Behavioural Brain Research 428 (2022) 113893

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Unravelling neural correlates of empathy deficits in Subjective Cognitive Decline, Mild Cognitive Impairment and Alzheimer's Disease☆

Giulia Giacomucci [a], Giulia Galdo [a], Cristina Polito [b], Valentina Berti [c,d], Sonia Padiglioni [e,f], Salvatore Mazzeo [a,b], Eleonora Chiaro [g], Maria Teresa De Cristofaro [d], Silvia Bagnoli [a], Benedetta Nacmias [a,b], Sandro Sorbi [a,b], Valentina Bessi [a,*]

[a] Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy
[b] IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy
[c] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Florence, Italy
[d] Nuclear Medicine Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
[e] Regional Referral Centre for Relational Criticalities - Tuscany Region, Italy
[f] Research and Innovation Centre for Dementia-CRIDEM, AOU Careggi, Florence, Italy
[g] University of Florence, Florence, Italy

ARTICLE INFO

Keywords:
Alzheimer's Disease
Mild Cognitive Impairment
Subjective Cognitive Decline
Empathy

ABSTRACT

Empathy is the ability to understand (cognitive empathy) and to feel (affective empathy) what others feel. The aim of the study was to assess empathy deficit and neuronal correlates in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) dementia. Twenty-four SCD, 41 MCI and 46 CE patients were included. Informer-rated Interpersonal Reactivity Index was used to explore cognitive (Perspective Taking-PT, Fantasy-FT) and affective (Empathic Concern-EC, Personal Distress-PD) empathy, before (T0) and after (T1) cognitive symptoms' onset. Emotion recognition ability was tested through Ekman-60 Faces Test. Cerebral FDG-PET SPM analysis was used to explore neural correlates underlying empathy deficits. FT-T1 scores were lower in AD compared to SCD (13.0 ± 8.0 vs 19.1 ± 4,7 $p = 0.008$), PD-T1 score were higher in AD compared to MCI and to SCD (27.00 ± 10.00 vs 25.3 ± 5.9 vs 20.5 ± 5.6, $p = 0.001$). A positive correlation was found between PT-T1 and metabolic disfunction of right middle gyrus (MFG) in MCI and AD. In AD group, a positive correlation between PT-T1 and insula and superior temporal gyrus (STG) metabolism was detected. A negative correlation was found between PD-T1 and superior parietal lobule metabolism in MCI, and between PD-T1 and STG metabolism in AD. Impairment of cognitive empathy starts at MCI stage. Increase of PD starts from preclinical phases and seems to be to be dissociated from cognitive decline. Loss of PT is related to a progressive involvement starting from right MFG in prodromal stage, extending to insula and STG in dementia. Heightened emotional contagion is probably related to derangement of mirror neurons systems in parietal regions in prodromal stages, and to impairment of temporal emotion inhibition system in advanced phases. Further studies are needed to clarify if alterations in emotional contagion might be a predictive feature of a cognitive decline driven by AD.

☆ This article has been selected as the Editor's Choice for Volume 428. Editor's Comments: "Empathy for a loss of empathy. Empathy, our ability to understand and to feel what others feel, is a major glue for complex societies where many human being interact. It helps to get along with them when understanding how they feel and getting an idea of why they feel this way. It appears that this capacity shrinks with aging and the frequently emerging loss of cognitive abilities. People with dementia of various type have increasing difficulties generating empathy for their surroundings. In this study, Giacomucci and colleges interrogate the brain mechanisms that start to become dysfunctional when empathy gets lost with the onset of cognitive impairments. Using FDG-PET, they report a number of brain areas and their metabolic dysfunction, which show a link to the emerging loss of empathy at its distinct dimensions. These findings may help in the future to better diagnose specific deficits in people with cognitive impairments by using metabolic imaging, and generate more empathy for them."

* Correspondence to: Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Azienda Ospedaliero-Universitaria Careggi, Largo Brambilla, 3, 50134 Florence, Italy.
E-mail address: valentina.bessi@unifi.it (V. Bessi).

https://doi.org/10.1016/j.bbr.2022.113893
Received 23 December 2021; Received in revised form 16 March 2022; Accepted 11 April 2022
Available online 14 April 2022

1. Introduction

Empathy is a complex construct and can be defined as the crucial ability to both feel and comprehend what others feel, the intentions and behaviours of others and adapting our own behaviour to achieve successful interpersonal social functioning [1].

Decety and Jackson defined the current model of empathy, which was considered as a multifaceted form of psychological inference, in which observation, memory, knowledge, and reasoning are combined to yield insights into the thoughts and feelings of others [2]. These authors proposed a distinction into two major components: affective (or emotional) empathy, which is the capacity to experience affective reactions to the observed experiences of others or share a "fellow feeling" creating an emotional response in the observer ("I feel what you feel"); on the other hand, cognitive empathy is a cognitive role-taking ability which includes the capacity to recognize and understand another's emotional state and to adopt another's psychological point of view ("I understand what you feel") [2].

Several studies described empathy deficits in neurodegenerative diseases. Severe loss of empathy has been widely described as a common feature of behavioural variant of Frontotemporal Dementia (bv-FTD) [3,4], in which both cognitive and affective empathy seems to be impaired [5]. However, studies that explored empathy deficit in Alzheimer's Disease (AD) are still relatively rare and results are far to be conclusive [6]. Previous works reported different results, ranging from no difficulties [7] to exclusively cognitive empathy deficit [5] to problems only in inferring more complex and sophisticated emotions [8]. Nevertheless, current research focused on a predominant impairment of cognitive empathy, with a relatively sparing of the affective domain in AD. However, at the state of the art, it is not clear if empathy deficits in AD are due to the general cognitive disfunctions or to a primary empathy impairment. According to the model proposed by Fischer et al. [6], empathy impairment can be mainly attributed to general cognitive impairment, particularly in executive functioning and memory. Nevertheless, this hypothesis needs to be confirmed.

Moreover, it is uncertain if empathy deficits arise in the prodromal or preclinical phases of dementia, in particular in AD. Little is known about empathy deficit in Mild Cognitive Impairment (MCI). Previous studies highlight that perspective taking ability, part of cognitive empathy, seems to be impaired in MCI patients; similarly, difficulties in facial emotion recognition have been described, but results are discordant, and it is not clear if these deficits are specific for negative emotions [9,10] or if they are present in amnestic or multi-domain MCI [10–12]. However, to the best of our knowledge, studies exploring empathy impairment in MCI with positive biomarkers of amyloid pathology have not been conducted so far. On the other hand, no studies have deeply analysed empathy changes in Subjective Cognitive Decline (SCD).

Current research is focusing on delineating neural substrate of empathy disruption in AD, in particular using voxel-based morphometry in MRI studies: Dermody et al. showed a correlation between cognitive empathy deficits and atrophy in left temporoparietal regions, including left temporal fusiform cortex, left inferior temporal gyrus, left angular gyrus, and bilateral middle and superior posterior temporal gyrus [5]. However, correlations between empathy impairment and regional hypometabolisms on cerebral Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) have not been explored so far neither in AD nor in MCI patients.

In this scenario, we aimed: (1) to investigate empathy deficits in SCD, MCI and AD dementia, trying to define specific impairment of cognitive or affective empathy in clinical, prodromal and preclinical phases of cognitive decline; (2) to explore neural correlates of empathy deficit in AD and in MCI with positive amyloid biomarker, in order to unveil a possible continuum in the involvement of empathy related brain regions in the AD continuum.

2. Materials and methods

2.1. Participants

A total of 111 subjects were longitudinally included in this study: 24 individuals with a clinical diagnosis of SCD [13], 41 with a diagnosis of MCI [14] and 46 affected by AD [15]. All participants underwent a comprehensive family and clinical history (either with the subject or with one/more knowledgeable informants), general and neurological examination, extensive neuropsychological investigation, evaluation of empathy through Interpersonal Reactivity Index (IRI) [16,17] and facial emotion recognition capacity through Ekman 60 Faces (EK-60 F) Test [18,19]. Eighty-two subjects underwent *APOE* genotyping. A positive family history was defined as one or more first-degree relatives with documented cognitive decline. Patients underwent clinical and neuropsychological follow-up every 12 or 24 months. Age at empathy assessment was defined as age at IRI and EK-60 F tests were administered. Age at onset was defined as age at the onset of cognitive symptoms, which were objectively detected on neuropsychological tests in MCI and AD patients, and not confirmed during neuropsychological evaluation in SCD patients.

Exclusion criteria included significant head injury, ongoing neurological or systemic disease (including conditions causing visual impairment), concomitant or recent history of mental illness, drug or alcohol abuse, and any concomitant causes of cognitive impairment.

2.2. Global cognitive assessment and neuropsychological evaluation

All subjects were evaluated by means of an extensive neuropsychological battery standardized and described in further detail elsewhere [20]. The battery consisted of global measurements (Mini-Mental State Examination), tasks exploring verbal and spatial short-term memory (Digit Span; Corsi Tapping Test), verbal long-term memory (Rey auditory Verbal Learning test immediate recall RVLT-I and delayed recall RVLT-D; Babcock Short Story Immediate and Delayed Recall), semantic memory (Category Fluency Task) and language (Token Test) [20,21]. Visual-spatial abilities were also evaluated by Rey-Osterrieth Complex Figure copy and visuo-spatial long-term memory was assessed by means of recall of Rey-Osterrieth Complex Figure test [22]; attention/executive function was explored by means of Dual Task [23], Phonemic Fluency Test [24], Trail Making Test (TMT) [25] and Visual Search [26]. Everyday memory was assessed by means of Rivermead Behavioral Memory Test (RBMT) [27]. All raw test scores were adjusted for age, education and gender according to the correction factor reported in validation studies for the Italian population [20–27].

2.3. Interpersonal Reactivity Index (IRI)

Empathy deficits were evaluated by Interpersonal Reactivity Index (IRI) [16,17], which is an instrument that detects empathic sensitivity through the combined measurement of cognitive and affective components. IRI consists in a 28-item questionnaire, divided in four different 7-item subscales. Each subscale evaluates a different aspect of empathy: Perspective Taking (PT) investigates the ability to adopt others' point of view; Fantasy (FT) explores the tendency to identify with fictional characters; Empathic Concern (EC) estimates the predisposition to feel compassion, concern and warmth towards others who live unpleasant experiences; Personal Distress (PD) measures general anxiety and emotional response to uncomfortable situations. Perspective Taking and Fantasy subscales better reflect cognitive empathy, while Empathic Concern and Personal Distress subscales greater assess the affective domain. PT and EC subscales are the ones that have been most used as index of empathy measurement by patients' caregivers [28,29]. On the other hand, PD subscale has been used as a measure of emotional contagion [30], that could be considered as the automatic total identification with another's behaviour in order to encourage affective

incentive and altruistic comportment [2]. Each item of IRI consists of an affirmation in respect to which the individual expresses his/her degree of agreement on a 5-points Likert Scale from 1 (does not describe me/the patient at all) to 5 (describes me/the patient very well). Some items are expressed in negative form with respect to the subscale's general sense; so, before proceeding with the analysis, their score must be inverted. IRI was rated by informants, since caregivers' ratings of empathy turned out to be an effective way for evaluation of patients affected by dementia [31]. Informants rated patients' empathy before (T0) and after (T1) cognitive symptoms' onset.

