific societies, with the aim to improve the diagnostic accuracy (Caroli et al., 2012; Frisoni et al., 2013, 2017; Garibotto et al., 2017; Guerra et al., 2015; Mattsson et al., 2017; Perani et al., 2014b).

SPM (Friston et al., 1994) is one of the most widespread methods to statistically analyse voxel-wise FDG-PET data. A recently developed and validated single-subject SPM procedure, takes advantage on a custom FDG-PET dementia-specific template, and of a large normal dataset for comparisons at the individual level, to obtain SPM t-maps with high statistical accuracy (Della Rosa et al., 2014; Perani et al., 2014a). This procedure allows the identification of disease-specific brain hypometabolism patterns at the single-subject level, outperforming both the clinical characterization of patients and the visual qualitative assessment of FDG-PET uptake images (Perani et al., 2014a). This optimized FDG-PET-SPM procedure provides patterns of brain hypometabolism specific for each neurodegenerative condition (Caminiti et al., 2017; Cerami et al., 2017; Perani, 2014; Perani et al., 2016), also in prodromal phases (Cerami et al., 2015; Perani et al., 2014a, 2016).

The same issues apply to CSF biomarkers, with the Alzheimer's Biomarkers Standardization Initiative stating that many factors (e.g., diagnostic procedures, samples processing and testing) challenge the validity and comparability of CSF results among different laboratories (Vanderstichele et al., 2012).

FDG-PET imaging, as well as CSF markers, are considered useful for the early differential diagnosis of AD vs. non-AD dementias (Gaugler et al., 2013). These biomarkers reflect different underlying brain changes, namely neural injury and brain amyloid deposition (Blennow et al., 2015; Perani, 2014). FDG-PET is a highly specific biomarker of neurodegeneration, thus able to detect typical and atypical AD dementia, as well as many non-AD dementia conditions, even in the preclinical and prodromal phase (Arbizu et al., 2013; Bohnen et al., 2012; Caroli et al., 2012; Cerami et al., 2015; Hinrichs et al., 2011; Mosconi et al., 2008; Perani, 2014; Perani et al., 2016; Shaffer et al., 2013; Teipel et al., 2015; Torosyan et al., 2017). On the other hand, CSF Aβ42 can only provide information regarding the presence of brain amyloidosis. Thus, even though low CSF Aβ42 levels well detect AD dementia cases, discriminating them from frontotemporal dementia (FTD) cases (Struyfs et al., 2015), reduced CSF Aβ42 concentrations have been reported in many non-AD conditions (e.g., Parkinson's disease, dementia with Lewy bodies, vascular dementia) (Blennow et al., 2005; Kaerst et al., 2014; Stefani et al., 2012). Concerning CSF Tau, increased concentrations of both t-Tau and p-Tau support the diagnosis of AD dementia. However, especially at the individual level, there is excessive overlap between Tau levels of patients with AD dementia and other dementias and even with controls, thus undermining its potentiality as an accurate biomarker (van Harten et al., 2011). This overlap in CSF levels essentially limits the use of CSF as a unique biomarker for differential diagnosis.

The combined use of biomarkers for neuronal dysfunction (e.g., FDG-PET or CSF Tau levels) and amyloidosis (e.g., CSF Aβ42 levels), assessed with validated and standardized procedures, is expected to improve their diagnostic effectiveness, also providing complementary information. Notwithstanding the increasing use of these biomarkers in research and clinical settings, available works in MCI populations, combining FDG-PET and CSF markers, are limited and strictly focused on conversion to AD dementia (Chen et al., 2016; Choo et al., 2013; Galluzzi et al., 2013; Gomar et al., 2014; Landau et al., 2010; Prestia et al., 2013a; Shaffer et al., 2013; Walhovd et al., 2010; Young et al., 2013). Since AD dementia constitutes only one of the possible clinical outcomes for MCI condition (Mitchell and Shiri-Feshki, 2009), data on validated biomarker accuracy for risk progression to different dementias in a large prodromal MCI sample are necessary, and currently lacking.

Here, we assessed the accuracy of FDG-PET using an optimized voxel-based procedure (Cerami et al., 2015; Della Rosa et al., 2014; Perani et al., 2014a, 2016) and CSF (i.e., Aβ42, t-Tau and p-Tau) biomarkers in the prediction of conversion to AD and non-AD dementias in a large sample of MCI belonging to different clinical centres. The aim of this multicentre study was to evaluate the individual and combined performance of the biomarkers in the risk prediction or, notably, in the exclusion of conversion to AD and non-AD dementia conditions.

2. Materials and methods

2.1. Patients

We retrospectively collected clinical and biomarker information in 80 MCI subjects belonging to a large database resulting from a collaborative multicentre Italian study on neurodegenerative dementias. The

criteria for retrospective inclusion were as follows: (1) a clinical diagnosis of MCI at baseline, made in accordance with Petersen criteria (Petersen et al., 2009); (2) Washington University Clinical Dementia Rating (CDR) scale = 0.5 (Hughes et al., 1982); (3) detailed clinical, neuropsychological and neurobehavioral assessment at baseline; (3) FDG-PET imaging performed within 6 months from baseline; (4) CSF Aβ42, t-Tau and p-Tau measurement; (4) clinical follow-up. The exclusion criteria were (1) presence of neoplastic or significant cerebrovascular lesions; (2) neurosurgery or other neurological conditions, including epilepsy, encephalitis or stroke (3) clinically relevant psychiatric disorders, in accordance with DSM-IV criteria; (4) current or a recent history of drug or alcohol abuse/dependence.

According to Petersen criteria (Petersen et al., 2009), the included MCI subjects were classified at baseline as either single-domain amnestic (aMCI n = 31), or non-amnestic (naMCI n = 8), or multi-domain amnestic (md aMCI n = 35) or non-amnestic (md naMCI n = 6) MCI. At follow-up, MCI subjects could either (1) meet criteria for a diagnosis of dementia (Armstrong et al., 2013; Gorno-Tempini et al., 2011; Litvan et al., 1996; McKeith et al., 2017; McKhann et al., 2011a; Rascovsky et al., 2011); (2) still fulfil criteria for MCI (Petersen et al., 2009) or (3) have reverted to normal cognition.

