Relationship between neuroimaging and emotion recognition in Mild Cognitive Impairment patients

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Abstract

Objective: Dementia is a major public health problem with high needs for early detection, efficient treatment, and prognosis evaluation. Social cognition impairment could be an early dementia indicator and can be assessed with emotion recognition evaluation tests. The purpose of this study is to investigate the link between different brain imaging modalities and cognitive status in Mild Cognitive Impairment (MCI) patients, with the goal of uncovering potential physiopathological mechanisms based on social cognition performance.

Methods: The relationship between the Reading the Mind in the Eyes Test (RMET) and some clinical and biochemical variables ([18F]FDG PET-CT and anatomical MR parameters, neuropsychological evaluation, and CSF biomarkers) was studied in 166 patients with MCI by using a correlational approach.

Results: The RMET correlated with neuropsychological variables, as well as with structural and functional brain parameters obtained from the MR and FDG-PET imaging evaluation. However, significant correlations between the RMET and CSF biomarkers were not found.

Discussion: Different neuroimaging parameters were found to be related to an emotion recognition task in MCI. This analysis identified potential minimally-invasive biomarkers providing some knowledge about the physiopathological mechanisms in MCI.

Keywords: emotion recognition, structural imaging, functional imaging, minimally-invasive biomarkers

1. Introduction

Dementia incidence is expected to increase in the following years due to the aging population [1]. Therefore, it is considered a major public health problem with high needs still unmet (early detection, efficient treatment, and prognosis evaluation) [1]. In a high number of cases, patients diagnosed with mild cognitive impairment (MCI) convert to dementia, while a few of them stay stable. So, MCI is an early stage with potentially relevant information regarding dementia prognostic and prevention. In fact, MCI is characterized by symptoms reflecting the initial deviation from normal aging, since subjects show problems with language, memory, and other cognitive ability, but no clear functional impairment as at dementia phase [2]. At molecular level, some alterations in mechanisms, like inflammation, cholinergic system and oxidative stress, could also play crucial roles triggering this cognitive dysfunction, progressive memory loss, and behavioural changes [3, 4]. However, more research about the physiopathological mechanisms involved in MCI development is required.

Nowadays, the standard MCI detection is based on a complete neuropsychological assessment (cognition, function), and imaging evaluation (temporoparietal hypometabolism by FDG-PET, medial temporal atrophy by MR). From these tests, if an objective cognitive impairment is detected, the amyloid status would be determined. This status is evaluated by determining cerebrospinal fluid (CSF) biomarkers levels (β-amyloid-42 (Aβ42), total Tau (t-Tau), phosphorylated Tau (p- Tau)) or fibrillary amyloid retention by amyloid positron emission tomography (amyloid PET) in order to distinguish between MCI patients at risk for Alzheimer Disease (AD) or not. In fact, AD is the main cause of dementia [5–8], and patients with impaired CSF biomarkers are a group of patients with high risk of progressing to AD. Nevertheless, CSF sampling has some disadvantages since it is an invasive technique, prone to patient's discomfort, and with some side- effects. So, the combination of imaging diagnosis and a sensitive neuropsychological evaluation could provide a promising minimally invasive alternative to MCI detection due to AD or another neurodegenerative disease (e.g., frontotemporal dementia (FTD), Dementia with Lewy Bodies (DLB)).

Recent neuropsychology research in dementia has focused attention on social cognition impairment that affects social relationships [9]. Studies from literature pointed that frontotemporal dementia (FDT) spectrum is more commonly and severely impaired on social cognition tasks than AD [10]. However, a previous study demonstrated that deficits in social cognition could be a relevant cognitive deficit in AD in comparison with other dementia types [11]. In this sense, social cognition assessment could be valuable for differential AD diagnosis [12]. More importantly, emotion recognition could be impaired in early AD stages [13–15] even when general cognition is unimpaired, as a recent meta-analysis demonstrated [16]. However, there is some controversy in this field. Dysfunction in complex social emotion recognition can be evaluated with the Reading the Mind in the Eyes Test (RMET) [17, 18]. The RMET, initially designed to detect subtle impairment in positive, negative, and neutral emotion recognition in autism, has been widely

used [19, 20]. In fact, neuroanatomical changes in MCI and AD (e.g., anterior medial frontal cortex, medial temporal cortex, amygdala) were related to social and cognitive deficits in these patients [21]. In addition**,** greater atrophy in the medial temporal lobes and the regions typically implicated in Theory of Mind (ToM) that include social cognition (prefrontal and orbitofrontal cortex, temporoparietal junction, precuneus, and insula) was reported in DLB and AD patients [22]. Therefore, future research combining social cognitive indicators (e.g., RMET) with other brain structure and function parameters (e.g., volumetric measures, glucose metabolism, blood flow, amyloid and Tau deposits, white matter hyperintensities) is required in order to increase AD prediction accuracy [23], as well as to evaluate its relationship with the general MCI. So, the application of emotion recognition tests such as the RMET could be important in order to advance in this knowledge.

The aim of this study was to evaluate the relationship between brain imaging techniques (MRI and FDG-PET) and a specific and sensitive neuropsychological evaluation (emotion recognition, RMET) as well as to identify potential physiopathological mechanisms associated to MCI, which could be used to advance in the knowledge of dementia development.