2.4. Ekman-60 Faces Test

Facial emotion recognition was assessed by Ekman-60 Faces (EK-60 F) Test. The EK-60 F test consists in sixty black and white photographs of the Ekman and Friesen series of Pictures of Facial Affect [18], representing ten actors' faces (six women and four men), each of which shows one of six basic emotions (anger, sadness, happiness, fear, disgust, surprise). Before administering the test, some questions to the patient were carried out, in order to verify the semantic recognition of the six emotions considered. Images were submitted via power point presentation on a computer screen, each of them for a maximum period of five seconds. Patients were asked to indicate which of the basic emotions better represents the facial emotion shown on the display. Each correct recognition gives one point, for a maximum of ten points for each emotion, and an overall maximum score of sixty.

2.5. Apolipoprotein E (APOE) genotyping

A standard automated method (QIAcube, QIAGEN Hilden, Germany) was used to isolate DNA from peripheral blood samples. APOE genotypes were investigated by HRMA [32]. Two sets of PCR primers were designed to amplify the regions encompassing rs7412 [NC_000019.9:g 0.45412079 C>T] and rs429358 (NC_000019.9:g 0.45411941 T > C). The samples with known APOE genotypes, which had been validated by DNA sequencing, were used as standard references. The APOE genotype was coded as APOE ε4- (no APOE ε4 alleles) and APOE ε4 + (presence of one or two APOE ε4 alleles).

2.6. Cerebral amyloidosis and neurodegeneration biomarkers analysis

Eighty-two patients were subjected to amyloidosis biomarkers analysis. Seventy-six patients (13 SCD, 28 MCI, 35 AD) underwent cerebrospinal fluid (CSF) biomarkers analysis. The CSF samples have been collected in early morning by lumbar puncture, immediately centrifuged and stored at − 80 °C until performing the analysis. Aβ1–42, Aβ1–42/1–40 ratio, t-tau, p-tau have been measured using ELISA kits (commercial enzyme-linked immunosorbent assay) or a chemiluminescent enzyme immunoassay (CLEIA) analyser LUMIPULSE G600 (Fujirebio). Cut-off values for CSF were determined following Fujirebio guidelines (Diagnostic sensitivity and specificity using clinical diagnosis and follow-up golden standard. November 19th, 2018). Cut-off values were: for Aβ1–42 > 670 pg/mL, Aβ42/40 ratio > 0.062, t-tau < 400 pg/mL and p-tau < 60 pg/mL [33].

Twenty patients (2 SCD, 7 MCI, 11 AD) underwent cerebral amyloid PET. Amyloid PET imaging was performed according to national and international standards [34], with any of the available fluorine18-labeled tracers (^{18}Florbetaben [FBB]-Bayer-Pyramal, ^{18}Flutemetamol [FMM]-General Electric). Images were rated as either positive or negative according to criteria defined by the manufacturers.

Patients were classified as A+ if at least one of the amyloid biomarkers (CSF or amyloid PET) revealed the presence of Aβ pathology and as A- if none of the biomarkers revealed the presence of Aβ pathology.

2.7. FDG-PET brain imaging

Seven SCD, 32 MCI and 41 AD patients underwent brain [18F]FDG-PET. Scans were performed using advanced hybrid PET-CT scanner in 3D list mode at the Nuclear Medicine Unit of Careggi University Hospital, Florence. All [18F]FDG-PET scans were acquired following the EANM procedure guidelines [35]. PET data were reconstructed using 3D iterative algorithm, corrected for attenuation, random and scatter using the manufacturer's software. [18 F]FDG-PET scans pre-processing and statistical analysis are described in Section 2.9.

2.8. Statistical analysis

All statistical analysis were performed via IBM SPSS Statistics Software Version 25 (SPSS Inc., Chicago, USA). All p-values were two-tailed and significance level for all analyses was set at $\alpha = 5\%$, corresponding to a threshold p of 0.05. All variables are described as mean and standard deviation. Distribution of all variables was assessed through Shapiro-Wilk test. Chi-square test was used to compare categorical data. Differences among groups in continuous variables were assessed through one-way ANOVA followed by Bonferroni *post-hoc* test. Variation of IRI variables along time was measured by comparing pre- and post-symptoms' onset values through Wilcoxon signed-rank test. Spearman's correlation was conducted to investigate the influence of socio-demographic features and neuropsychological measures on current empathy and on facial emotion recognition ability. Bonferroni correction for multiple comparisons was applied for correlations between each IRI subscales and socio-demographic features ($p = 0.012$) and neuropsychological measures ($p = 0.002$); similarly, it was applied for correlations between facial emotion recognition ability and socio-demographic features ($p = 0.012$) and neuropsychological measures ($p = 0.002$). Multiple regression analyses were run in order to evaluate the influence of demographic and neuropsychological factors on IRI subscales. Multiple-way MANCOVA was used to determine the interaction effect among EK-60 F total and partial scores controlling for demographic and neuropsychological covariates.

2.9. SPM analysis

In order to explore the relation between empathy deficits and regional hypometabolism in the AD continuum, a total of forty-two patients were considered: 24 CE and 18 MCI patients with at least one positive amyloid biomarker (A+), encompassed by AD continuum [36]. We excluded for FDG-PET analysis all patients with a diagnosis of SCD, diagnosis of MCI with amyloid biomarker negativity (A-), and AD patients with atypical presentation (logopenic variant Primary Progressive Aphasia, poster cortical atrophy and cortico-basal syndrome). [18 F]FDG-PET images were normalized to the MNI space using a validated procedure. Images were smoothed with an isotropic 3D Gaussian kernel with a FWHM of 8 mm in each direction, and then were used for a single subject SPM-based routine for diagnostic purposes [37]. Age was included in the two-sample t-test analysis as a covariate. The SPM multiple regression design was used to explore the correlation between IRI subscales, resulting from behavioral data analysis, and brain hypometabolism in the AD and MCI groups, both separately and as a whole group. Age and MMSE were entered in the linear model as nuisance variables. The threshold was set at p *value* < 0.001, uncorrected, to test for correlations also in the small subsamples of AD (n = 24) and MCI (n = 18) patients taken apart. Only clusters containing more than 50 voxels were considered significant.

2.10. Standard protocol approvals and patient consents

The local ethics committee approved the protocol of the study. All participants gave informed consent to participate in the study. All procedures involving experiments on human subjects have been done in

Table 1
Demographic features in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) groups.

	SCD	MCI	AD
	n = 24	n = 41	n = 46
Gender (M/F)	3/21 *	14/27	22/24 *
Age at onset (years)	$54.92 \pm 9.54^{\circ\varsigma}$	$66.92 \pm 8.07^{\circ}$	$66.95 \pm 6.56^{\varsigma}$
Age at empathy (years)	$60.23 \pm 8.96^{\Psi\varpi}$	$71.79 \pm 8.06^{\Psi}$	$69.19 \pm 6.22^{\varpi}$
Disease duration (years)	$7.62 \pm 7.45^{\lambda\eta}$	$5.41 \pm 3.26^{\lambda}$	$3.00 \pm 1.43^{\eta}$
Family history of AD	19/23 (82.6%)^§	19/39 (48.7%)^	21/42 (50%)§
Years of education	12.13 ± 3.54	10.20 ± 3.89	10.34 ± 4.57
MMSE	$28.92 \pm 1.11^{\Upsilon}$	$26.59 \pm 2.57^{\zeta}$	$18.75 \pm 5.45^{\Upsilon\zeta}$
APOE ε4 +	4/17 (30.77%)	15/30 (50.00%)	17 (50.00%)

Values are reported as mean and standard deviation or frequencies or percentages for continuous variables and categorical variables respectively. Statistically significantly different values among groups are reported as underlined character. M: males; F: females; MMSE: Mini Mental State Examination. * $\chi^2 = 8.57$, $p = 0.016$; $^{\circ}$ $p < 0.001$; $^{\varsigma}$ $p < 0.001$; ^ $\chi^2 = 7.0$, $p = 0.014$, § $\chi^2 = 6.67$, $p = 0.004$; $^{\Upsilon}$ $p < 0.001$; $^{\zeta}$ $p < 0.001$; $^{\Psi}$ $p < 0.001$; $^{\varpi}$ $p = 0.003$; $^{\lambda}$ $p = 0.001$; $^{\eta}$ $p < 0.001$.

accordance with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accordance with the Helsinki Declaration of 1975. Specific national laws have been observed.

3. Results

3.1. Demographic features

Demographic variables are summarized in Table 1. Considering the whole sample, 72 patients were females and 39 males. SCD and AD groups significantly differed in sex distribution, with a higher prevalence of females in SCD group as compared to AD (87.5% vs 52.2%, χ^2=8.57, $p = 0.016$). Age at onset was significantly different among the three groups (F [2104]=21.782, $p < 0.001$), since it was lower in SCD subjects (54.92 ± 9.54) as compared to MCI (66.92 ± 8.07, $p < 0.001$) and AD (66.95 ± 6.56, $p < 0.001$) patients. Age at empathy assessment was significantly different among groups too (F [2108]=8.085, $p < 0.001$), in particular it was lower in SCD (54.92 ± 9.54) as compared to MCI (71.79 ± 8.06, $p < 0.001$) and AD (69.19 ± 6.22, $p = 0.003$) patients. Mini Mental State Examination (MMSE) was significantly different among the groups (F [2108]=80.355, $p < 0.001$) with poorer scores in AD (18.75 ± 5.45) compared to SCD (29.92 ± 1.11, $p < 0.001$) and MCI (26.59 ± 2.57, $p < 0.001$). Eighty-one patients underwent APOE genotype analysis: 44.44% resulted to be APOE ε4 carriers.

3.2. Amyloidosis and neurodegeneration biomarkers analysis

Seventy-six patients (13 SCD, 28 MCI, 35 AD) underwent amyloidosis and neurodegeneration biomarkers CSF analysis (Aβ1–42, Aβ1–42/1–40 ratio, t-tau, p-tau). Twenty patients (2 SCD, 7 MCI, 11 AD) were subjected to cerebral Amyloid PET, detecting amyloid deposition in 19 patients (2 SCD, 7 MCI, 10 AD). Basing on the positivity for at least one cerebral amyloidosis biomarker, 65 out of 82 patients (79.27%, 5 SCD, 22 MCI, 38 AD) were classified as A+.

