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Disentangling empathy impairment along Alzheimer's disease continuum: From subjective cognitive decline to Alzheimer's dementia

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ABSTRACT

Little is known about empathy changes from the early stages of Alzheimer's Disease (AD) continuum. The aim of this study is to investigate empathy across AD spectrum from Subjective Cognitive Decline (SCD) to Mild Cognitive Impairment (MCI) and AD dementia (AD-d).

Forty-five SCD, 83 MCI and 80 AD-d patients were included. Empathy was assessed by Interpersonal Reactivity Index (IRI) (Perspective Taking – PT, Fantasy – FT, Empathic Concern – EC, and Personal Distress – PD), rated by caregivers before (T0) and after (T1) cognitive symptoms' onset. IRI was also administered to SCD patients to have a self-reported empathy evaluation. Facial emotion recognition was assessed by Ekman-60 Faces Test.

Twenty-two SCD, 54 MCI and 62 AD-d patients underwent CSF biomarkers analysis and were classified as carriers of AD pathology (AP+) when they were A+/T+ (regardless of N), or non-carriers (AP−) when they were A− (regardless of T and N), or A+/T−/N−, or A+/T−/N+ according to the A/T(N) system. Cerebral FDG-PET SPM analysis was used to explore neural correlates underlying empathy deficits.

PD scores significantly increased from T0 to T1 in SCD, MCI and AD-d ($p < .001$), while PT scores decreased in MCI and in AD-d ($p < .001$). SCD AP+ showed a greater increase in PD

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scores over time (ΔPD T0 − T1) than SCD AP− ($p < .001$). SCD self-reported PT scores were lower than those of general Italian population (14.94 ± 3.94, 95% C.I. [13.68–16.20] *vs* 17.70 ± 4.36, 95% C.I. [17.30–18.10]). In AD continuum (SCD AP+, MCI AP+, AD-d), a positive correlation was detected between PT-T1 and brain metabolism in left posterior cingulate gyrus, precuneus and right frontal gyri; a negative correlation was found between ΔPT and brain metabolism in bilateral posterior cingulate gyri.

PT may be subtly involved since the preclinical phase of AD. Changes over time of PD are influenced by the underlying Alzheimer's pathology and could potentially serve as an early AD neuropsychological marker.

1. Introduction

Alzheimer's Disease (AD) is a progressive debilitating neurodegenerative disease, with a prevalence estimated at 50 million people worldwide and projected to triple by 2050 (Scheltens et al., 2021).

Beyond the cognitive domains typically affected such as memory, language and praxis, little is known about the involvement of social cognition. Indeed, while social cognition and empathy dysfunction are part of the diagnostic criteria of the behavioural variant of Fronto-Temporal Dementia (bv-FTD), little is known about what happens in AD and if these complex cognitive functions are impaired since the early stages of the disease, such as Mild Cognitive Impairment (MCI) and Subjective Cognitive Decline (SCD) (Fischer et al., 2019).

As part of social cognition, empathy is a complex function which can be defined as the capacity to both feel and comprehend what others feel (Bartochowski et al., 2018). According to the current model of empathy defined by Decety and Jackson, empathy may be divided into two major components: affective empathy, which is the capacity to experience affective reactions of others or share a "fellow feeling", and cognitive empathy, which may be defined as the ability to recognize and understand another's emotional state of others and to adopt another's psychological point of view (Decety & Jackson, 2004).

Despite previous works reported different results about empathy impairment in AD, it has been finally hypothesized that loss of cognitive empathy, together with a relative preservation of affective empathy and with a heightening of emotional contagion, may be considered distinctive of AD (Fischer et al., 2019; Giacomucci et al., 2022; Sturm et al., 2013). Moreover, studies that explored empathy in MCI reported discordant results, probably because of the different methods of patients' selection and the aetiology underlying MCI condition. However, it has been recently demonstrated that MCI patients might experience an impairment of perspective taking (part of cognitive empathy) together with an increase of personal distress, as a measure of emotional contagion (the most primitive structure of affective empathy); moreover, facial emotion recognition seems to be impaired too (Giacomucci et al., 2022; McCade et al., 2013; Weiss et al., 2008). To the best of our knowledge, empathy in SCD population has not been thoroughly explored so far. Recently, it has been suggested that SCD patients experience changes along time of personal distress, and that personal distress increases from before to after the onset of cognitive symptoms only in SCD patients with positive amyloid biomarkers (Giacomucci et al., 2022). Moreover, empathy capacity of SCD patients has never been compared with the demographically adjusted Italian normative data, which have been only recently collected (Maddaluno et al., 2022). Consequently, it has not been clearly stated if pathological changes in empathy are a neuropsychological feature of SCD.

Finally, there have been recent attempts to identify neural substrate of empathy impairment in AD using both voxel-based morphometry in MRI and, less frequently, cerebral Fluorodeoxyglucose Positron Emission Tomography (FDG-PET), showing that empathy deficits seems to be correlated with the involvement of specific empathy related brain regions (Dermody et al., 2016; Giacomucci et al., 2022). However, neural basis of empathy disruption along the AD continuum has not been explored so far.