2. Materials and methods

2.1 Dataset description

All patients were retrospectively recruited from Hospital Universitari I Politècnic La Fe (HULAFE, Valencia, Spain). The initial database included patients with loss of memory and other cognitive abilities symptoms (n=310), who were assessed within the Cognitive Disorders Unit in the Neurology Service. The diagnosis was based on a neuropsychological evaluation (Clinical Dementia Rating Scale (CDR), Mini-Mental State Examination (MMSE), Repeatable Battery of Neuropsychological Assessment (RBANS), and RMET) carried out from 2019 to 2021 by accredited neuropsychologists, brain image tests ([^{18}F]FDG PET-CT or MR) with a time gap with respect to the neuropsychology tests shorter than 12 months, and CSF biomarkers. All these patients showed mild cognitive impairment (MCI) at the moment of performing the tests (brain imaging, CSF biomarkers). In fact, MCI is defined as a cognitive impairment that does not meet criteria for dementia, but it is not considered as normal ageing. It is as measurable cognition deficit in at least one domain (learning, memory, language, executive function, complex attention, perceptual-motor, social cognition), without impairment in everyday activities (ICD-11 MB21). Specifically, the MCI condition was defined by the regulated neuropsychological evaluation of CDR. This cognitive impairment was considered for ≥6 months of progression, and it was objective. Regarding the dementia status, the patients showed impairment in ≥2 cognitive domains, representing a decline from the individual previous level of functioning (CIE-11 definition).

From the initial sample, patients without a medical image ([^{18}F]FDG PET-CT or MR) were excluded (n=60); then, patients whose difference between their imaging test and the RMET test was larger than a year were discarded (n=18). Also, individuals that had no CSF molecular analysis were excluded (n=18). The remaining subjects (n=214) were classified into two groups based on whether they had an FDG-PET (n=126) or MR image (n=181) test. However, patients with tumours and other brain pathologies (e.g., basal ganglia calcification, haemorrhage, or arteriovenous malformation) were excluded from the FDG-PET group (n=2) and from the MR group (n=9), since the brain image quantification could be affected. In addition, 82 patients were excluded from the MR group given that no 3D T1 series were included in the MR study. Finally, 5 patients were also discarded from the MR group due to bad image quality. To sum up, the final PET group consisted of 124 individuals, whereas the MR group consisted of 85.

For the dataset creation these 2 groups were gathered. Hence, the final dataset was composed by a total of 166 subjects who met the eligibility criteria (n=81 patients with FDG-PET image, n=42 patients with MR image, and n=43 patients with both images modalities). Figure 1 shows inclusion and exclusion criteria.