3.3. IRI Empathy results

3.3.1. Evaluation of pre-morbid empathy capacity

One-way ANOVA with Bonferroni *post-hoc* test was conducted to assess if there were any differences in socioemotional functioning before cognitive symptoms' onset among SCD, MCI and AD. No significant differences were detected neither in IRI total score T0 (F [2104]=2.533, $p = 0.084$) nor in the single FT-T0 (F [2105]=2.073, $p = 0.131$), PT-T0 (F [2105]=0.848, $p = 0.431$), EC-T0 (F [2105]=1.262, $p = 0.287$) and PD-T0 (F [2105]=2.267, $p = 0.109$) among the three groups.

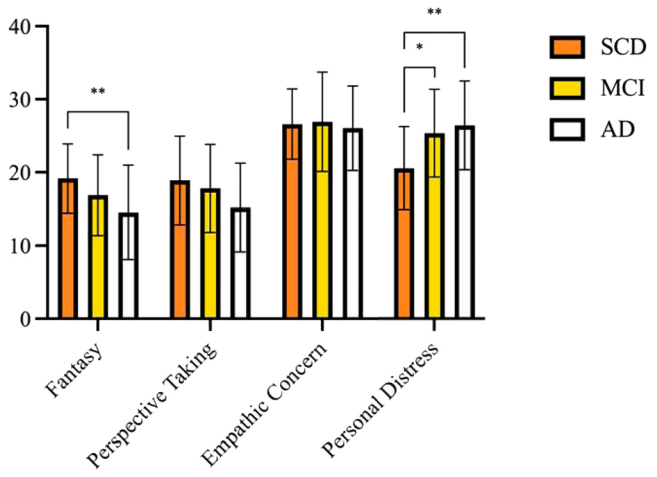

Fig. 1. Current empathy assessed by Interpersonal Reactivity Index (IRI) in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). *$p < 0.05$; **$p < 0.01$.

3.3.2. Evaluation of current empathy capacity

In order to evaluate differences in current empathy deficits among the three groups, one-way ANOVA with Bonferroni *post-hoc* test was performed. FT-T1, PT-T1 and PD-T1 resulted to be significantly different among groups at one-way ANOVA (FT-T1 F [2105]=5.031, $p = 0.008$; PT-T1 F [2105]=3.472, $p = 0.035$; PD-TI F [2105 =7.421, $p = 0.001$), while no significant differences were detected among groups at IRI-T1 and EC-T1. At Bonferroni *post-hoc* test, AD patients were rated significantly lower by informants than SCD (14.5 ± 6.4 vs. 19.1 ± 4.7, $p = 0.008$) on the FT-T1 subscale. Both MCI (25.3 ± 5.9, $p = 0.01$) and AD (26.4 ± 6.07, $p = 0.001$) presented higher scores than SCD (20.5 ± 5.6) on PD-T1 ratings. No significant differences were found in EC-T1 scores among groups (Fig. 1).

3.3.3. Trend of empathy capacity along time

Wilcoxon signed-rank test was used to estimate the course of empathy, in its cognitive and affective components, from before to after cognitive symptoms' onset, in all groups (Table 2). A significant increase of IRI (82.09 ± 9.43 vs 85.27 ± 12.11, $z = 2.48$, $p = 0.013$) and EC (25.91 ± 4.65 vs 26.59 ± 4.81, $z = 2.22$, $p = 0.001$) ratings in SCD patients, as well as a significant increase of PD in all the groups considered were underlined (SCD $z = 3.34$, $p = 0.001$; MCI $z = 5.45$, $p < 0.001$; AD $z = 5.76$, $p < 0.001$). Concerning cognitive empathy, a significant decline in PT (MCI $z = -3.88$, $p < 0.001$, AD $z = -5.22$, $p < 0.001$) and FT subscales (MCI $z = -2.58$, $p = 0.01$, AD $z = -2.43$, $p = 0.015$) were found both in MCI and AD patients (Table 2).

Comparing SCD and MCI patients based on A+ /A- status, a significant increase of PD scores over time in A+ SCD subjects (16.60 ± 4.27 vs 21.60 ± 6.22, $z = 2.03$, $p = 0.042$) was detected, not underlined in A- SCD. On the other hand, a significant improvement of PD ratings was observed in both A+ (17.33 ± 4.23 vs 25.52 ± 6.11, $z = 4.02$, $p < 0.001$) and A- (20.67 ± 3.35 vs 25.56 ± 4.72, $z = 2.67$, $p = 0.007$) MCI patients. The same analysis was not performed in AD subgroup as only one AD patient was A-.

3.4. Emotion recognition ability assessed by Ekman-60 Faces Test

In order to evaluate differences in facial emotion recognition ability among the three groups, we performed one-way ANOVA followed by Bonferroni *post-hoc* test. All the variables considered resulted to be significantly different among the three groups (Table 3). At EK-60 F global score, AD (32.34 ± 7.58) performed significantly poorer than MCI (42.39 ± 5.17, $p < 0.001$) and SCD (47.33 ± 5.16, $p < 0.001$), as well as MCI presented lower scores than SCD ($p = 0.008$). Concerning

Table 2
Trend of empathy capacity from before to after the cognitive symptoms' onset in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD).

	SCD			MCI			AD		
	Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*
IRI 0	82.09 ± 9.43	2.485	**0.013** *	86.33 ± 12.29	1.19	0.232	80.48 ± 13.04	1.57	0.115
IRI 1	85.27 ± 12.11			86.85 ± 15.07			82.26 ± 14.03		
FT 0	18.82 ± 3.36	0.085	0.393	18.30 ± 5.24	-2.58	**0.010** *	16.59 ± 5.149	-2.43	**0.015** *
FT 1	19.18 ± 4.71			16.85 ± 5.49			14.54 ± 6.43		
PT 0	19.86 ± 5.34	-1.02	0.304	21.93 ± 6.00	-3.88	**< 0.001** *	21.28 ± 6.22	-5.22	**< 0.001** *
PT 1	18.91 ± 6.05			17.78 ± 5.99			15.20 ± 6.06		
EC 0	25.91 ± 4.65	2.22	**0.026** *	27.80 ± 5.59	-1.34	0.179	26.48 ± 4.46	-0.92	0.356
EC 1	26.59 ± 4.81			26.88 ± 6.79			26.04 ± 5.78		
PD 0	17.64 ± 4.51	3.34	**0.001** *	18.30 ± 4.82	5.45	**< 0.001** *	16.13 ± 4.94	5.76	**< 0.001** *
PD 1	20.59 ± 5.67			25.35 ± 5.98			26.46 ± 6.07		

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**.

Table 3
Differences in facial emotion recognition ability among Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) assessed by Ekman 60 Faces Test (EK-60 F).

	SCD	MCI	AD	*F*	*p*	*p* between SCD and MCI	*p* between MCI and AD	*p* between SCD and AD
EK-60 F total score	47.33 ± 5.164	42.39 ± 5.171	32.34 ± 7.588	50.574	**< 0.001**	**0.008**	**< 0.001**	**< 0.001**
Execution time (seconds)	288.58 ± 57.677	362.78 ± 69.14	436.34 ± 113.42	22.353	**< 0.001**	**0.004**	**0.001**	**< 0.001**
Anger	8.00 ± 3	6.00 ± 3	5.10 ± 2.24	9.440	**< 0.001**	0.332	**0.012**	**< 0.001**
Disgust	8.50 ± 2	8.00 ± 3	5.07 ± 2.51	21.720	**< 0.001**	1	**< 0.001**	**< 0.001**
Fear	5.08 ± 2.448	3.00 ± 3	3.00 ± 3	10.427	**< 0.001**	**< 0.001**	1	**< 0.001**
Happiness	10.00 ± 0	10.00 ± 1	9.00 ± 2	12.930	**< 0.001**	1	**< 0.001**	**< 0.001**
Sadness	8.00 ± 4	7.00 ± 3	4.61 ± 2.60	19.989	**< 0.001**	1	**< 0.001**	**< 0.001**
Surprise	10.00 ± 1	9.00 ± 2	6.10 ± 2.66	31.915	**< 0.001**	0.174	**< 0.001**	**< 0.001**

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**.

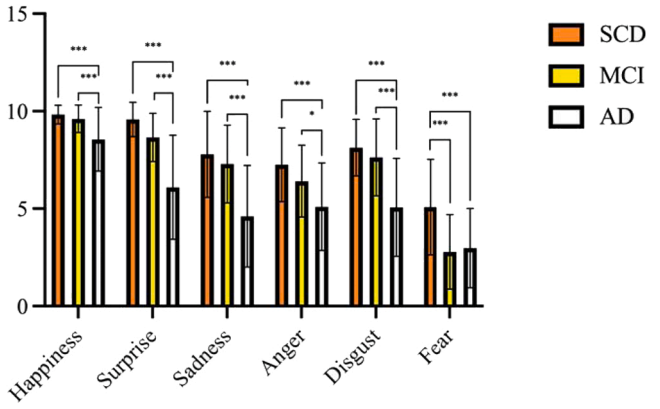

Fig. 2. *Emotional recognition ability, assessed by Ekman-60 Faces Test, in* Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). *p < 0.05; * *p < 0.01; * **p < 0.001.

the single emotions' recognition, AD showed more difficulties in anger (AD 5.10 ± 2.24, MCI 6.41 ± 1.84, SCD 7.25 ± 1.89), disgust (AD 5.07 ± 2.51, MCI 7.63 ± 1.97, SCD 8.13 ± 1.45), sadness (AD 4.61 ± 2.60, MCI 7.29 ± 1.99, SCD 7.79 ± 2.20), surprise (AD 6.10 ± 2.66, MCI 8.66 ± 1.23, SCD 9.58 ± 0.88), and happiness (AD 8.56 ± 1.62, MCI 9.61 ± 0.70, SCD 9.83 ± 0.48) detection than MCI (anger $p = 0.012$, all other $p < 0.001$) and SCD (all $p < 0.001$). On the other hand, both AD (2.98 ± 2.03) and MCI (2.78 ± 1.91) performed lower on fear identification than SCD (5.08 ± 2.44, both $p < 0.001$) (Fig. 2, Table 3).