Expert neurologists and neuropsychologists provided data on patients' history, neurological and neuropsychological status, and clinical assessment at follow-up (19.4 ± 10.1 months). The diagnosis at follow-up was obtained according to the current diagnostic criteria for each dementia type (Armstrong et al., 2013; Gorno-Tempini et al., 2011; Litvan et al., 1996; McKeith et al., 2017; McKhann et al., 2011a; Rascovsky et al., 2011), and constituted the reference standard for the present study.

The study was conducted in accordance with the provisions of the Helsinki Declaration and was approved by the Ethic Committee of each centre. Written informed consent was obtained from each participant.

2.2. CSF acquisition and analysis

CSF was obtained by lumbar puncture in the L3-L4 or L4-L5 interspace from all the included MCI subjects. The procedure was always performed early in the morning. No serious adverse events were reported. The CSF sample (8–10 ml) was collected in sterile polypropylene tubes: part of it was used to determine routine chemical parameters (leucocyte and erythrocyte cell count, glucose measurement, protein total content) and the remaining CSF was centrifuged for 10 min at 4000*g* at 4 °C. The aliquots were then stored at −80 °C until analysis, to ensure the stability of the CSF biomarkers. Measurement of CSF Aβ42, Tau, and p-Tau was performed using commercially available ELISA kit according to the manufacturer's protocol and blinded to clinical diagnoses.

2.3. FDG-PET acquisition and processing

FDG-PET scan acquisitions were performed in each centre following standardized procedures, in compliance with the European Association of Nuclear Medicine (EANM) guidelines (Varrone et al., 2009). Before radiopharmaceutical injection, subjects were fasted for at least six hours to ensure measured blood glucose level was < 120 mg/dl. Static emission images were acquired starting 30–45 min after injecting 185–250 MBq of [^{18}F]FDG via a venous cannula. This post-injection time interval allows to obtain an equal distribution of the tracer across the entire brain, with negligible blood flow-dependent differences, thus achieving an optimal signal-to-noise ratio (Signorini et al., 1999). Static acquisition scan duration ranged from 10 to 15 min. PET images were reconstructed using an ordered subset expectation maximization (OSEM) algorithm. Attenuation correction was based on the software provided by the manufacturer integrated in each scanner. The following CT scans provided the FDG-PET images: Discovery GE Healthcare ST PET/CT (Perugia), Discovery GE Healthcare STE PET/CT (San Raffaele Hospital, Milan), Byograph mCT PET/CT (Brescia), Byograph Truepoint 64 PET/CT (Policlinico, Milan) and Siemens Hirez PET/CT (Genoa).

Image analysis was centralized and performed at San Raffaele Hospital (Milan) according to a voxel-based Statistical Parametrical Mapping (SPM) procedure at the single-subject level previously validated in dementias (Della Rosa et al., 2014; Perani et al., 2014a, 2016). Notably, since this voxel-based SPM procedure provided optimal reliability with different scanners (Presotto et al., 2017), it was equally applied to these multicentre FDG-PET data.

2.4. Biomarker analysis

2.4.1. CSF

CSF biomarker variables included Aβ42, t-Tau, and p-Tau (i.e. phosphorylated at threonine 181 or p-Tau181p) levels in ng/L, as well as ratios (t-Tau/Aβ42 and p-Tau/Aβ42). Each CSF measure was dichotomously classified as positive or negative for AD according to validated cut-off values: CSF Aβ42 values ≥ 500 ng/l, t-Tau ≤ 450 ng/l and p-Tau ≤ 61 ng/l (Sjogren et al., 2001).

We further classified the CSF measures following the Erlangen Score Diagnostic Algorithm. According to this algorithm, the CSF measures were scored into five groups, covering all possible CSF data combinations. The scores range from 0, if all CSF biomarkers were normal, to 1–3 points reflecting intermediate CSF abnormality, and up to 4 points, when frank abnormalities in Aβ42 pathology and t-Tau or p-Tau were detected (Lewczuk et al., 2009).

2.4.2. FDG-PET-SPM classification

Each subject image was (1) evaluated for accuracy in acquisition and reconstruction; (2) normalized to a FDG-PET specific template (Della Rosa et al., 2014); (3) tested for relative “hypometabolism” on a voxel-by-voxel basis by means of a two-sample *t*-test (i.e., 1 patient vs. 112 healthy control subjects), entering age as a nuisance covariate (Perani et al., 2014a). Threshold was set at $p < 0.05$, FWE-corrected for multiple comparisons at the voxel level. Only clusters with > 100 voxels were deemed significant.

Each FDG-PET-SPM hypometabolic pattern was classified by 5 independent neuroimaging experts, blinded to clinical-neuropsychological and CSF information. The raters had to make a forced decision among different options: 1) ‘AD’ patterns (i.e., ‘typical-AD’ (McKhann et al., 2011a) and ‘atypical-AD’ patterns, namely the asymmetric pattern of the logopenic variant of AD (Gorno-Tempini et al., 2011), the posterior cortical atrophy pattern (PCA) (Cerami et al., 2016), and the frontal-AD pattern (Kalpouzos et al., 2005)); 2) ‘FTD’ patterns (e.g., the behavioral variant of frontotemporal dementia (bvFTD) pattern (Rascovsky et al., 2011), the corticobasal degeneration pattern (CBD) (Armstrong et al., 2013); the progressive supranuclear palsy (PSP) pattern (Litvan et al., 1996), the semantic variant FTD pattern (Drzezga et al., 2008); 3) the dementia with Lewy bodies (DLB) pattern (McKeith et al., 2017) and 4) the negative pattern (i.e., no statistical significant hypometabolism in the comparison with normal controls). The independent classifications performed by each rater were merged into a single variable (i.e., the FDG-PET-SPM classification), consisting in the classification performed by the majority of raters. The Cohen's k coefficient was used to evaluate the inter-raters agreement.