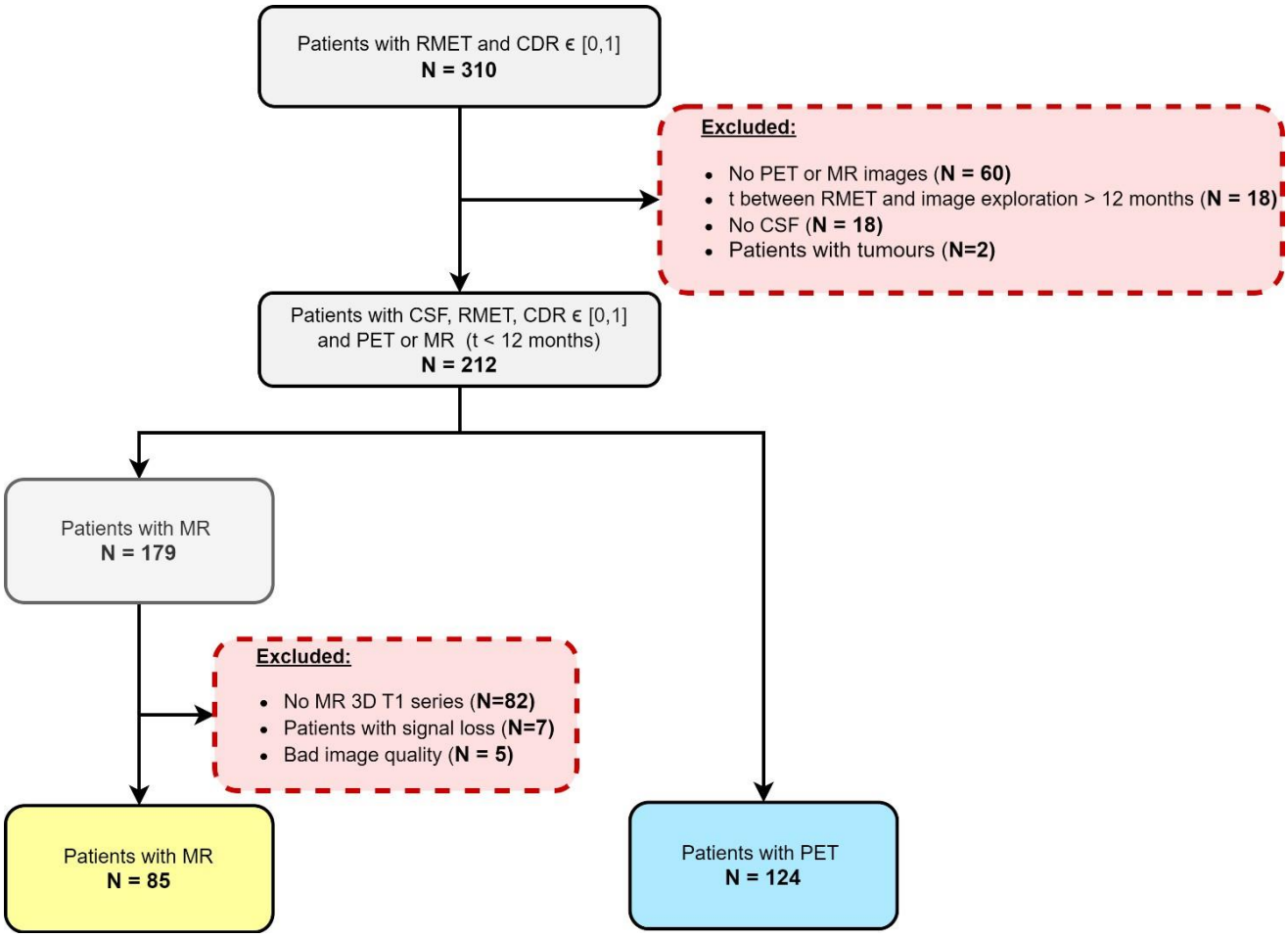

Fig. 1 *Inclusion and exclusion criteria for the study. RMET: Reading the Mind in the Eyes Test; CDR: Clinical Dementia Rating; PET: Positron Emission Tomography; MR: Magnetic Resonance; CSF: Cerebrospinal Fluid.*

The final dataset composed of 166 patients included data about medical imaging (SUVr from FDG-PET images and volumetric from MR), CSF biomarkers, and neuropsychological data (CDR, MMSE, RBANS, RMET). According to the clinical classification, all the MCI participants showed CDR scores of 0.5, or CDR 0 with other domain impaired. Approximately, half of these MCI cases were due to neurodegenerative diseases, showing alterations in CSF biomarkers or neuroimaging performance, which meet the criteria of any neurodegenerative disease; the other MCI cases did not meet the criteria for any neurodegenerative disease known (normal CSF biomarkers and neuroimaging test) [24]. In this sense, Table 1 shows a description of the enrolled patients for further information about the sample. It describes the number of patients in each clinical diagnosis group, age, sex, and neuropsychological tests.

Clinical diagnosis	**N**	**Age (years, mean ± sd)**	**Sex (female, N (%))**	**MMSE (mean ± sd)**	**RMET total (mean ± sd)**	**RBANS (sum of index, mean ± sd)**
MCI due to neurodegenerative disease	82	68 ± 7	48 (59)	23 ± 4	16 ± 5	330 ± 55
MCI not due to neurodegenerative disease	84	65 ± 8	49 (58)	26 ± 3	18 ± 5	398 ± 66

Table 1 Demographical description of enrolled patients. sd: Standard deviation

All images were obtained from the Picture Archiving and Communication System (PACS), whereas patient's data (demographic, clinical) were obtained from the hospital clinical records. For the dataset creation, all this information was completed with neuropsychological data (CDR, MMSE, RBANS, RMET). The Ethics Committee (CEIC) at the Health Research Institute La Fe (Valencia) approved the study protocol (reference: 2021-854-1, date: 22/12/2021) and an informed consent was obtained from all the study participants.

2.2 Imaging Data processing

2.2.1 MR

Anatomical MRI data were acquired using 1.5 and 3T MR scanners from different vendors (Philips, Siemens and GE). All studies included a whole-brain high resolution 3D T1-w sequence with a minimum of 120 sagittal contiguous slices. These images were downloaded from the PACS, reoriented to the AC-PC plane (setting the MNI origin), and transformed into NIfTI.

Image preprocessing was carried out by means of the Computational Anatomy Toolbox [CAT12, https://neuro-jena.github.io/cat/] for the Statistical Parametric Mapping (SPM12) package [https://www.fil.ion.ucl.ac.uk/spm/] under MATLAB environment. The CAT12 preprocessing is based on the unified segmentation approach [25], which includes initial registration, bias correction, and segmentation. We followed the standard preprocessing steps, which included: 1) segmentation of the images into gray matter (GM), white matter (WM), and CSF; 2) affine registration to the International Consortium of Brain Mapping (ICBM) template; 3) normalisation to the MNI space via optimized shooting registration (resized to a 113 × 137 × 113 resolution with 1.5 × 1.5 × 1.5 mm voxel size); and 4) modulation by the affine + non-linear (SPM12) components derived from the spatial normalisation. Additionally, we also extracted the GM volumes from regions of interest (ROIs) in native space. The ROIs were defined by using the Hammers parcellation. This atlas, based on Alexander Hammers' brain atlas, made available for the Euripides project, Nov 2009 (http://brain-development.org/). The Hammers atlas is based on 95 entirely manually delineated regions drawn on MR images of 30 healthy adult subjects in native space prior to spatial normalisation to MNI space [26, 27].This atlas is freely distributed for academic use within the CAT12. Subsequently, a data quality control was conducted in CAT12 via the "check sample homogeneity" module. The quality metrics revealed 5 patients with poor data quality so they were excluded for further analyses.

Prior to the analysis, the total intracranial volume (TIV) was also extracted for each patient. The TIV is a major confounder when analysing brain volumes given that differences in raw volumes may stem from differences in brain size between males and females. So, we corrected the ROI GM volumes by applying the power-corrected proportion (PCP) method [28]. This approach has been proposed as the best approximation to eliminate TIV variation [29]. The resulting TIV-corrected ROI GM volumes were taken as covariates of interest in the following statistical analyses.