3.5. Influence of demographic and neuropsychological variables on IRI subscale and emotion recognition ability

In the whole sample, no correlations were found between demographic variables and each IRI subscales (Table 4). Concerning neuropsychological evaluation, PT-T1 was directly correlated with tests assessing for attention/executive function (Phonemic Fluency Test, Spearman's $\rho = 0.360$, $p = 0.001$; Visual Search, Spearman's $\rho = 0.382$, $p = 0.002$) and inversely correlated with Trail Making Test (TMT) part A (Spearman's $\rho = -0.347$, $p = 0.002$). In order to evaluate which factors might influence PT-T1 scores, we ran a multiple regression analysis. We considered PT-T1 scores as dependent variable, diagnosis, age at empathy assessment and significantly correlated neuropsychological tests as covariates. The multiple regression model significantly predicted PT-T1 scores (F [1,64] = 8.89, $p = 0.004$, adj. $R^2 = 0.122$). Among the covariates, only Visual Search (B=0.159 [95% CI 0.053:0.266], $p = 0.004$) were statistically significant (Table 5). FT-T1 directly

Table 4
Correlations between emotional recognition ability assessed by Ekman 60 Faces Test (EK-60 F) and current empathy investigated by Interpersonal Reactivity Index (IRI) and socio-demographic variables.

	Age		Schooling	
	Spearman's ρ	*p*	Spearman's ρ	*p*
IRI total score	-0.095	0.332	0.012	0.902
Fantasy	-0.112	0.251	0.040	0.686
Perspective Taking	-0.195	0.043	0.243	0.013
Empathic Concern	-0.152	0.117	0.064	0.517
Personal Distress	0.216	0.025	-0.238	0.014
EK-60 F total score	-0.266	**0.006**	0.287	**0.003**
Execution time	0.432	**< 0.001**	-0.323	**< 0.001**
Anger	-0.135	0.167	0.112	0.258
Disgust	-0.074	0.499	0.184	0.063
Fear	-0.225	0.021	0.193	0.050
Happiness	-0.135	0.168	0.047	0.640
Sadness	-0.205	0.035	0.190	0.054
Surprise	-0.210	0.031	0.266	**0.007**

Significant differences at $p < 0.012$ are reported in **bold character**.

Table 5
Multiple regression models for IRI subscales.

	B	95% C.I. for B		β	p
		lower	upper		
PT-T1					
(Constant)	10.052	5.243	14.862		< 0.001
Visual Search	0.159	0.053	0.266	0.349	0.004
FT-T1					
(Costant)	10.727	7.186	14.269		< 0.001
Rey auditory Verbal Learning test immediate recall	0.164	0.068	0.259	0.380	0.001
PD-T1					
(Costant)	45.601	33.528	57.673		< 0.001
Diagnosis	-3.785	-7.060	-0.511	-0.463	0.024
Category Fluency Task	-0.252	-0.408	-0.096	-0.599	0.002
Rey–Osterrieth complex figure test recall	-0.324	-0.593	-0.055	-0.432	0.019

Unstandardized Regression Coefficients (B) and 95% Confidence Intervals (95% C.I.), standardized coefficient (β) and *p*-value (*p*), are reported (significant differences at $p < 0.05$).

correlated with tests assessing for memory (Rey auditory Verbal Learning test immediate recall RVLT-I, Spearman's $\rho = 0.434$, $p < 0.001$; RVLT-D, Spearman's $\rho = 0.357$, $p = 0.002$), attention/executive function (Phonemic Fluency Test, Spearman's $\rho = 0.389$, $p < 0.001$), semantic memory (Category Fluency Task Spearman's $\rho = 0.371$, $p = 0.001$). In order to evaluate which factors might influence FT-T1 scores, we ran a multiple regression analysis. We considered FT-T1 scores as dependent variable, diagnosis, age at empathy assessment and significantly correlated neuropsychological tests as covariates. The multiple regression model significantly predicted FT-T1 scores (F [1,69] = 11.62, $p < 0.001$, adj. R^2=0.144). Among the covariates, only RVLT-I (B=0.164 [95% CI 0.068:0.259], $p = 0.001$) was statistically significant (Table 5).

PD-T1 was inversely correlated with tests assessing for memory (RVLT-I, Spearman's ρ = -0.400, $p = 0.001$; Babcock Short Story Delayed Recall, Spearman's ρ = -0.384, $p = 0.002$), semantic memory (Category Fluency Task, Spearman's ρ = -0.508, $p < 0.001$), attention/executive function, (Visual Search, Spearman's ρ = -0.453, $p < 0.001$); on the other hand, a direct correlation was detected between PD-T1 and TMT part A (Spearman's $\rho = 0.341$, $p < 0.001$) and part B (Spearman's $\rho = 0.367$, $p = 0.002$). PD-T1 presented an inverse correlation with tests assessing for visuo-spatial abilities, such as Rey–Osterrieth complex figure test copy (Spearman's ρ = -0.465, $p < 0.001$), and with visuo-spatial long-term memory, such as Rey–Osterrieth complex figure test recall (Spearman's ρ = -0.499, $p < 0.001$). In order to evaluate which factors might influence PD-T1 scores, we ran a multiple regression analysis. We considered PD-T1 as dependent variable and diagnosis, age at empathy assessment and significantly correlated neuropsychological tests as covariates. The multiple regression model significantly predicted PD-T1 scores (F [3,51] = 10.36, $p < 0.001$, adj. R^2 =0.379). Among the covariates, diagnosis (B=−3.785 [95% CI −7.060:−0.511], $p = 0.024$), Category Fluency Task (B=−0.252 [95% CI −0.408:−0.096], $p = 0.002$) and Rey–Osterrieth complex figure test recall (B=−0.324 [95% CI −0.593:−0.055], p = 0.019) were statistically significant (Table 5). Finally, we did not find any correlation between EC-T1 and with neuropsychological tests.

Correlations between emotional recognition ability and demographic variables were analysed too (Table 4). In the whole cohort, EK-60 F total score was inversely correlated with age at empathy assessment (Spearman's $\rho = -0.266$, $p = 0.006$) and directly correlated schooling (EK-60 F Spearman's $\rho = 0.287$, $p = 0.003$). On the other hand, EK-60 F execution time was directly correlated to age (Spearman $\rho = 0.432$, $p < 0.001$) and inversely correlated to years of education (Spearman's $\rho = -0.323$, $p < 0.001$). Considering single emotion recognition, surprise was directly correlated with years of education (Spearman's $\rho = 0.266$, $p = 0.007$). We also analysed correlations between neuropsychological tests and emotion recognition ability (both EK-60 F total score and single emotion recognition scores): results are summarized in Table 6.

In order to detect differences of facial emotion recognition ability (EK-60 F total score, single emotion recognition scores and EK-60 F execution time) among the among the three groups controlling for age at empathy assessment and neuropsychological test, we performed a multivariate analysis of covariance (MANCOVA). There was no statistically significant difference among the three groups (F [16,40] = 0.984, $p = 0.491$, Wilks' $\Lambda = 0.515$, partial $\eta^2 = 0.282$). However, among the covariates, only Category Fluency Task still was significantly associated with anger recognition ($p = 0.017$) and surprise recognition ($p = 0.041$).

3.6. SPM results

SPM multiple regression analysis showed several significant correlations between IRI subscales and brain metabolism both in the MCI and

Table 6
Correlations between Ekman 60 Faces Test (EK-60 F) total and single scores and neuropsychological tests.

	Ekman 60 Faces Test							
	EK-60 F total score	EK-60 F execution time	Anger	Disgust	Fear	Happiness	Sadness	Surprise
RVLT-I	**0.641**	**-0.568**	0.335	0.330	**0.489**	**0.403**	**0.405**	**0.464**
RVLT-D	**0.568**	**-0.499**	0.302	0.224	**0.482**	**0.389**	**0.368**	**0.390**
BS-I	**0.474**	**-0.393**	0.257	0.280	0.329	0.313	0.292	0.257
BS-R	**0.524**	**-0.518**	**0.324**	0.175	**0.389**	**0.398**	0.344	0.263
PFT	**0.705**	**-0.518**	**0.490**	**0.487**	0.227	**0.481**	**0.473**	**0.561**
CFT	**0.657**	**-0.472**	**0.381**	**0.380**	**0.400**	**0.436**	**0.423**	**0.476**
TMT A	**-0.558**	**0.581**	-0.227	**-0.405**	-0.287	**-0.398**	**-0.393**	**-0.456**
TMT B	**-0.644**	**0.652**	-0.257	**-0.402**	**-0.461**	**-0.429**	**-0.425**	**-0.522**
TMT B-A	**-0.396**	**0.438**	-0–046	-0.192	**-0.421**	-0.179	-0.286	-0.294
RFC	**0.572**	**-0.485**	**0.702**	**0.502**	**0.547**	0.311	0.252	**0.465**
RFDR	**0.547**	**-0.530**	0.324	0.180	**0.374**	**0.429**	**0.383**	**0.363**
VS	**0.681**	**-0.641**	0.343	**0.443**	0.309	**0.577**	**0.474**	**0.547**
SS-F	**0.504**	**-0.409**	**0.377**	0.302	0.121	**0.386**	**0.368**	**0.411**
VS-B	**0.392**	**-0.432**	0.266	0.312	0.068	**0.416**	0.305	0.225
VS-F	**0.390**	**-0.404**	0.208	**0.360**	0.062	**0.367**	**0.358**	**0.359**
SCWT-E	**-0.476**	0.226	-0.141	-0.261	**-0.482**	-0.319	-0.359	-0.203
SCWT-T	**-0.561**	**0.467**	-0.036	**-0.502**	**-0.403**	-0.303	**-0.405**	**-0.390**

RVLT-I Rey auditory Verbal Learning test immediate recall; RVLT-D Rey auditory Verbal Learning test delayed recall; BS-I Babcock Short Story immediate recall; BS-D Babcock Short Story delayed recall; PFT Phonemic Fluency Test; CFT Category Fluency Task; TMT Trail Making Test; RFC Rey-Osterrieth Complex Figure copy; RFDR Rey-Osterrieth Complex Figure delayed recall; ViS Visual Search; SS-F Spatial Span forward; VS-B Verbal Span backward; VS-F Verbal Span forward; SCW-E Stroop Colors and Words Test errors; SCW-T Stroop Colors and Words Test time. Significant differences at $p < 0.002$ are reported in **bold character**.