The Erlangen Score Diagnostic Algorithm was aided by FDG-PET-SPM classification when the cases were classified according to the Erlangen Score Diagnostic Algorithm as 1 = AD improbable; 2 = AD possible; 3 = AD possible, thus with uncertainty. The FDG-PET-SPM classified these cases as either AD or non-AD, according to the specific pattern of hypometabolism. Patients' classification was modified according only to the FDG-PET-SPM classification.

2.5. Statistical analyses

ANOVA (with Bonferroni post-hoc correction) and Pearson's Chi-

squared tests were used to assess differences across MCI sub-classifications (i.e. aMCI and naMCI single and multi-domain) on baseline sociodemographic variables (age, gender and education), disease severity (MMSE score), CSF measures and FDG-PET-SPM classification.

We then assessed the association between the clinical progression at follow-up and the following variables: I) baseline MCI sub-classification; II) FDG-PET-SPM classification; III) CSF measures. We used ANOVA with Bonferroni post-hoc correction for continuous variables (CSF measures), and Pearson's Chi-squared test for dichotomous variables (CSF Aβ42, t-Tau and p-Tau positivity, MCI sub-classification (i.e., aMCI and naMCI), and FDG-PET-SPM classification (i.e., 'AD' and 'non-AD' patterns). Then, we assessed the concordance between each CSF biomarker positivity/negativity and the Erlangen Score with FDG-PET-SPM classification, using Pearson's Chi-squared test.

2.5.1. AD vs. non-AD predictive model

We considered measures of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−) and overall accuracy (AUC) for assessing the diagnostic classification accuracy of CSF Aβ42, t-Tau and p-Tau positivity, CSF t-Tau/Aβ42 and p-Tau/Aβ42 ratios, Erlangen Score, FDG-PET-SPM classification and Erlangen Score aided by FDG-PET-SPM classification in the prediction of MCI conversion to AD dementia. We tested the AUCs differences between biomarkers using the non-parametric DeLong test for paired samples (DeLong et al., 1988). Further, we estimated the predictive power of FDG-PET-SPM classification and CSF biomarkers separately, through two different logistic regression models, with diagnosis at follow-up (AD-nonAD) as dependent variable. Variables significantly predicting progression in the separate models were then jointly assessed in a multivariate stepwise logistic regression analysis. Reliability of multivariate logistic regression models was assessed by means of a bootstrap resampling procedure, in which the logistic regression analysis was reiterated 1000 times.

2.5.2. FTD vs. non-FTD predictive model

Being meant to establish the presence (or absence) of AD pathophysiological processes only, CSF biomarkers were not included in the FTD vs. non-FTD biomarkers' predictive accuracy analysis. Thus, we assessed the predictive accuracy in FTD vs. non-FTD conversion of FDG-PET-SPM classification only. As above, we considered measures of sensitivity, specificity, LR+ and LR- and overall accuracy (AUC). We estimated the predictive power of FDG-PET-SPM classification through a logistic regression model including diagnosis at follow-up (FTD-nonFTD) as dependent variable. A bootstrap resampling procedure was performed to assess logistic regression reliability.

The statistical analyses were performed with SPSS for Windows (Statistical Package for Social Sciences, IBM, Armonk, New York, USA, Version 23).

In order to provide further assessment of the predictive value of FDG-PET biomarker' performance, we took into account alternative independent follow-up outcomes. We considered CDR scores at follow-up, as a measure of dementia conversion. We tested concordance between FDG-PET-SPM classification and CDR, by means of Pearson's Chi-squared test. Further, we tested FDG-PET-SPM classification predictive value using a logistic regression model.

3. Result

3.1. MCI progression at follow up

MCI subgroups did not show differences in sociodemographic variables (Table 1). Of note, the clinical MCI classification (Petersen et al., 2009) was not associated with specific FDG-PET-SPM or CSF patterns.

At follow-up, 50 out of 80 MCI subjects developed dementia, namely 39 converted to AD dementia, 10 to dementia within the FTD spectrum and 1 to DLB, while 27 remained stable and 3 reverted to normal cognition (Table 2).

Out of 39 MCI who converted to AD, 28.2% were single-domain aMCI (11), 56.4% multi-domain aMCI (22), 12.8% single-domain naMCI (5), and 2.6% multidomain naMCI (1). Three multi-domain naMCI, 4 single-domain and 3 multi-domain aMCI subjects converted to FTD. One multi-domain a-MCI converted to DLB. Two single-domain aMCI and one multidomain naMCI subjects returned to cognitive normality (i.e. classified as reverters). The remaining subjects were stable at the follow-up visit.

3.2. CSF measures

At baseline, the Aβ42 CSF concentration was significantly lower in the MCI who converted to AD dementia as compared to cognitively stable and FTD converter subjects. In addition, p-Tau, t-Tau/Aβ42 and p-Tau/Aβ42 ratios were all significantly increased in the AD converters (Table 2). The 52.1% of MCI cases with "normal" CSF, remained stable or reverted to normal cognition at follow-up, the remaining 47.9% MCI with 'normal' CSF, converted to dementia (Table 2).

As for Erlangen Score, 14 out of 39 MCI who converted to AD showed Aβ42 and Tau measures within the Erlangen Score = 4. The majority of stable (21 out of 27) and reverter (3 out of 3) MCI subjects, showed Erlangen Scores ≤ 2. The MCI with intermediate score levels (1 to 3) progressed to AD dementia in 25 out of 39 cases and to FTD dementia in 6 out of 10 cases, remained stable in 10 out of 27 cases, reverted in 1 out of 3 cases.