2.2.2 [18F]FDG PET-CT

The European Association of Nuclear Medicine procedure guidelines for brain PET imaging using [^{18}F]FDG, version 2 were followed for the acquisition protocol [30]. Subjects fasted for at least 4 hours. 20-30min before [^{18}F]FDG administration and during the uptake phase all patients were positioned comfortably in a quiet, dimly lit room. A total scan length of 20 min image was acquired 20-30 min post-injection. The injected dose was 155±25 MBq [^{18}F]FDG. Glycemia levels measured before [^{18}F]FDG injection were under 200 mg/dL.

Images with 128 × 128 × 90 matrix resolution, and 2 × 2 × 2 mm voxel size were downloaded in the DICOM format from the PACS. The scanner used for the patient acquisitions was Philips Gemini TF 64 PET/CT. The algorithm employed by this device for the 3D image reconstruction was Ordered Subset Expectation Maximization (OSEM) using time of flight. After the image reconstruction process images were quality checked by a nuclear medicine physician.

In the standardization procedure PET images were spatially normalised to the Montreal Neurological Institute. In this process, all scans were resized to a 121 × 145 × 121 resolution with 1.5 × 1.5 × 1.5 mm voxel size as to match with the probability map resolution and voxel size. The software Statistical Parametric Mapping 12 (SPM12) in MATLAB was used for this task.

The voxel values of PET images were converted to standardized uptake value (SUV). In order to calculate the mean SUV value for the different PET regions of interest (ROI), a modification of the brain Hammers atlas was performed. Given that PET images have lower resolution than the MR, and to simplify posterior statistical analyses, we used a modified Hammers atlas by grouping some of the brain regions (e.g., anterior temporal lobe lateral part, superior temporal gyrus middle part, middle and inferior temporal gyrus, fusiform gyrus, posterior temporal lobe and superior temporal gyrus anterior part were grouped as Temporal Lateral region). After this modification, the modified atlas (AtlasLaFe) consisted of a total number of 28 regions (Anterior Cingulate L, Anterior Cingulate R, Cerebellum Whole, Occipital Lateral L, Occipital Lateral R, Parietal Inferior L, Parietal Inferior R, Parietal Superior and Precuneus L, Parietal Superior and Precuneus R, Brainstem, Posterior Cingulate L, Posterior Cingulate R, Prefrontal Lateral L, Prefrontal Lateral R, Prefrontal Medial L, Prefrontal Medial R, Primary Visual L, Primary Visual R, Sensorimotor L, Sensorimotor R, Temporal Lateral L, Temporal Lateral R, Temporal Mesial L, Temporal Mesial R, Basal ganglia L, Basal ganglia R, Insula L and Insula R) [31]. This atlas was used for the mean SUV value computation for each region whereas the SUV ratio (SUVr) was calculated by selecting the brainstem as the region of reference.

2.3 Neuropsychological evaluation

Patients performed several neuropsychological tasks. They included a global dementia rating (CDR), a general mental state (MMSE), and a battery of different cognitive domains (RBANS), functionality and emotion recognition.

First, the CDR scale was administered to determine the severity of dementia. It is a semi-structured interview protocol applied to the patient and an appropriate informant by experienced neuropsychologists[32]. The CDR evaluated cognition and functionality performance classified in six boxes (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). The global score staged the severity of symptoms of dementia using a five growing numeric scale that indicated normal cognition (CDR=0), questionable (CDR=0,5), mild (CDR=1), moderate (CDR=2), or severe (CDR=3) dementia, respectively.

Then, the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) was performed for the psychometric evaluation of five cognitive domains [33]. The RBANS is a structured battery with 12 subtests that report five index scores according to five domains assessed (immediate memory [RBANS.IM], visuospatial/constructional [RBANS.V/C], language [RBANS.L], attention [RBANS.A], and delayed memory [RBANS.DM]). The score of each domain was informed in typical scores (≤85 implies deficit). In addition, a total score was obtained by summing the five index scores [RBANS.SI]).

The general mental state was evaluated by the Mini-Mental State Examination (MMSE)[34], a standardized general screening test used to evaluate cognitive impairment and its severity. The total scores on the MMSE range between 0 and 30, with higher scores indicating better cognition. A MMSE total score from 21 to 26 implied MCI, whereas MMSE ≥ 27 implied a normal cognition.

2.4 Emotion recognition (social cognition)

The emotion recognition was measured by the Spanish version of the RMET. In general, it is used to measure Theory of Mind (ToM). However, in this process the individual has to recognize the emotion in the first place and integrate that emotion in the understanding of another person's mental state. The RMET includes 36 photographs of the eyes zone that express different complex emotions. The 36 images were categorized in three valences based on Harkness et al. work[20]: 8 positives (e.g., friendly), 12 negatives (e.g., upset), and 16 neutrals (e.g., reflective). Participants chose among four adjectives (three wrong adjectives and one accurate adjective) the one that best fit with each picture. When needed, the definition of the adjectives was provided. The total score was the sum of correct answers. The RMET has been widely used in neuropsychological research aimed at assessing socio-cognitive functions. So, the RMET has become a frequent used task when evaluating ToM states (the so-called "mentalising") in adults [17].