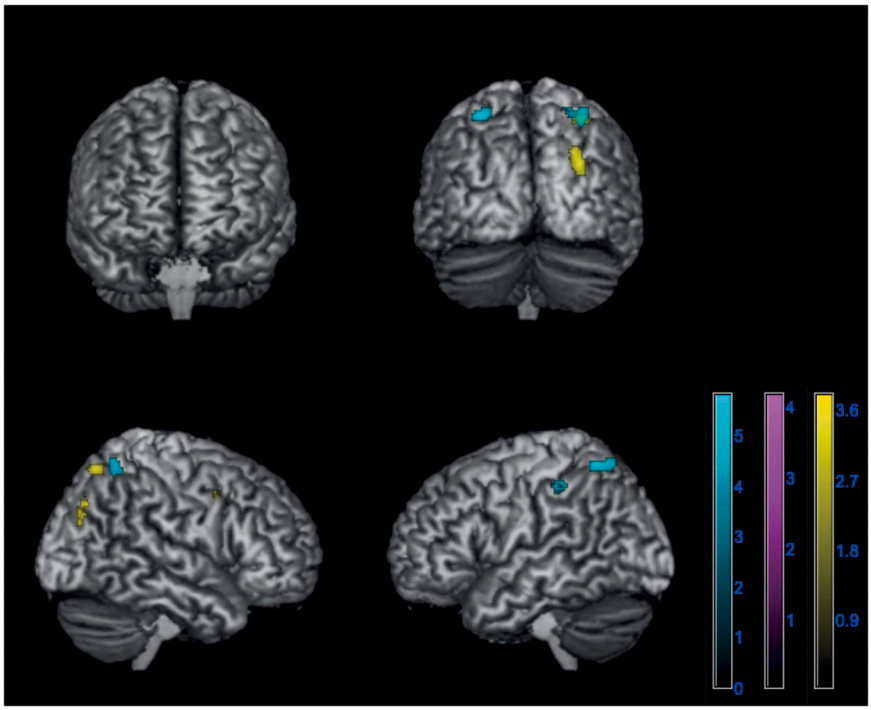

Fig. 3. *Negative correlation between emotional contagion assessed by PD-T1 IRI subscale and brain metabolism in MCI and AD patients at 18 F-FDG-PET SPM analysis.* Significant clusters projected on the standardized Montreal Neurological Institute (MNI) magnetic resonance imaging (MRI) render surface. Colour grading: Cyan= MCI, Violet= AD, Yellow=MCI & AD. $p < 0.001$, cluster size > 50 voxels.

Table 7
Negative correlation between emotional contagion assessed by PD-T1 IRI subscale and brain metabolism in AD continuum at 18 F-FDG-PET SPM analysis.

	Cluster extent	Talairach Coordinates (mm)			BA	T score
		x	y	z		
MCI						
L Superior Parietal Lobule	92	-30.0	-51.0	58.0	7	5.80
L Superior Parietal Lobule		-28.0	-61.0	58.0	7	4.90
L Postcentral Gyrus	60	-40.0	-29.0	46.0	40	5.64
R Superior Parietal Lobule	94	32.0	-52.0	56.0	7	5.19
R Superior Parietal Lobule		24.0	-51.0	60.0	7	4.15
R Precuneus		18.0	-44.0	57.0	7	4.64
AD						
R Superior Temporal Gyrus	51	46.0	-21.0	3.0	22	4.17
MCI + AD						
R Precuneus	123	30.0	-70.0	33.0	19	3.78
R Superior Temporal Gyrus	89	48.0	-23.0	3.0	22	3.57
R Superior Parietal Lobule	55	34.0	-63.0	57.0	7	3.43
R Precentral Gyrus	65	36.0	8.0	35.0	9	3.29

Abbreviations: MCI = Mild Cognitive Impairment; AD= Alzheimer's Disease; BA = Brodmann Area; L = left; R = right. Significant differences at $p < 0.001$ in MCI, $p < 0.001$ in AD and $p < 0.005$ in the whole group.

AD group, taken separately, and in the whole group. In detail:

1. PD T1 negatively correlated with brain metabolism (Fig. 3, Table 7):
   a. In the whole group in right Precuneus (BA 19), Superior Parietal Lobule (SPL, BA 7), Superior Temporal Gyrus (STG, BA 22), and Precentral Gyrus (PreG, BA 9).
   b. In the MCI group in bilateral SPL (BA 7), in right Precuneus (BA 7) and in left Postcentral Gyrus (PostG, BA 40).
   c. In the AD group in right STG (BA 22).
2. PT T1 was positively correlated with brain metabolism (Fig. 4, Table 8):

a. In the whole group in right STG (BA 22), Inferior Temporal Gyrus (BA 20), Middle Frontal Gyrus (MFG, BA 6 & 8) and SPL (BA 7). Significant correlations were found also with cerebellar metabolism, in detail in right Cerebellar Tonsil, in addition to left Pyramis and Inferior Semilunar Lobule.
b. In the MCI group in right MFG (BA 10 & 46).
c. In the AD group in right Insula (BA 13), STG (BA 22), MFG (BA 6).

No significant correlations were found between FT T1 subscale and brain metabolism.

4. Discussion

To the best of our knowledge, this is the first study exploring empathy impairment along the continuum of cognitive decline, in order to identify subtle changes in prodromal and preclinical phases.

First of all, the univariate analysis highlighted a significant decrease in PT and FT and an increase in PD from SCD to AD, suggesting a significant damage in cognitive empathy that worse with the progression of cognitive decline, united to a relative sparing of EC (part of affective empathy). Our findings are in line with previous studies reporting cognitive empathy disruption in AD patients, evaluated through PT IRI subscale [5,31,38,39]. Concerning MCI, despite empathy results in this category are more controversial and less investigated, Pernigo et al. [40] found out that MCI patients had significantly lower scores in the PT IRI subscale than controls. This is the first study reporting significant changes in FT IRI subscale in AD. In fact, previous works did not consider this scale since it has been shown to not be most relevant to patient care [5,41]. However, we also reported a significant worsening

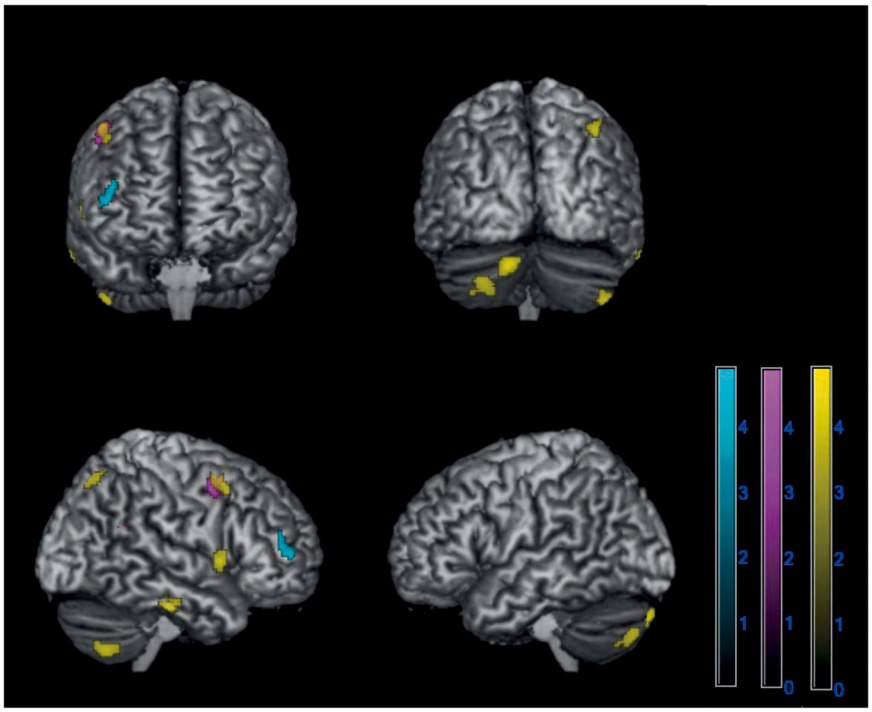

Fig. 4. *Positive correlation between cognitive empathy assessed by PT-T1 IRI subscale and brain metabolism in MCI and AD patients at 18 F-FDG-PET SPM analysis.* Significant clusters projected on the standardized Montreal Neurological Institute (MNI) magnetic resonance imaging (MRI) render surface. Colour grading: Cyan= MCI, Violet= AD, Yellow=MCI & AD. $p < 0.001$, cluster size > 50 voxels.

Table 8
Positive correlation between cognitive empathy assessed by PT-T1 IRI subscale and brain metabolism in AD continuum at 18 F-FDG-PET SPM analysis.

	Cluster extent	Talairach Coordinates (mm)			BA	T score
		x	y	Z		
MCI						
R Middle Frontal Gyrus	69	50.0	55.0	5.0	10	5.37
R Middle Frontal Gyrus		44.0	47.0	7.0	46	4.63
AD						
R Middle Frontal Gyrus	79	50.0	6.0	42.0	6	4.52
R Middle Frontal Gyrus		48.0	8.0	49.0	6	4.14
R Insula	147	42.0	-42.0	22.0	13	4.87
R Superior Temporal Gyrus		40.0	-49.0	21.0	22	4.79
MCI + AD						
L Uvula	104	-14.0	-87.0	-23.0		4.82
R Cerebellar Tonsil	71	46.0	-62.0	-42.0		4.24
L Pyramis	125	-28.0	-79.0	-33.0		4.01
L Inferior Semi-Lunar Lobule		-34.0	-72.0	-37.0		3.37
R Superior Temporal Gyrus	62	57.0	8.0	1.0	22	4.41
R Inferior Temporal Gyrus	97	69.0	-24.0	-21.0	20	4.40
R Middle Frontal Gyrus	98	50.0	8.0	51.0	6	4.38
R Middle Frontal Gyrus		46.0	14.0	42.0	8	3.61
R Superior Parietal Lobule	61	40.0	-67.0	51.0	7	3.91
R Superior Parietal Lobule		44.0	-59.0	56.0	7	3.62

Abbreviations: MCI = Mild Cognitive Impairment; AD= Alzheimer's Disease; BA = Brodmann Area; L = left; R = right. Significant differences at $p < 0.001$.

of this ability, leading to the hypothesis that every aspect of cognitive empathy seems to be impaired along the continuum of cognitive impairment.

On the other hand, we also detected a relative preservation of affective empathy both in SCD, and in MCI and in AD dementia, as previously described [5,31,38,39]: in fact, no changes in EC was found, leading to the hypothesis that affective empathy is not involved in AD, in contrast to FTD [5,31]. However, our results showed a progressive increase in PD starting from SCD to AD. Personal distress mirrors emotional contagion, which could be considered as a primitive structure of emotional empathy that expresses the tendency of individuals to automatically adopt the behavior of another person [42]. A higher emotional contagion in MCI and AD has been previously described [6,30]: Sturm et al. used PD IRI subscale to measure emotional contagion in controls, MCI and AD, concluding that emotional contagion might increase linearly from healthy controls to MCI and AD patients, with AD patients having the highest degree of emotional contagion [30]. Interestingly PD has never been investigated in SCD patients so far.

Moreover, no studies have analyzed changes in empathy capacity from before to after cognitive symptoms onset in AD spectrum. Interestingly, a significant decline in FT and PT was found in MCI and AD patients, but not in SCD subgroup. This might suggest that a significant change of cognitive empathy from before to after cognitive symptoms onset starts to be significant at MCI stage. On the other hand, we found a significant increase of PD from before to after cognitive disturbs onset not only in MCI and AD, but also in SCD patients.