3.3. FDG-PET-SPM classification

Since we found a good agreement among the five experts in the FDG-PET-SPM classification (Cohen's k = 0.82), we merged the independent classifications into a single variable. The expert raters identified the following FDG-PET-SPM patterns, suggestive of different neurodegenerative conditions according to the previous literature: 43 AD typical and atypical-AD patterns (i.e., 15 typical AD, 6 frontal-AD, 13 asymmetric logopenic AD variant and 9 PCA); 17 FTD patterns (i.e., 11 bv-FTD, 3 semantic variants, 2 CBD, and 1 PSP); 1 DLB pattern and 19 negative patterns (see Supplementary Fig. 1 for FDG-PET-SPM patterns examples). A significant association was found between AD, DLB and FTD FDG-PET-SPM patterns classification and, respectively, AD dementia, DLB and FTD conversions at follow-up (Table 2). FDG-PET-SPM classification identified 14 MCI subjects with hypometabolism patterns specific for dementias but showing cognitive stability at follow-up, namely 5 AD and 9 FTD patterns. None of them reverted to normal cognition (Table 2). In addition, there were 16 negative FDG-PET-SPM patterns that accurately predicted stable condition or reversion to normal cognition (Table 2). Three MCI cases with negative FDG-PET-SPM patterns that were diagnosed as AD dementia at follow-up showed unspecific hypometabolic patterns, suggestive of underlying minor cerebrovascular pathology (Heiss et al., 1986).

3.4. FDG-PET-SPM patterns and CSF association

We found a significant association (high concordance) between FDG-PET-SPM AD patterns and CSF Aβ42, t-Tau and p-Tau positivity for AD pathology ($p < 0.05$); the presence of FDG-PET-SPM FTD patterns was instead associated with negative CSF Aβ42, positive p-Tau and t-Tau levels and Erlangen Scores of 0, 1, 2. In details, 10/17 cases had Erlangen Score equal to 0, indicative of non-AD pathology; 1/17 cases had Erlangen Score equal to 1, indicative of improbable AD; 6/17 cases had Erlangen Score equal to 2, suggesting possible AD (see Table 3 and Fig. 1). No significant difference in CSF biomarkers was found between typical and atypical AD FDG-PET-SPM patterns (Supplementary Fig. 2).

Concerning the stable or reverter cases with FDG-PET-SPM negative

Table 1
Sociodemographic, clinical and biomarkers measures divided by MCI sub-type at baseline.

SAMPLE		Total	aMCI	NaMCI	md aMCI	md naMCI	p-value
N		80	31	8	35	6	–
Gender	M/F	37/43	17/14	5/3	13/22	2/4	ns
Age (years)	Mean	70.03	70.39	73.05	69.81	65.33	ns
	SD	7.29	6.29	8.92	7.08	10.61	
Education (years)	Mean	9.69	10.50	9.75	9.44	6.67	ns
	SD	3.84	4.13	4.68	3.40	2.16	
MMSE	Mean	25.60	25.93	25.79	25.18	26.03	ns
	SD	2.73	2.81	3.16	2.62	2.66	
Aβ42 < 500 (ng/l)	Mean	562.76	609.81	498.38	510.74	701.09	ns
	SD	289.39	333.97	317.16	225.76	313.63	
t-Tau > 450 (ng/l)	Mean	488.40	534.84	546.39	460.31	332.63	ns
	SD	375.10	414.30	193.56	394.39	152.06	
p-Tau > 61 (ng/l)	Mean	70.77	78.07	94.18	61.61	52.50	ns
	SD	35.69	36.23	39.55	32.79	22.49	
t-Tau/Aβ42	Mean	1.16	1.26	1.41	1.12	0.54	ns
	SD	1.07	1.19	0.77	1.08	0.34	
p-Tau/Aβ42	Mean	0.17	0.19	0.26	0.14	0.09	ns
	SD	0.13	0.15	0.17	0.11	0.04	
FDG SPM AD	n	43	14	5	22	2	ns
FDG SPM FTD	n	17	9	2	5	1	ns
FDG SPM DLB	n	1	0	0	1	0	ns
FDG SPM negative	n	19	8	1	7	3	ns

Abbreviations: MCI = mild cognitive impairment, aMCI = amnestic (single-domain) MCI, md aMCI = multi-domain amnestic MCI, naMCI = non-amnestic (single-domain) MCI, md naMCI = multi-domain non-amnestic MCI, SD = standard deviation, AD = Alzheimer's disease, FTD = frontotemporal lobar degeneration, DLB = dementia with Lewy bodies, n = number. Statistical differences were assessed performing ANOVA and Chi-square analyses.

Table 2
Biomarkers measures compared according to the clinical conversion at follow-up.

SAMPLE		AD	FTD	DLB	Stable	Reverter	Total	P-value
N		39	10	1	27	3	80	–
CSF Aβ42 (ng/l)	Mean	416.4*	750.3	200	721.7	578.7	562.7	< 0.001
	SD	194.9	233.8	–	319.7	152.7	289.4	
Positive < 500 (ng/l)	N	31*	1	1	8	1	42	< 0.05
CSF t-Tau (ng/l)	Mean	595.7	479.7	521.0	367.0	180.0	488.8	ns
	SD	448.9	351.1	–	209.4	46.2	375.1	
Positive > 450 (ng/l)	N	21*	4	1	9	0	35	< 0.05
CSF p-Tau (ng/l)	Mean	83.8*	64.7	59.0	56.6	45.3	70.8	0.01
	SD	34.9	40.8	–	30.1	5.1	35.7	
Positive > 61 (ng/l)	N	29*	5	0	11	0	45	< 0.05
CSF p-Tau/Aβ42 ratio	Mean	0.2*	0.1	0.3	0.1	0.08	0.17	< 0.01
	SD	0.14	0.06	–	0.1	0.01	0.13	
CSF t-Tau/Aβ42 ratio	Mean	1.6*	0.7	2.6	0.7	0.3	1.2	< 0.05
	SD	1.2	0.5	–	0.63	0.01	1.1	
FDG-PET 'AD' pattern	N	35*	3	0	5	0	43	< 0.05
FDG-PET 'FTD' pattern	N	1	7*	0	9*	0	17	< 0.05
FDG-PET "DLB" pattern	N	0	0	1*	0	0	1	< 0.05
FDG-PET 'negative' pattern	N	3	0	0	13*	3*	19	< 0.05

Abbreviations: CSF = cerebrospinal fluid; t-Tau = total Tau; p-Tau = phosphorylated Tau; AD = Alzheimer's disease, FTD = frontotemporal dementia, DLB = dementia with Lewy bodies. Statistical differences were assessed performing ANOVA and Chi-square analyses.