2.5 Statistical analysis

The program R was used for the statistical analysis. Correlations between all the different variables were studied through the Spearman's rank correlation coefficient, which enables to compare not only two variables that are continuous but also 2 variables that are ordinal. These correlation coefficients were plotted in different correlogram plots grouped by the variables of interest. The original plots with the colour bar represented the actual value of the correlation. For better visualization of the correlations, the coefficients were categorised according to the magnitude of the correlation. That is, correlation coefficients between 0.5 and 1, which represent strong relationship strength, were set to 1; correlations coefficients between 0.3 and 0.5 were set to 0.5 (moderate) and correlation coefficients between 0 and 0.3 were set to 0 (small/no correlation). Although correlograms study simple correlations and it is not mandatory to perform any correction to reduce Type I errors, only simple correlations with p values < 0.001 were reported.

3. Results

Correlations between all variables (CSF biomarkers, MR, FDG-PET, and neuropsychological tests (CDR, RBANS, MMSE, RMET)) were studied through the Spearman's rank correlation coefficient. Table 2 shows a summary of the different variables and the number of patients contained in each of the correlogram plots (Figures 2-4 of the manuscript and Figures 1-3 of Supplementary Material). For better visualization, the categorised coefficient plots results are shown in Figures 2-4. All p-values can be consulted in the xlsx of Supplementary Material. Additionally, results only show those correlations with a moderate or strong effect size (>0.3). We would like to highlight that the combination of RMET + CDR + CSF + MMSE + RBANS + UPLC + Vgm (MR) was not considered for the statistical analysis due to the small sample (n=12).

Figure	Variables	Patients (N)	Diagnosis group (%)
Fig.2	RMET + CDR + CSF biomarkers + MMSE + RBANS	166	51 – 49
Fig.3	RMET + CDR + CSF biomarkers + MMSE + RBANS + SUVr (FDG PET)	124	53 – 47
Fig.4	RMET + CDR + CSF biomarkers + MMSE + RBANS + Vgm (MR)	85	51 – 49

Table 2 summary of the different variables and the number of patients contained in each of the correlogram plots.

Results showed that correlations between the standard neuropsychological evaluation (RBANS, CDR, MMSE) and CSF biomarkers levels (Aβ42, Tau, p-Tau) were statistically significant. However, RMET scores did not correlate with CSF biomarkers, although strong correlations were observed with other neuropsychological tests (see Figure 2). So, RMET did not show any relationship with the biological AD diagnosis; nonetheless, it showed a consistent relationship with cognitive indices such as the CDR, MMSE and RBANS.

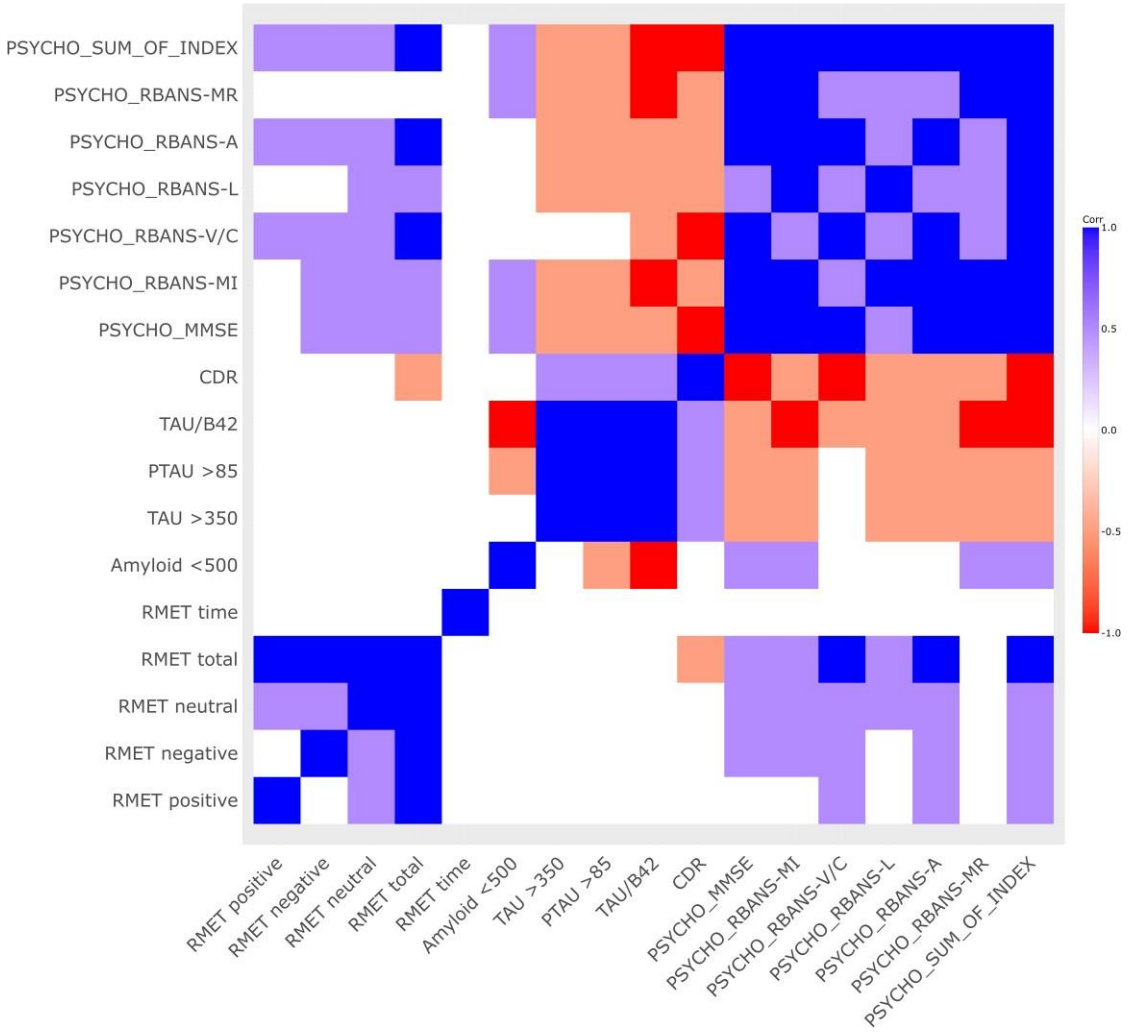

Fig. 2 *Correlogram plot of the CSF and neuropsychological data with categorised coefficients according to the magnitude of the correlation.*