We also found out that this increase in PD was still significant only in SCD with A+ status. This result is very challenging to discuss. We might suggest that a degeneration driven by AD pathology might underly this heightening in emotional contagion. However, biomarkers analysis was conducted only on a small SCD subgroup: consequently, our finding needs to be confirmed. On the other hand, both A+ and A- MCI patients showed an increase of emotional contagion over time. This finding might be explained by the fact that MCI represents a defined pathological condition which could be driven by several pathologies, not only AD [43]. Consequently, we might speculate that changes in emotional contagion might be related not only to AD, but also to other conditions which could affect empathy in this population [14,43].

Moreover, SCD patients presented an increase in EC over time. Our

results did not highlighted changes of this IRI subscale along the continuum of cognitive decline, suggesting that affective empathy seems to be spared. This increase of EC over time in SCD subgroup might be explained by the fact that SCD is a heterogeneous entity and could also be due to non-neurodegenerative conditions which might influence affective empathy (i.e. depression, anxiety, personality traits, physical health) [44–46].

Furthermore, we also performed multiple regression analyses in order to evaluate which demographic factors and neuropsychological tests might influence IRI subscales and so cognitive and affective empathy. As previously described, the univariate analysis showed PT decrease from SCD to AD. The multiple regression analysis showed an association with attentive-executive functions, suggesting an influence on cognitive empathy. This finding might be explained by the fact that frontal brain areas involved in cognitive empathy and perspective taking ability (i.e. prefrontal cortices) play a key role also in executive functions [47].

Moreover, univariate analysis showed PD increase from SCD to AD. Interestingly, when we ran the multiple regression analysis, we detected an inverse association between PD scores and diagnosis. In other words, during the progression from SCD to AD, PD seems to have an opposite trend compared to semantic and visuo-spatial memory, suggesting a dissociation between cognitive decline and emotional contagion. This may be in contrast with previous works, which showed higher PD scores in AD as compared to healthy controls [30]. However, the empathy changes in AD spectrum including SCD have not been explored so far. Our findings suggest that the increase of PD from SCD to AD seems to be dissociated from cognitive decline. This result needs to be confirmed in future analysis to better explore this point.

We also explored emotion recognition ability through EK-60 F test along AD spectrum. According to our results, emotional recognition ability decreased from SCD to AD dementia. In fact, we detected a significant difference among the three groups in overall emotional detection scores. Our results are in line with previous studies reporting severe difficulties in identification of facial emotions in AD and with the only study comparing this impairment in MCI and in SCD [40,48–50].

Particularly, a significant reduction in fear detection capacity between SCD and MCI patients as well as between SCD and AD patients, was underlined; this outcome is consistent with previous findings reflecting an impaired performance within MCI patients in fearful recognition. This result was attributed to the fact that fear can be considered as a subtle expression, so more difficult to recognize [48,49].

The multivariate analysis showed an influence of age at empathy assessment on emotional recognition ability. Our result is in line with previous reports of age-related decrease in identification of emotional facial expression. Interestingly, we also detected an influence of semantic memory on anger and surprise recognition. This finding might be challenging to discuss. In fact, previous reports have described correlations between cognitive abilities, particularly attention and executive functioning, and emotional recognition ability, especially for negatively valued emotions [40,51,52], hypothesizing that the impairment of emotional recognition might be attributed to difficulties in maintaining an adequate degree of attention to extract the necessary information from a face [52]. However, an influence of semantic memory on emotion recognition has not been explored so far. We might speculate that impairment in semantic memory might influence the specific recognition of anger and surprise, probably because these emotions are more complex to distinguish.

As second aim of our study, we tried to explore neural correlates of empathy deficit in AD and in MCI with positive amyloid biomarker, in order to unveil a possible continuum in the involvement of empathy related brain regions in AD continuum.

First of all, we found an impairment of cognitive empathy in AD continuum which was related to hypometabolism of specific brain regions, mainly located on the right hemisphere. This is in line with several previous works, which underlined the critical dominance played by the right hemisphere compared to the left one in emotional processing and social cognitive functioning [53–56].

Cognitive empathy deficits were correlated with involvement of right middle frontal gyrus in MCI patients. Middle frontal gyrus is part of the dorsolateral prefrontal cortex (DLPFC), a brain region which is involved in planning, inhibition, and abstract reasoning [57]. Several MRI studies also suggested that DLPFC plays a key role in cognitive Theory of Mind (ToM) [58,59]. ToM has been defined as the capacity to infer and represent someone else's thoughts, beliefs, intentions, and desires [2,3]. Like empathy, ToM may be distinguished into two different aspects: cognitive ToM refers to the ability to make inferences regarding other people's beliefs, while affective ToM refers to inferences one makes regarding others' emotions. Despite these distinctions, since cognitive empathy allows to comprehend the point of view of another individual, several authors suggested that it is clearly related to ToM in both its cognitive and affective aspects and that they may overlap, at least in part [6]. de Waal and Preston also described that perspective-taking tasks, part of cognitive empathy, engage several brain regions, including DLPFC [60]. Furthermore, Brodmann's area 10 (part of DLPFC), which was correlated with perspective taking impairment in our MCI patients, seems to actively and intentionally inhibit the self-perspective in order to allow the other's perspective to be considered: this ability is necessary and essential in cognitive empathy [31]. Finally, it has been demonstrated that is involved in emotion evaluation, in particular in valence attribution of emotional stimuli [61]. Considering these previous evidences, our findings might suggest that loss of perspective taking ability may be related to the impairment of DLPFC, whose functional involvement date back to prodromal phases of AD.

Besides middle frontal gyrus, right insula and right superior temporal gyrus were correlated with cognitive empathy deficits in AD patients. Previous works described that right superior temporal gyrus seems to participate to both cognitive and affective empathy [5,62]. Interestingly, superior temporal gyrus plays a role in mentalizing activity and perspective-taking tasks [60,63] through its connections with temporal poles and medial prefrontal cortex, which seems to be involved in social-emotional cognition [64]. Several studies described insula as a brain region with an important integrative role in sensation, affect, and cognition. In more details, anterior insula plays a major role in representing and integrating internal and emotional feeling states. Through the connections with several brain regions, it has been suggested that anterior insula and anterior cingulate cortex are involved in cognitive empathy since they generate forward models of feeling states for others that, together with certainty computations, may enable one to predict and understand the social and affective behavior of others [42,60,65]. These neurophysiological bases might explain the association between insula and superior temporal gyrus impairment and perspective taking deficits in our AD patients.

Taking together our results and previous findings, we might speculate that deficits in perspective taking ability seems to be related to a primary involvement of right middle frontal gyrus (including DLPFC) starting in prodromal phases, and to a subsequent involvement of insula and superior temporal gyrus which arise with the progression of the disease in the AD continuum.

Furthermore, considering the whole group of AD continuum, we detected an involvement of right inferior temporal gyrus, as well as superior parietal lobule and bilateral cerebellum correlated with cognitive empathy deficits. de Waal and Preston have already described the contribution of superior parietal lobule in empathy processes, especially in cognitive empathy [60]. Its role in cognitive empathy seems to be related to the functional involvement of superior parietal lobule in working memory [66], the cognitive domain essential for high level cognitive performances, which has been demonstrated to be related to cognitive empathy [67].

Last but not least, we found a peculiar correlation between cognitive empathy impairment and the involvement of cerebellum's posterior lobe. Our results are in line with previous reports in MRI studies of

cognitive empathy's damage associated to cerebellum's atrophy in MCI [40] and in AD patients [5]. In fact, cerebellum's posterior lobe seems to play a key role in modulation of higher functions and behavior, through its connections to parietal and prefrontal cortices, determining cognitive dysfunction when damaged [68]. Moreover, bilateral lesions of cerebellar posterior vermis and hemispheres result in empathy and ToM deficits [69]. A recent study also found that cerebellum has a role in cognitive empathy towards fictional characters, leading the authors to hypothesize that, when the subject empathizes with fictional characters, the cerebellar forward model potentially generates representations and predictions regarding the feelings of the character [70]. These findings could explain cerebellar involvement in cognitive empathy, but this field needs to be further explored.

Besides cognitive empathy, significant changes in personal distress were found. As previously described, personal distress mirrors emotional contagion [42]. Our results showed that the amplification of emotional contagion was correlated with the involvement of bilateral parietal lobes only in MCI patients, and with right superior temporal gyrus in AD subgroup. The involvement of parietal regions in MCI patients could be explained by the already known presence of neurons belonging to Mirror Neurons System (MNS) in these areas. In fact, it is necessary to underline that emotional contagion is related to MNS, which converts other's behavior representations into one's own representations and it is involved in understanding others' actions according to Perception-Action Model (PAM) [65].

On the other hand, the detection of the involvement of right superior temporal gyrus in AD patients is in line with a previous work by Sturm et al. [30]. These authors have already described an association between heightened emotional contagion in AD and atrophy detected by MRI in predominantly right-hemisphere temporal lobe regions, including superior temporal gyrus. The authors speculated that the increase of emotional contagion reflects a biological change in the neural systems that support and inhibit emotion. In fact, temporal structures are important for socioemotional stimulus detection and emotions inhibitions and, when atrophy involves these regions, degradation of social-cognitive resources may increase anxiety because patients are less accurate in their appraisal of socioemotional stimuli. Consequently, the authors hypothesized that less efficient emotion inhibition may lead to a change in interpersonal emotional reactivity, thus to a dysregulation of emotional contagion and to an intensification of automatic affective sharing [30].

Considering our results and previous findings, we might speculate that the heightened emotional contagion seems to be related with derangement of MNS in parietal regions in prodromal stages, while it could be related to impairment of temporal region in more advanced phases of AD spectrum, with a damage in the neural systems of emotion inhibition.

Finally, in the whole group of AD spectrum, we found a correlation between emotional contagion and involvement of precentral gyrus. The participation of this area to emotional contagion in AD continuum results in accord with previous reports of its contribution to this primitive mechanism of affective empathy [71].