* Significance at $p < 0.05$.

pattern (n = 13 and n = 3, respectively) we found, as for CSF measures, 9 cases with pathological values of either of Aβ42, p-Tau, t-Tau and Erlangen Score > 0.

3.5. AD dementia vs. non-AD dementia predictive model

The CSF dichotomous classifications provided the following levels of accuracy in the prediction of conversion to AD dementia: Aβ42 AUC = 0.77 (95% C.I. 0.67–0.88, $p < 0.001$); t-Tau AUC = 0.61 (95% C.I. 0.48–0.73, $p = 0.10$); p-Tau AUC = 0.67(95% C.I. 0.55–0.79, $p = 0.01$); t-Tau/Aβ42 ratio AUC = 0.81 (95% C.I. 0.72–0.91, $p < 0.001$), with the highest level of accuracy provided by the p-Tau/Aβ42 ratio AUC = 0.84 (95% C.I. 0.75–0.93, $p < 0.001$). The Erlangen Score (≥3) provided an AUC equal to 0.81 (95% C.I. 0.71–0.91, $p < 0.001$) in the prediction of AD dementia conversion.

FDG-PET-SPM classification showed the best accuracy in the prediction of conversion to AD dementia AUC = 0.85 (95% C.I. 0.76–0.94, $p < 0.001$).

The Erlangen Score aided by FDG-PET-SPM classification, allowed to correctly classify AD dementia converters in 35 out of 39 cases, providing an AUC equal to 0.82 (95% C.I. 0.73–0.92, $p < 0.001$).

We found that AUC for FDG-PET-SPM classification was not statistically different from CSF Aβ42 ($Z = 1.35$, $p = 0.18$), t-Tau/Aβ42 ratio ($Z = 0.63$, $p = 0.53$) and p-Tau/Aβ42 ratio ($Z = 0.17$, $p = 0.86$). This indicates the important role of these CSF biomarkers in AD diagnosis. Of note, AUC for FDG-PET-SPM classification was significantly higher than CSF t-tau AUC ($Z = 4.08$, $p < 0.001$) and CSF p-tau AUC ($Z = 2.97$, $p < 0.005$). No significant difference was found between

Table 3
Contingency table for the concordance between FDG-PET SPM and CSF classification.

CSF		FDG-PET SPM Classification				
		AD	FTD	DLB	Negative	Total
Aβ42	Neg	11	17*	0	10	38
	Pos	32*	0	1	9	42
t-Tau	Neg	18	11	0	16	45
	Pos	25	6	1	3	35
p-Tau	Neg	11	12*	1	11	35
	Pos	32	5	0	8	45
Erlangen Score	0	1	10*	0	7	18
	1	3	1	0	2	6
	2	16	6	0	5	27
	3	7	0	0	2	9
	4	16	0	1	3	20

Abbreviations: AD = Alzheimer's disease, FTD = Frontotemporal dementia, DLB = dementia with Lewy bodies, Neg = negative, Pos = positive. Statistical differences were assessed performing Chi-square analysis.

* Significance at $p < 0.05$.

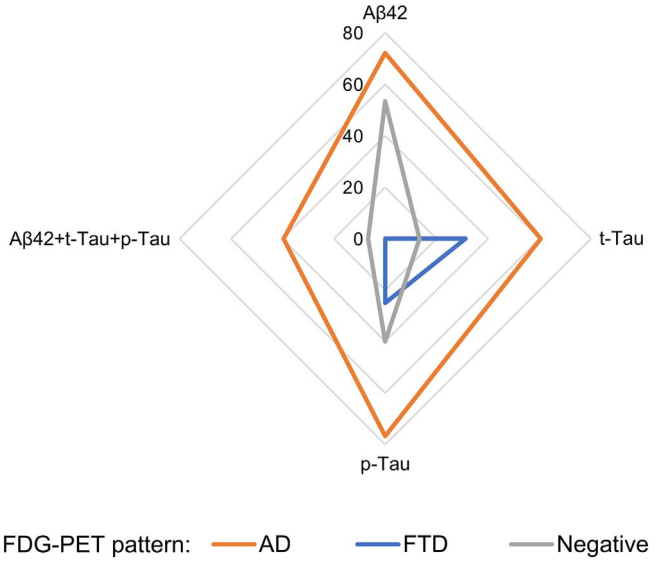

Fig. 1. Concordance between baseline CSF dichotomous values and FDG-PET SPM classification. For each of the three FDG-PET based categories (AD, FTD and negative patterns), the percentage of subjects with positive CSF assessment is reported. CSF positivity for Aβ42, t-Tau and p-Tau is highly prevalent among MCI with an AD FDG-PET pattern at baseline. A minor portion of FTD patients show increased t-Tau and p-Tau levels. Aβ42 positivity characterize also ca. half of the MCI with a negative FDG-PET pattern.

FDG-PET SPM classification AUC and Erlangen Score AUC ($Z = 1.023$, $p = 0.31$) as well as between FDG-PET SPM classification AUC and Erlangen Score aided by FDG-PET SPM classification AUC ($Z = 1.36$, $p = 0.18$).