Regarding the FDG-PET SUVr, data showed strong correlations with CSF biomarkers and the neuropsychological tests (see Figure 3). Likewise, regarding the correlation analysis between FDG-PET and RMET results, some significant correlations were observed. Specifically, there was a positive correlation between RMET (total score and negative group) and SUVr in the following areas: prefrontal medial L and R (r=0.36), posterior cingulate L and R (r=0.34), parietal inferior L and R (r=0.31), anterior cingulate L and R (r=0.33), prefrontal lateral L and R (r=0.33), temporal lateral R (r=0.33) insula R (r=0.31), and basal ganglia R (r=0.30). So, a reduction in the metabolic activity of all these regions were found to be associated with a disfunction in emotion recognition in MCI patients.

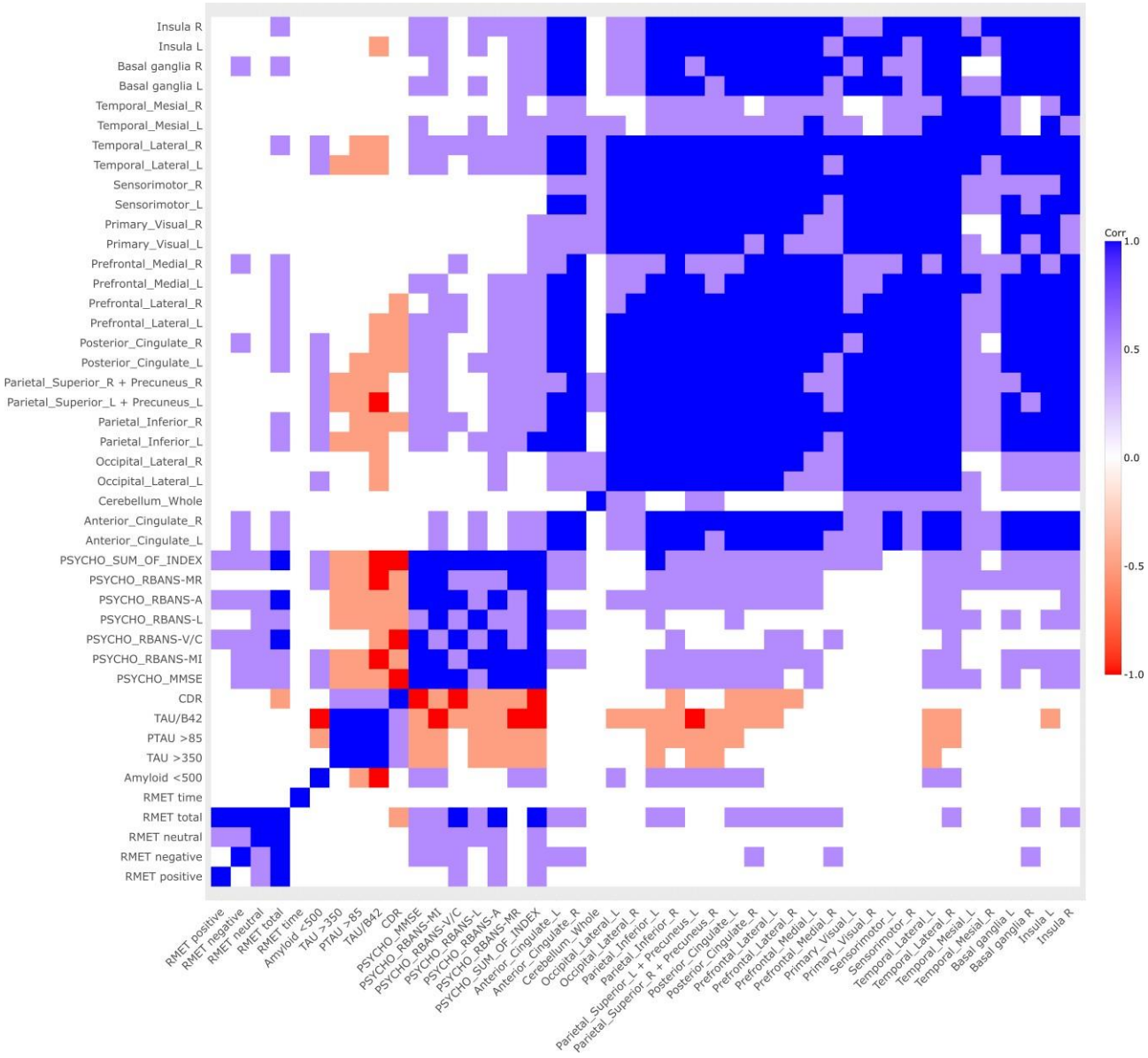

Fig. 3 *Correlogram plot of the CSF, neuropsychological and FDG-PET SUVr data with categorised coefficients according to the magnitude of the correlation.*