Our study has some remarkable strengths. First of all, this is the first study analysing empathy changes along the AD continuum, in a relatively large cohort of well characterized patients. In more details, to the best of our knowledge, we widely explored empathy changes and emotion recognition in SCD population for the first time. Another strength is the use of FDG-PET: this analysis could be more suitable to detect early neural correlates of empathy impairment, since hypometabolism seems to come before atrophy occurs [72]. In fact, previous studies were based on MRI and VBM, analysing brain atrophy. Moreover, for the first time we conducted a SPM analysis in AD continuum, indeed only in MCI and AD patients with at least one positive amyloid biomarker. This is an important detail, since it helps to identify peculiar empathy changes in AD continuum, also in prodromal phases, detecting specific brain areas involved in AD. The main limitation of our study is the lack of the analysis of metabolic correlates of empathy in the preclinical subgroup. In fact, at the time of data acquisition, only few patients have undergone FDG-PET and A+ SCD patients were not enough to conduct this kind of analysis. We are going to improve our data in order to explore this category. Another limitation is the lack of corrections for multiples comparisons in the correlation analysis between empathy deficits and hypometabolism in FDG PET analysis: this is due to the small sample size, hence to explore the metabolic correlates of empathy also in the small subsamples of AD and MCI individually considered, we chose to use a more exploratory threshold.

5. Conclusions

In conclusion, our study described for the first time a peculiar involvement of specific brain areas in empathy deficit in AD continuum. In particular, loss of perspective taking ability may be strictly related to a progressive involvement starting from right middle frontal gyrus in prodromal stage and extending to insula and superior temporal gyrus arising in dementia phase. Furthermore, the heightened emotional contagion is probably related to derangement of MNS in parietal regions in prodromal stages, and to impairment of the more complex neural systems of emotion inhibition in temporal region in more advanced phases of AD spectrum. Moreover, the increase of emotional contagion seems not to be correlated with cognitive decline. Further studies are needed to clarify if this alteration of affective empathy might be a predictive feature of a cognitive decline driven by AD.

Funding

This research project was funded by Tuscany Region (GRANT no 20RSVB—PREVIEW: PRedicting the EVolution of SubjectIvE Cognitive Decline to Alzheimer's Disease With machine learning).

CRediT authorship contribution statement

Giulia Giacomucci: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft; Writing – review & editing, **Giulia Galdo**: Conceptualization, Data curation, Investigation, Validation, Visualization, Writing – original draft, **Cristina Polito**: Data curation, Formal analysis, Software, Investigation, Validation, Visualization, Writing – original draft, **Valentina Berti**: Resources, Validation, Visualization. **Sonia Padiglioni**: Resources, Validation, Visualization. **Salvatore Mazzeo**: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization. **Eleonora Chiaro**: Resources, Validation, Visualization. **Maria Teresa De Cristofaro**: Resources, Validation, Visualization. **Silvia Bagnoli**: Resources, Validation, Visualization. **Benedetta Nacmias**: Resources, Validation, Visualization. **Sandro Sorbi**: Conceptualization, Resources, Validation, Supervision, Visualization. **Valentina Bessi**: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing.

Declaration of competing interest

The authors have nothing to disclose.

References

[1] Z. Bartochowski, S. Gatla, R. Khoury, R. Al-Dahhak, G.T. Grossberg, Empathy changes in neurocognitive disorders: a review, Ann. Clin. Psychiatry 30 (2018) 220–232.
[2] J. Decety, P.L. Jackson, The functional architecture of human empathy, Behav. Cogn. Neurosci. Rev. 3 (2004) 71–100.
[3] K.P. Rankin, J.H. Kramer, P. Mychack, B.L. Miller, Double dissociation of social functioning in frontotemporal dementia, Neurology 60 (2003) 266–271.
[4] C. Cerami, A. Dodich, S. Iannaccone, A. Marcone, G. Lettieri, C. Crespi, L. Gianolli, S.F. Cappa, D. Perani, Right limbic FDG-PET hypometabolism correlates with

emotion recognition and attribution in probable behavioral variant of frontotemporal dementia patients, PLoS One 10 (2015), e0141672.
[5] N. Dermody, S. Wong, R. Ahmed, O. Piguet, J.R. Hodges, M. Irish, Uncovering the neural bases of cognitive and affective empathy deficits in Alzheimer's Disease and the behavioral-variant of frontotemporal dementia, J. Alzheimers Dis. 53 (2016) 801–816.
[6] A. Fischer, J. Landeira-Fernandez, F. Sollero de Campos, D.C. Mograbi, Empathy in Alzheimer's Disease: review of findings and proposed model, J. Alzheimers Dis. 69 (2019) 921–933.
[7] S. Alladi, S. Ch, M. Shailaja, C. Santhoshi, R. Nigam, S. Kaul, Empathy and frontal behavioral patterns discriminate between vascular dementia, Alzheimer's disease and frontotemporal dementia, Alzheimer's Dement. 7 (2011) e43–e44.
[8] D. Fernandez-Duque, S.D. Hodges, J.A. Baird, S.E. Black, Empathy in frontotemporal dementia and Alzheimer's Disease, J. Clin. Exp. Neuropsychol. 32 (2010) 289–298.
[9] I. Spoletini, C. Marra, F. Di Iulio, W. Gianni, G. Sancesario, F. Giubilei, A. Trequattrini, P. Bria, C. Caltagirone, G. Spalletta, Facial emotion recognition deficit in amnestic mild cognitive impairment and Alzheimer disease, Am. J. Geriatr. Psychiatry 16 (2008) 389–398.
[10] D. McCade, G. Savage, A. Guastella, I.B. Hickie, S.J.G. Lewis, S.L. Naismith, Emotion recognition in mild cognitive impairment: relationship to psychosocial disability and caregiver burden, J. Geriatr. Psychiatry Neurol. 26 (2013) 165–173.
[11] E.M. Weiss, C.G. Kohler, J. Vonbank, E. Stadelmann, G. Kemmler, H. Hinterhuber, J. Marksteiner, Impairment in emotion recognition abilities in patients with mild cognitive impairment, early and moderate Alzheimer disease compared with healthy comparison subjects, Am. J. Geriatr. Psychiatry 16 (2008) 974–980.
[12] A. Varjassyová, D. Hořínek, R. Andel, J. Amlerova, J. Laczó, K. Sheardová, H. Magerová, I. Holmerová, M. Vyhnálek, O. Bradáč, Y.E. Geda, J. Hort, Recognition of facial emotional expression in amnestic mild cognitive impairment, J. Alzheimers Dis. 33 (2013) 273–280.
[13] F. Jessen, R.E. Amariglio, R.F. Buckley, W.M. van der Flier, Y. Han, J.L. Molinuevo, L. Rabin, D.M. Rentz, O. Rodriguez-Gomez, A.J. Saykin, S.A.M. Sikkes, C.M. Smart, S. Wolfsgruber, M. Wagner, The characterisation of subjective cognitive decline, Lancet Neurol. 19 (2020) 271–278.
[14] M.S. Albert, S.T. DeKosky, D. Dickson, B. Dubois, H.H. Feldman, N.C. Fox, A. Gamst, D.M. Holtzman, W.J. Jagust, R.C. Petersen, P.J. Snyder, M.C. Carrillo, B. Thies, C.H. Phelps, The diagnosis of mild cognitive impairment due to Alzheimer's Disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement 7 (2011) 270–279.
[15] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack, C.H. Kawas, W.E. Klunk, W.J. Koroshetz, J.J. Manly, R. Mayeux, R.C. Mohs, J.C. Morris, M. N. Rossor, P. Scheltens, M.C. Carrillo, B. Thies, S. Weintraub, C.H. Phelps, The diagnosis of dementia due to Alzheimer's Disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimer's amp; Dement. 7 (2011) 263–269.
[16] M.H. Davis, Measuring individual differences in empathy: evidence for a multidimensional approach, J. Personal. Soc. Psychol. 44 (1983) 113–126.
[17] P. Albiero, A. Lo Coco, S. Ingoglia, Contributo all'adattamento italiano dell'Interpersonal Reactivity Index, Test. Psicometria Metodol. (2007) 107–125.
[18] P. Ekman, W. Friesen, Pictures of Facial Affect, Consulting Psychologists Press, Palo Alto, 1976.
[19] A. Dodich, C. Cerami, N. Canessa, C. Crespi, A. Marcone, M. Arpone, S. Realmuto, S.F. Cappa, Emotion recognition from facial expressions: a normative study of the Ekman 60-Faces Test in the Italian population, Neurol. Sci. 35 (2014) 1015–1021.
[20] L. Bracco, L. Amaducci, D. Pedone, G. Bino, M.P. Lazzaro, F. Carella, R. D'Antona, R. Gallato, G. Denes, Italian Multicentre Study on Dementia (SMID): a neuropsychological test battery for assessing Alzheimer's DIsease, J. Psychiatr. Res 24 (1990) 213–226.
[21] G. Carlesimo, I. Buccione, L. Fadda, A. Graceffa, M. Mauri, S. Lorusso, G. Bevilacqua, C. Caltagirone, Normative data of two memory tasks: Short-Story recall and Rey's Figure, Nuova Riv. di Neurol. 12 (2002) 1–13.
[22] P. Caffarra, G. Vezzadini, F. Dieci, F. Zonato, A. Venneri, Rey-Osterrieth complex figure: normative values in an Italian population sample, Neurol. Sci. 22 (2002) 443–447.
[23] A. Baddeley, S. Della Sala, C. Papagno, H. Spinnler, Dual-task performance in dysexecutive and nondysexecutive patients with a frontal lesion, Neuropsychology 11 (1997) 187–194.
[24] Spinnler H., Tognoni G. (1987) *Standardizzazione e taratura italiana di test neuropsicologici: gruppo italiano per lo studio neuropsicologico dell'invecchiamento*, Masson Italia Periodici, Milano.
[25] A.R. Giovagnoli, M. Del Pesce, S. Mascheroni, M. Simoncelli, M. Laiacona, E. Capitani, Trail making test: normative values from 287 normal adult controls, Ital. J. Neurol. Sci. 17 (1996) 305–309.
[26] A. Basso, E. Capitani, M. Laiacona, Raven's coloured progressive matrices: normative values on 305 adult normal controls, Funct. Neurol. 2 (1987) 189–194.
[27] M. Brazzelli, S. Della Sala, M. Laiacona, Calibration of the Italian version of the Rivermead Behavioural Memory Test: a test for the ecological evaluation of memory, Boll. di Psicol. Appl. 206 (1993) 33–42.
[28] P.J. Eslinger, P. Moore, C. Anderson, M. Grossman, Social cognition, executive functioning, and neuroimaging correlates of empathic deficits in frontotemporal dementia, J. Neuropsychiatry Clin. Neurosci. 23 (2011) 74–82.
[29] S.G. Shamay-Tsoory, J. Aharon-Peretz, D. Perry, Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions, Brain 132 (2009) 617–627.
[30] V.E. Sturm, J.S. Yokoyama, W.W. Seeley, J.H. Kramer, B.L. Miller, K.P. Rankin, Heightened emotional contagion in mild cognitive impairment and Alzheimer's Disease is associated with temporal lobe degeneration, Proc. Natl. Acad. Sci. 110 (2013) 9944–9949.
[31] K.P. Rankin, M.L. Gorno-Tempini, S.C. Allison, C.M. Stanley, S. Glenn, M. W. Weiner, B.L. Miller, Structural anatomy of empathy in neurodegenerative disease, Brain 129 (2006) 2945–2956.
[32] S. Sorbi, B. Nacmias, P. Forleo, S. Latorraca, I. Gobbini, L. Bracco, S. Piacentini, L. Amaducci, ApoE allele frequencies in Italian sporadic and familial Alzheimer's disease, Neurosci. Lett. 177 (1994) 100–102.
[33] D. Alcolea, J. Pegueroles, L. Muñoz, V. Camacho, D. López-Mora, A. Fernández-León, N.L. Bastard, E. Huyck, A. Nadal, V. Olmedo, F. Sampedro, V. Montal, E. Vilaplana, J. Clarimón, R. Blesa, J. Fortea, A. Lleó, Agreement of amyloid PET and CSF biomarkers for Alzheimer's Disease on Lumipulse, Ann. Clin. Transl. Neurol. 6 (2019) 1815–1824.
[34] S. Minoshima, A.E. Drzezga, H. Barthel, N. Bohnen, M. Djekidel, D.H. Lewis, C. A. Mathis, J. McConathy, A. Nordberg, O. Sabri, J.P. Seibyl, M.K. Stokes, K. Van Laere, SNMMI procedure standard/EANM practice guideline for amyloid PET imaging of the brain 1.0, J. Nucl. Med 57 (2016) 1316–1322.
[35] A. Varrone, S. Asenbaum, T. Vander Borght, J. Booij, F. Nobili, K. Någren, J. Darcourt, Ö.L. Kapucu, K. Tatsch, P. Bartenstein, K. Van Laere, EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2, Eur. J. Nucl. Med. Mol. Imaging 36 (2009) 2103–2110.
[36] C.R. Jack, D.A. Bennett, K. Blennow, M.C. Carrillo, B. Dunn, S.B. Haeberlein, D. M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, E. Liu, J.L. Molinuevo, T. Montine, C. Phelps, K.P. Rankin, C.C. Rowe, P. Scheltens, E. Siemers, H.M. Snyder, R. Sperling Contributors, NIA-AA Research framework: toward a biological definition of Alzheimer's Disease, Alzheimers Dement 14 (2018) 535–562.
[37] D. Perani, P.A. Della Rosa, C. Cerami, F. Gallivanone, F. Fallanca, E.G. Vanoli, A. Panzacchi, F. Nobili, S. Pappatà, A. Marcone, V. Garibotto, I. Castiglioni, G. Magnani, S.F. Cappa, L. Gianolli, EADC-PET Consortium, Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting, Neuroimage Clin. 6 (2014) 445–454.
[38] P. Narme, H. Mouras, M. Roussel, A. Devendeville, O. Godefroy, Assessment of socioemotional processes facilitates the distinction between frontotemporal lobar degeneration and Alzheimer's Disease, J. Clin. Exp. Neuropsychol. 35 (2013) 728–744.
[39] R.L. Bond, L.E. Downey, P.S.J. Weston, C.F. Slattery, C.N. Clark, K. Macpherson, C. J. Mummery, J.D. Warren, Processing of Self versus Non-Self in Alzheimer's Disease, Front Hum. Neurosci. 10 (2016) 97.
[40] S. Pernigo, G. Gambina, V. Valbusa, M.T. Condoleo, E. Broggio, A. Beltramello, G. Moretto, V. Moro, Behavioral and neural correlates of visual emotion discrimination and empathy in mild cognitive impairment, Behav. Brain Res. 294 (2015) 111–122.
[41] M. Hojat, S. Mangione, G.C. Kane, J.S. Gonnella, Relationships between scores of the Jefferson Scale of Physician Empathy (JSPE) and the Interpersonal Reactivity Index (IRI), Med Teach. 27 (2005) 625–628.
[42] B.C. Bernhardt, T. Singer, The neural basis of empathy, Annu Rev. Neurosci. 35 (2012) 1–23.
[43] E.G. Tangalos, R.C. Petersen, Mild cognitive impairment in geriatrics, Clin. Geriatr. Med. 34 (2018) 563–589.
[44] Y.-W. Cheng, T.-F. Chen, M.-J. Chiu, From mild cognitive impairment to subjective cognitive decline: conceptual and methodological evolution, NDT Volume 13 (2017) 491–498.
[45] M.J. Slavin, H. Brodaty, N.A. Kochan, J.D. Crawford, J.N. Trollor, B. Draper, P. S. Sachdev, Prevalence and predictors of "subjective cognitive complaints" in the sydney memory and ageing study, Am. J. Geriatr. Psychiatry 18 (2010) 701–710.
[46] H.C. Comijs, D.J.H. Deeg, M.G. Dik, J.W.R. Twisk, C. Jonker, Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics, J. Affect. Disord. 72 (2002) 157–165.
[47] S.G. Shamay-Tsoory, R. Tomer, D. Goldsher, B.D. Berger, J. Aharon-Peretz, Impairment in cognitive and affective empathy in patients with brain lesions: anatomical and cognitive correlates, J. Clin. Exp. Neuropsychol. 26 (2004) 1113–1127.
[48] I. Spoletini, C. Marra, F.D. Iulio, W. Gianni, G. Sancesario, F. Giubilei, A. Trequattrini, P. Bria, C. Caltagirone, G. Spalletta, Facial emotion recognition deficit in amnestic mild cognitive impairment and Alzheimer disease, Am. J. Geriatr. Psychiatry 16 (2008) 389–398.
[49] E.M. Weiss, C.G. Kohler, J. Vonbank, E. Stadelmann, G. Kemmler, H. Hinterhuber, J. Marksteiner, Impairment in emotion recognition abilities in patients with mild cognitive impairment, early and moderate alzheimer disease compared with healthy comparison subjects, Am. J. Geriatr. Psychiatry 16 (2008) 974–980.
[50] J. Pietschnig, R. Aigner-Wöber, N. Reischenböck, I. Kryspin-Exner, D. Moser, S. Klug, E. Auff, P. Dal-Bianco, G. Pusswald, J. Lehrner, Facial emotion recognition in patients with subjective cognitive decline and mild cognitive impairment, Int Psychogeriatr. 28 (2016) 477–485.
[51] M. Virtanen, A. Singh-Manoux, G.D. Batty, K.P. Ebmeier, M. Jokela, C.J. Harmer, M. Kivimäki, The level of cognitive function and recognition of emotions in older adults, PLoS One 12 (2017), e0185513.
[52] B. Torres Mendonça De Melo Fádel, R.L. Santos De Carvalho, T.T. Belfort Almeida Dos Santos, M.C.N. Dourado, Facial expression recognition in Alzheimer's Disease: a systematic review, J. Clin. Exp. Neuropsychol. 41 (2019) 192–203.
[53] G. Gainotti, Emotions and the right hemisphere: can new data clarify old models? Neuroscientist 25 (2019) 258–270.
[54] G. Gainotti, Unconscious processing of emotions and the right hemisphere. Handbook of Clinical Neurology, Elsevier, 2021, pp. 27–46.