In addition, AUC for Aβ42 was significantly higher than AUC for t-tau ($Z = 2.43$, $p < 0.05$), whereas AUCs for both t-Tau/Aβ42 ratio and p-Tau/Aβ42 ratio were significantly higher than AUC for t-tau ($Z = 6.897$, $p < 0.001$; $Z = 5576$, $p < 0.001$, respectively) and p-tau ($Z = 2.83$, $p < 0.01$; $Z = 3.97$, $p < 0.001$, respectively).

As for Erlangen Score and Erlangen Score aided by FDG-PET-SPM classification, the corresponding AUCs were significantly higher than AUCs for CSF t-tau ($Z = 4.056$, $p < 0.001$; $Z = 3.826$, $p < 0.001$, respectively) and p-tau ($Z = 2.165$, $p < 0.05$; $Z = 2.347$, $p < 0.05$, respectively).

LR+ and LR− values are represented for each biomarker in Fig. 2.

Considering the logistic regression models, in the CSF biomarkers model, Aβ42 (Expβ = 11.4, 95% C.I. 3.6–36, $p < 0.01$) and p-Tau CSF positivity (Expβ = 5.2, 95% C.I. 1.5–17.7, $p < 0.01$) significantly predicted conversion to AD dementia; the model with FDG-PET 'AD' SPM classification significantly predicted conversion to AD dementia (Expβ = 36.1, 95% C.I. 9.9–131.2, $p < 0.001$). The multivariate logistic model identified FDG-PET 'AD' SPM classification (Expβ = 19.35, 95% C.I. 4.8–77.8, $p < 0.001$) and CSF Aβ42 (Expβ = 6.5, 95% C.I. 1.64–25.43, $p < 0.05$) as the best predictors of the conversion from MCI to AD dementia. This predictive model was significantly more effective than the null one ($\chi 2 = 52.82$, $p < 0.001$) in the prediction of conversion to AD dementia at follow-up. Results were confirmed at bootstrap resampling.

3.6. FTD vs. non-FTD predictive model

FDG-PET-SPM classification showed a good accuracy in the prediction of conversion to FTD AUC = 0.78 (95% C.I. 0.60–0.95, $p = 0.005$).

Concerning the logistic regression model for the FDG-PET-SPM classification, the 'FTD' SPM classification significantly predicted conversion to FTD at follow-up (Expβ = 14, 95% C.I. 3.1–63, $p < 0.001$). Results were confirmed at bootstrap resampling.

We found high concordance between FDG-PET evidence of neurodegeneration and CDR (Chi-squared = 23.197, $p < 0.001$).Consistent with reported results using clinical diagnosis at follow-up as gold standard, FDG-PET-SPM maps significantly predicted dementia conversion according to CDR (Expβ = 17.9, 95% C.I. 4.55–70.456, $p < 0.001$). This suggests limited bias due to the circularity and confirms the overall robustness in the reported results.

4. Discussion

In MCI, the neuropsychological information and the derived subclassification is poorly accurate in predicting the conversion to different dementias (Löppönen et al., 2003; Storandt and Morris, 2010). Notably, in our cohort, both aMCI and naMCI converted to AD and non-AD dementias, in line with previous studies (Fischer et al., 2007; Ravaglia et al., 2005).

In this study, we aimed at assessing the role of CSF and FDG-PET biomarkers, individually and combined, in the prediction of conversion to dementia in a large multicentre cohort of MCI subjects. Both biomarkers are considered as supporting information for AD dementia diagnosis (McKhann et al., 2011a), and, in MCI condition for early detection of AD (Albert et al., 2011).

FDG-PET-SPM classification and CSF Aβ42 positivity, both individually and combined, significantly predicted the conversion from MCI to AD dementia at follow-up. These data align well with recent findings showing that CSF Aβ42 is a reliable biomarker for AD dementia, differentiates patients from healthy controls and detects MCI subjects who will convert to AD dementia (Olsson et al., 2016; Tang et al., 2014).

Of note, in the present study, the p-Tau/Aβ42 ratio showed good accuracy in predicting MCI conversion to AD dementia (Fig. 2). This result is also consistent with previous studies, in which the p-Tau/Aβ42 ratio was found to be the most accurate CSF measure for predicting MCI conversion to AD dementia (Landau et al., 2010; Parnetti et al., 2012). On the contrary, CSF t-Tau showed poor accuracy in prediction of MCI conversion to AD dementia (Fig. 2; Table 2). Tau CSF levels may be abnormally increased in several neurodegenerative disorders and their relationship with AD and FTD brain pathology is still not fully understood (van Harten et al., 2011).

Another crucial point concerns those patients with intermediate CSF values, often close to cut-off, who cannot be assigned neither to the 'normal' nor to the entirely pathological categories. In these cases, the adoption of a dichotomous classification for CSF biomarkers might produce an increased number of false positive or false negative, leading to serious diagnostic misclassifications (Lewczuk et al., 2015). Consistently, in our cohort, the use of the Erlangen Score algorithm