In relation with the structural MR data, strong and moderate correlations were found between the ROI GM volumes, CSF biomarkers and the neuropsychological evaluation tests. Nonetheless, only a few significant correlations were observed when analysing the RMET scores (see Figure 4). Specifically, the RMET total scores correlated with the straight gyrus L (r=0.40), superior frontal gyrus L (r=0.37), insula anterior inferior cortex R (r=0.36), fusiform gyrus R (r=0.36), anterior cingulate gyrus R (r=0.36), insula anterior short gyrus L (r=0.36), posterior (r=0.36) and anterior (r=0.35) cingulate gyrus L, and anterior orbital gyrus L (r=0.35). Therefore, we found the volumetric morphology of these regions to be related with emotion recognition in MCI patients.

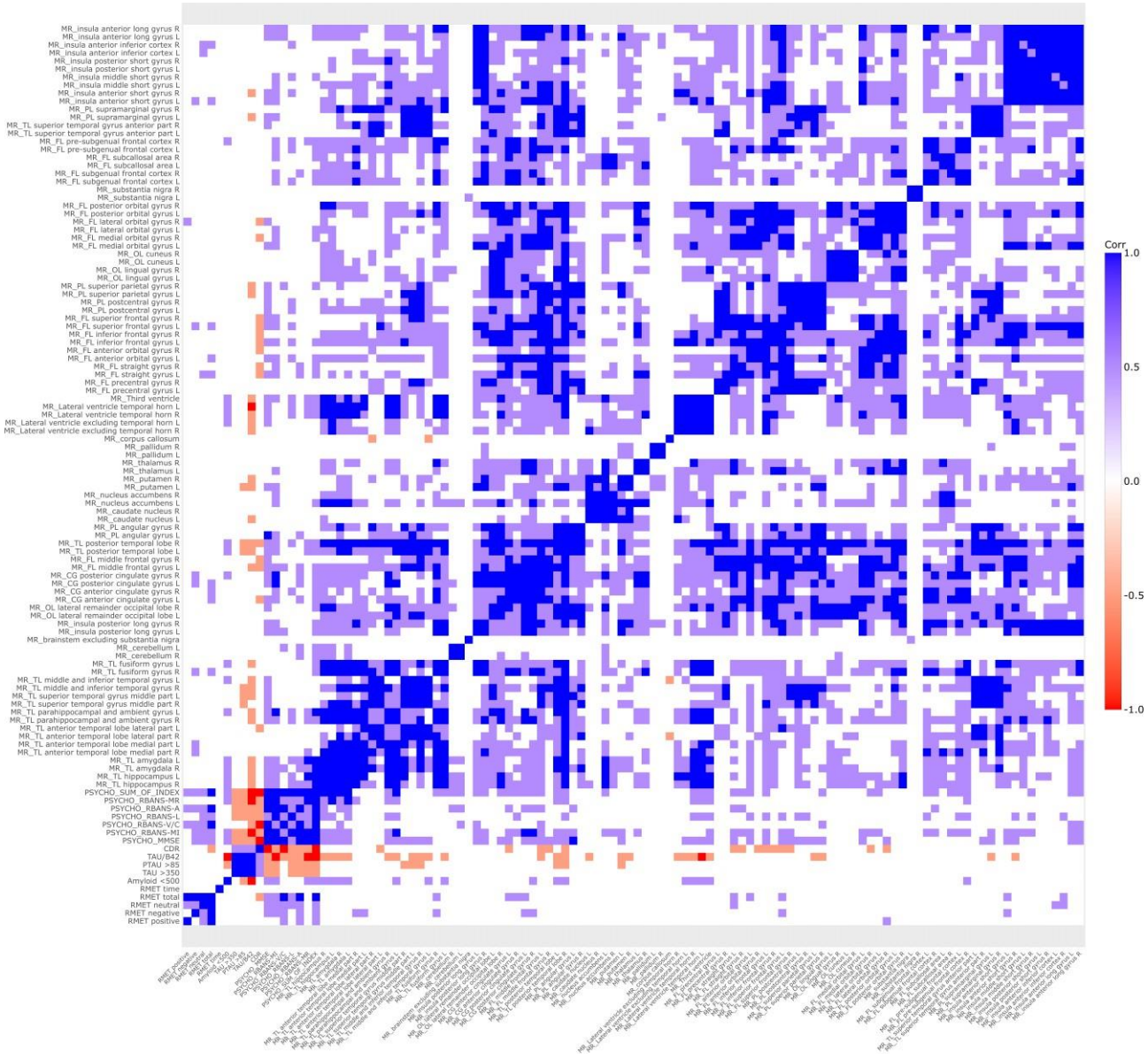

Fig. 4 *Correlogram plot of the CSF, neuropsychological and MR volumetric data with categorised coefficients according to the magnitude of the correlation.*

4. Discussion

The relationship between brain imaging techniques (MRI and FDG-PET) and clinical variables for cognitive impairment detection (CSF biomarkers and neuropsychological evaluation) could provide important information for further biomarkers identification, as well as to identify potential physiopathological mechanisms involved in MCI. Nonetheless, this association between brain (structure and function) and cognitive measures could be largely enriched by analysing other socio-cognitive domains such as emotion recognition and ToM, an underrepresented topic in MCI and brain imaging research. So, in this study we paid special attention to the relationship between clinical cognitive impairment variables (FDG-PET and anatomical MR metrics) and the socio-cognitive status (RMET) in MCI patients.