[55] M. Sommer, K. Döhnel, B. Sodian, J. Meinhardt, C. Thoermer, G. Hajak, Neural correlates of true and false belief reasoning, NeuroImage 35 (2007) 1378–1384.
[56] K. Vogeley, P. Bussfeld, A. Newen, S. Herrmann, F. Happé, P. Falkai, W. Maier, N. J. Shah, G.R. Fink, K. Zilles, Mind reading: neural mechanisms of theory of mind and self-perspective, NeuroImage 14 (2001) 170–181.
[57] Guilford Press, The Human Frontal Lobes: Third Edition: Functions and Disorders.
[58] E. Kalbe, M. Schlegel, A.T. Sack, D.A. Nowak, M. Dafotakis, C. Bangard, M. Brand, S. Shamay-Tsoory, O.A. Onur, J. Kessler, Dissociating cognitive from affective theory of mind: a TMS study, Cortex 46 (2010) 769–780.
[59] S.G. Shamay-Tsoory, The neural bases for empathy, Neuroscientist 17 (2011) 18–24.
[60] F.B.M. de Waal, S.D. Preston, Mammalian empathy: behavioural manifestations and neural basis, Nat. Rev. Neurosci. 18 (2017) 498–509.
[61] V. Nejati, R. Majdi, M.A. Salehinejad, M.A. Nitsche, The role of dorsolateral and ventromedial prefrontal cortex in the processing of emotional dimensions, Sci. Rep. 11 (2021) 1971.
[62] M. Schurz, J. Radua, M.G. Tholen, L. Maliske, D.S. Margulies, R.B. Mars, J. Sallet, P. Kanske, Toward a hierarchical model of social cognition: A neuroimaging meta-analysis and integrative review of empathy and theory of mind, Psychol. Bull. 147 (2021) 293–327.
[63] U. Frith, C.D. Frith, Development and neurophysiology of mentalizing, Philos. Trans. R. Soc. Lond. B 358 (2003) 459–473.
[64] C. Wong, J. Gallate, The function of the anterior temporal lobe: a review of the empirical evidence, Brain Res. 1449 (2012) 94–116.
[65] G. Rizzolatti, C. Sinigaglia, The mirror mechanism: a basic principle of brain function, Nat. Rev. Neurosci. 17 (2016) 757–765.
[66] M. Koenigs, A.K. Barbey, B.R. Postle, J. Grafman, Superior parietal cortex is critical for the manipulation of information in working memory, J. Neurosci. 29 (2009) 14980–14986.
[67] Z. Gao, T. Ye, M. Shen, A. Perry, Working memory capacity of biological movements predicts empathy traits, Psychon. Bull. Rev. 23 (2016) 468–475.
[68] C.J. Stoodley, J.D. Schmahmann, Functional topography of the human cerebellum. Handbook of Clinical Neurology, Elsevier, 2018, pp. 59–70.
[69] E. Gerschcovich, D. Cerquetti, E. Tenca, R. Leiguarda, The impact of bilateral cerebellar damage on theory of mind, empathy and decision making, Neurocase 17 (2011) 270–275.
[70] E. Picerni, D. Laricchiuta, F. Piras, D. Vecchio, L. Petrosini, D. Cutuli, G. Spalletta, Macro- and micro-structural cerebellar and cortical characteristics of cognitive empathy towards fictional characters in healthy individuals, Sci. Rep. 11 (2021) 8804.
[71] C. Lamm, C.D. Batson, J. Decety, The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal, J. Cogn. Neurosci. 19 (2007) 42–58.
[72] C.R. Jack, D.S. Knopman, W.J. Jagust, L.M. Shaw, P.S. Aisen, M.W. Weiner, R. C. Petersen, J.Q. Trojanowski, Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, Lancet Neurol. 9 (2010) 119–128.