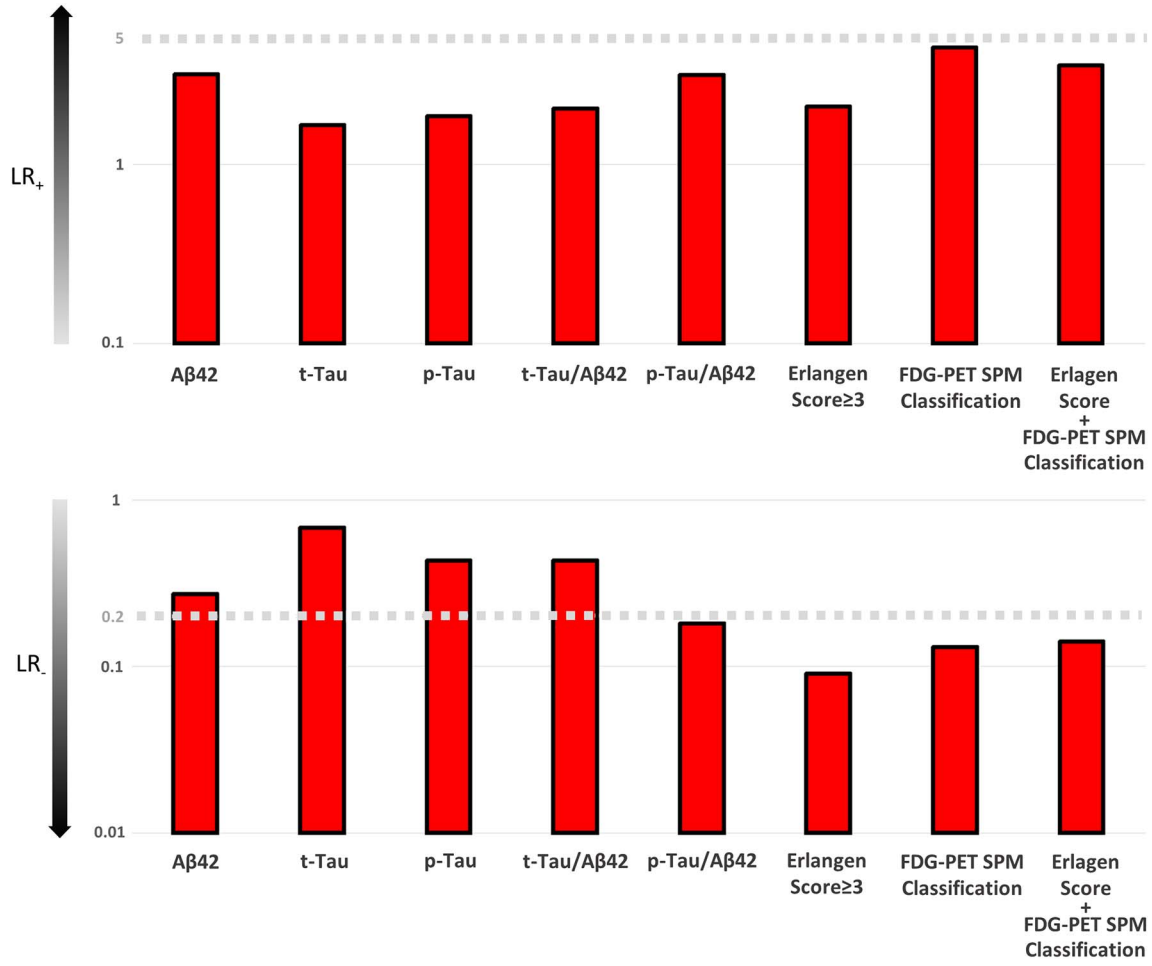

Fig. 2. Positive and negative likelihood ratio (LR+ and LR−) for correct classification of MCI subjects converting to AD dementia.
LR+ > 5 indicates that the biomarker positive classification is associated with the disease occurrence. LR− < 0.2 indicates a relevant association between the negative biomarker classification and the absence of the dementia condition at follow up. LR values are represented on a logarithmic scale.

(Lewczuk et al., 2009) with five discrete CSF levels outperformed the dichotomous classification. Namely, an Erlangen Score > 2 predicted AD dementia conversion with an AUC of 0.81, thus being more precise as compared to the standard dichotomous division (AUC = 0.68).

However, the Erlangen Score classification still provided high percentages of false positives, i.e. cases with high scores (3 and 4) with no conversion at follow-up, lowering the specificity of the CSF biomarkers. We hypothesize that, for some of these cases, a longer follow-up might be needed in order to capture the conversion; further, the false positives might be accounted for by the presence of incidental amyloidosis as previously shown (Iaccarino et al., 2017; Jansen et al., 2015). This last point is also strongly supported by coexistence of pathological CSF values for Aβ42 with negative FDG-PET-SPM maps. Notably, aiding the intermediate Erlangen scores (1–3 range) by means of FDG-PET-SPM classification positively impacted on the specificity levels. In addition, the FDG-PET-SPM classification seems to be particularly relevant in aiding better identification of cases with possible non-amyloid-based neurodegeneration (Perani, 2014).

FDG-PET-SPM classification was the most accurate biomarker (Fig. 2), able to correctly differentiate subjects who converted to AD dementia or to other dementias (FTD and DLB) from those who remained stable or reverted to normal cognition. FDG-PET imaging, as a biomarker of local synaptic dysfunction, can early recognize disease-specific alterations in neurodegenerative diseases (Caminiti et al., 2017; Cerami et al., 2015; Iaccarino et al., 2017; Perani, 2013, 2014; Perani et al., 2016; Teune et al., 2010).

First, these findings are consistent with the current literature on AD diagnostic strategies, that shows higher accuracy for FDG-PET as compared to other biomarkers (Bloudek et al., 2011; Dukart et al., 2015; Fellgiebel et al., 2007; Iaccarino et al., 2017; Landau et al., 2010; Perani et al., 2016; Robb et al., 2017; Shaffer et al., 2013; Yuan et al., 2009). Of note, a recent study on the prognostic value of the NIA-AA (McKhann et al., 2011b), IWG-2 and IWG-1 criteria (Dubois et al., 2007, 2014), showed that classification based on the NIA-AA criteria for AD dementia diagnosis, in which amyloid PET and FDG-PET biomarkers are considered, reached the highest prediction accuracy in a clinical setting (Vos et al., 2015). Second, this is the first study, in a large MCI samples, demonstrating the high value of FDG-PET with a validated voxel-wise analysis for the assessment of the risk of progression to different dementia conditions, considering the very limited evidence in previous literature (Cerami et al., 2015; Chiba et al., 2013; Fujishiro et al., 2013; Perani et al., 2016). Third, a crucial evidence in favour of the FDG-PET-SPM usefulness is its exclusionary role. Sixteen out of 19 negative FDG-PET cases did not convert to any dementia or even reverted to normal cognition. A negative FDG-PET-SPM pattern should strongly suggest reconsidering a diagnosis of neurodegenerative disease (Lo et al., 2011). High specificity and low negative LR value mean that a negative or normal scan in the presence of the suspicion of dementia makes the diagnosis of a neurodegenerative disease very unlikely (Fig. 2). On the contrary, the CSF measures showed normal values in only half of the stable or reverter cases, thus confirming the fundamental value of FDG-PET in excluding underlying neurodegenerative process in the MCI stage as compared to the other biomarkers.