To our knowledge, this is the first study carried out in a large cohort of old-aged (50-80 years old) patients with MCI due to different causes (neurodegenerative and not neurodegenerative diseases).

Socio-cognitive abilities underlying individual differences in ToM are a topic of interest within the AD continuum research ([14, 15], revealing domain-specific deficits in MCI stage. In this line, our results also showed a consistent pattern linking RMET scores with different neuropsychological tests assessing cognitive status in MCI (e.g., CDR, MMSE and RBANS). So, our correlational approach allowed us to identify, in MCI patients, individual differences in complex emotion recognition. That is, whereas RMET performance declines gradually with age [35], the physiopathological mechanisms linked to MCI could make these deficits worse. Indeed, a recent review postulated the AD patients' impaired ability to recognize facial emotions [36]. Noticeably, however, we did not observe a correlation between RMET performance and CSF biomarkers of AD in our study. Therefore, the social cognition impairment observed in MCI was not specific for AD, which in turn could reflect common, but also different neurodegenerative trajectories. Thus, the RMET could reveal that an early significant impairment in emotion recognition could not be specific for AD. All these results provide further evidence and highlight the added value of social cognitive assessment in neuropsychological evaluations of patients at risk of dementia [37, 38].

MR results also revealed a robust pattern relating brain anatomy and socio-cognitive status in MCI. In particular, we found that MCI patients with a poorer performance on the RMET reported lower GM volume (greater atrophy) in key emotional and cognitive areas. Remarkably, we observed that the GM volume of the medial (e.g., straight gyrus) and lateral (e.g., superior and anterior orbital gyri) prefrontal cortex, fusiform gyrus, insula, and anterior and posterior cingulate gyri, were all robust predictors of RMET performance. The relationship of these regions with socio-cognitive and emotion recognition abilities is not surprising. In fact, most of these regions have been previously related with recognition of facial expressions [39, 40]. A recent functional neuroimaging meta-analysis performed on ToM and RMET revealed the key role of the inferior frontal gyrus (IFG), the insula, and the anterior cingulate cortex (ACC) in these tasks [41]. Relevantly, the GM volume of these regions [e.g., the ACC, the IFG (including insular regions) and the straight gyrus/orbitofrontal cortex (OFC)] has been stablished as a positive predictor of RMET performance in patients with MCI [42]. Likewise, the ACC and OFC GM volume was also positively correlated with the performance on emotion recognition tasks in MCI patients [43]. These brain areas have been linked to self-other representations (ACC) and affective processing and social-related decision making (IFG and OFC, respectively [42]). Thus, our results align with these previous reports and confirm, in a larger sample, the predictive value of brain atrophy in key emotional and cognitive ROIs when analysing the risk of dementia.

FDG-PET results showed a similar pattern. Specifically, we observed that MCI patients scoring low on the RMET showed lower SUVr values in medial and lateral prefrontal regions, the anterior and posterior cingulate cortices, inferior parietal and temporal lateral regions, the insula, and the basal ganglia. These results are similar to the results published by Orso et al. [44], who studied the relationship between RMET and FDG-PET in patients with AD and frontotemporal dementia. In their study, they found a correlation between brain regions associated to RMET and hypometabolism in some of those regions (cingulate, frontal regions and lateral temporal regions), even though their methodology was slightly different from our study (they used the Tailarach atlas and the whole brain mean value as reference for SUVr). As aforementioned, some of these structures are pivotal when processing affective material. Relevantly, recent research analysing perspective taking (PT, a proxy of ToM) highlighted the progressive metabolic disfunction of the middle frontal gyrus (MFG) in MCI and AD, whereas the insula metabolism was the only predictor for PT in AD [45]. On the other hand, the relationship between FDG-PET and CSF biomarkers has been widely investigated with some results that are in concordance to the results we obtained, specifically the negative relationship between Tau levels and glucose metabolism in parietal and temporal regions [46], which strengths these findings.

Finally, this work has some limitations. One of them is that primary emotion recognition deficits were not assessed in these participants. Likewise, the history of traumatic brain injuries (TBI) was not systematically evaluated. In addition, this study analysed correlations between clinical variables (MR and FDG-PET) and social cognition in MCI patients, but further analyses would be needed to clearly depict the neuropathological trajectories of specific pathologies (e.g., MCI-AD *vs* MCI non-AD). However, these analyses would require larger subgroup samples. Although none of these limitations comprise the present results, these factors should be taken into account in future studies.

5. Conclusions

The behavioural and neuroimaging results from this study reveal an association between social cognition impairment and brain alterations (both structural and functional) in key cognitive and emotional areas (e.g., prefrontal cortex, insula, ACC). Taken together, the convergence between the MR and FDG-PET results establishes a brain multimodal pattern related to individual differences in social cognitive abilities in patients with MCI. Specifically, the variability in emotional sociocognitive behaviours (e.g., the RMET) and the anatomy and function of cerebral hotspots observed in old-aged MCI patients would involve an important step in neurodegeneration knowledge. However, further studies focusing on different neurodegenerative diseases are required to advance in early and differential diagnosis of neurodegenerative disease.

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Conflicts

The authors report no conflict of interest.

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Consent Statement

All human subjects provided informed consent