Despite most MCI subjects presenting patterns of hypometabolism at

baseline progressed to dementia, a proportion of them remained stable (14 out of 61, 23%) (Table 2). In these cases, as aforementioned, a longer clinical follow-up would be necessary to ascertain the eventual conversion to dementia.

The combined use of FDG-PET and CSF Aβ42 biomarkers agreed in predicting conversion to AD dementia at follow-up (Fig. 1; Table 3). In addition, FDG-PET-SPM FTD patterns were associated with normal values of CSF Aβ42 in all subjects (Fig. 1; Table 3).

MCI subjects with FDG-PET-SPM patterns suggestive of typical or atypical AD variants did not differ in CSF biomarker profiles, confirming that CSF measures are similar across different AD variants (Ossenkoppele et al., 2015; Seguin et al., 2011; Warren et al., 2012), thus not providing a fine-grained differentiation (see Supplementary Fig. 2). At difference with CSF, the hypometabolism patterns detected by FDG-PET-SPM classification at the single-subject level were suggestive of different AD variants (see Supplementary Fig. 1), supporting also a more precise prodromal differential diagnosis (Bohnen et al., 2012; Perani et al., 2014b). Thanks to the ability to capture disease-specific patterns, FDG-PET hypometabolism has been included as a supportive feature in the clinical/research diagnostic criteria of multiple neurodegenerative conditions (Armstrong et al., 2013; Gorno-Tempini et al., 2011; Litvan et al., 1996; McKeith et al., 2017; McKhann et al., 2011a; Rascovsky et al., 2011). Overall, FDG-PET represents a crucial biomarker for the classification scheme in dementia.

In the up-to-date literature, the predictive power of FDG-PET in MCI conversion to AD dementia varied widely and ranged from 25% to 100% for sensitivity and from 15% to 100% for specificity (Anchisi et al., 2005; Arbizu et al., 2013; Chen et al., 2016; Chételat et al., 2003; Landau et al., 2010; Ossenkoppele et al., 2013; Perani et al., 2014a, 2016). As also highlighted by the EANM reply to the Cochrane review (Smailagic et al., 2015), the variability observed in the different FDG-PET studies, and the low accuracy obtained in the prediction of MCI progression to dementia, might be caused by specific technical issues (e.g. poorer sensitivity and lower spatial resolution of PET scanners and small controls group for the statistical comparison), and, crucially, by the lack of adequate biomarker quantification (Morbelli et al., 2015). Notably, we report high prognostic accuracy of the FDG-PET assessment that could be traced back to the optimized features of the SPM single-subject procedure, namely the use of i) dementia-specific template for normalization of FDG-PET images, and ii) large normal dataset for statistical comparisons at the individual level (Della Rosa et al., 2014; Perani et al., 2014a). Specificity and sensitivity values for both early and differential diagnosis of dementia significantly increase in clinical settings when semi-quantitative approaches are used (Perani et al., 2014b).

5. Conclusions

An early and differential diagnosis of neurodegenerative dementias is essential to improve patient management and clinical trial design. Biomarkers can help to correctly select the candidates for clinical trials and to plan effective rehabilitative programmes, with an overall improvement of patients' and caregivers' quality of life and with public costs saving. The appropriate use of PET tracers is crucial for a prompt diagnosis and targeted evaluation of newly developed drugs aimed at slowing or preventing dementia.

The fundamentals of FDG-PET are well established and are based on extensively explored molecular mechanisms (Perani, 2014). Various neuropathological events can contribute to synaptic dysfunction in neurodegenerative diseases, e.g. altered intracellular signalling cascades, mitochondria bioenergetics, impaired neurotransmitter release, and proteinopathies (Kato et al., 2016; Perani, 2014). Though these events can be localized, they can trigger long-distance alterations with consistent disease-specific patterns that are accurately detected by FDG-PET (Caminiti et al., 2017; Cerami et al., 2016, 2017; Iaccarino et al., 2015; Perani, 2014; Perani et al., 2016; Teipel et al., 2015; Teune et al., 2010), even before manifest brain atrophy (Bateman et al., 2012; Chételat et al., 2008; Perani, 2014). In the last years, growing evidence on the positive diagnostic and prognostic value of FDG-PET fostered the scientific community to promote the relevance of cerebral FDG-PET in the diagnostic work-up in neurodegenerative diseases.

The use of topographical (FDG-PET) and CSF measures, tailored on individual cases and measured with validated approaches can remarkably improve early differential diagnosis and prediction or exclusion of progression risk to dementia in MCI subjects. In the future, optimized automated methods for CSF quantification might reduce inter-centres analytical variability (Bittner et al., 2016). This will increase reliability and comparability of CSF quantification when performed across different centres (Ewers et al., 2015; Mattsson and Zetterberg, 2010) and narrow the “grey zone” of biomarker uncertainty given by analytical variability (Simonsen et al., 2017).

This study has some limitations. First, a longer clinical-neuropsychological follow-up is certainly needed in non-converter subjects with CSF measures and FDG-PET SPM maps classification indicative of underling neurodegeneration.

Both CSF and FDG-PET data were considered in the follow-up diagnostic work-up. This may have in part contributed to the agreement between biomarkers and clinical diagnosis at follow-up. The high consistency of FDG-PET biomarker' performance when using CDR as an alternative outcome, indicates an overall robustness of its predictive value. Another limitation for this and other similar studies is the lack of *post-mortem* neuropathological confirmation of the final diagnosis.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.01.019.

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