Considering these previous findings, we hypothesized that empathy may be compromised also in AD, albeit in a manner different from what occurs in FTD. Furthermore, we speculate that empathy impairment begins even in the earliest stages of AD continuum, such as in SCD. Indeed, SCD patients might present a selective and subtle involvement of specific empathy components that they might go unnoticed. Thus, changes in empathy might be considered as a neuropsychological biomarker of AD in SCD population. On these bases, the aims of this study were.

(1) to investigate empathy in SCD, MCI and AD dementia, confirming previously published results about the specific empathic impairment in the AD continuum.
(2) to compare empathy capacity of SCD population with recently collected, demographically adjusted Italian normative data, in order to detect potential "objectively demonstrated" pathological impairment.
(3) to explore neural correlates of empathy deficit in SCD and MCI patients carrying Alzheimer's Pathology (with both amyloid and tau positive biomarkers) and in AD demented patients using FDG-PET, in order to detect a suggestive involvement of empathy related brain regions in the AD continuum.

2. Methods

2.1. Participants

We longitudinally included 208 subjects in this study: 45 individuals with a clinical diagnosis of SCD (Jessen et al., 2020), 83 with a diagnosis of MCI (Albert et al., 2011) and 80 affected by AD dementia (AD-d) (McKhann et al., 2011). All participants underwent a comprehensive family and clinical history collection, general and neurological examination, extensive neuropsychological investigation, evaluation of empathy through Interpersonal Reactivity Index (IRI) (Albiero et al., 2007; Davis, 1983) and facial emotion recognition capacity through Ekman 60 Faces (EK-60 F) Test (Dodich et al., 2014; Ekman & Friesen, 1976). One hundred and forty-seven subjects underwent *APOE* genotyping (32 SCD, 55 MCI, 60 AD-d). A positive family history was defined as one or more first-degree relatives with documented cognitive decline. Age at empathy assessment was defined as age at IRI and EK-60 F tests administration. Age at onset was defined as age at the onset of cognitive symptoms.

Exclusion criteria, which were established prior to data analysis, 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.

Study procedures and data analysis were performed in accordance with the Declaration of Helsinki and with the ethical standards of the Committee on Human Experimentation of our Institute. The study was approved by the local Institutional Review Board (reference 15691oss). All individuals involved in this research agreed to participate and agreed to have details and results of the research about them published.

2.2. Neuropsychological assessment

All subjects were evaluated by an extensive neuropsychological battery consisting of global measurements (Mini-Mental State Examination, MMSE) and specific tasks exploring each cognitive function.

- Verbal and spatial short-working and long-term memory (Digit and Visuo-spatial Span forward and backward (Monaco et al., 2013), Rey auditory Verbal Learning test immediate recall RVLT-I and delayed recall RVLT-D (Carlesimo et al., 1996); Babcock Short Story Immediate and Delayed Recall (De Renzi et al., 1977), Rey–Osterrieth complex figure recall (Caffarra et al., 2002a)),
- Attention (Trail Making Test A (Giovagnoli et al., 1996), visual search (Della Sala et al., 1992)),
- Language (Category Fluency Task (Novelli et al., 1970), Phonemic Fluency Test (Spinnler & Tognoni, 1987)),
- Constructional praxis (Rey–Osterrieth Complex Figure copy (Caffarra et al., 2002a)),
- Executive functions (Trail Making Test B (Giovagnoli et al., 1996), Stroop Test (Caffarra et al., 2002b)).

In patients with SCD, we estimated cognitive complaints using a survey based on the Memory Assessment Clinics-Questionnaire (MAC-Q) (Crook et al., 1992). We defined the presence of cognitive complaints if participants perceived a decline in cognitive capacity compared to the past or if they reported difficulties in carrying out at least four of the following activities: remembering the name of a person just introduced to them; recalling telephone numbers or zip-codes used on a daily or weekly basis; recalling where they put objects in their home or office; remembering specific facts from a newspaper or magazine article just read; remembering the item(s) they intend to buy when arriving at the grocery store or pharmacy.

2.3. Interpersonal Reactivity Index (IRI)

Empathy deficits were evaluated by Interpersonal Reactivity Index (IRI) (Albiero et al., 2007; Davis, 1983), 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 (Eslinger et al., 2011; Shamay-Tsoory et al., 2009). On the other hand, PD subscale has been used as a measure of emotional contagion (Sturm et al., 2013), that could be considered as the automatic total identification with another's behaviour in order to encourage affective incentive and altruistic comportment (Decety & Jackson, 2004). 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; thus, 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 (Rankin et al., 2006). Informants rated patients' empathy before (T0) and after (T1) cognitive symptoms' onset (objective in MCI and AD-d and subjective in SCD). Differences from T0 to T1 of the scores of each scale were quantified as Delta (Δ T0–T1): ΔFT, ΔPT, ΔEC and ΔPD.

In SCD subgroup, IRI was also administrated to SCD patients themselves to have a self-evaluation of empathy capacity in this category. IRI scores rated by SCD patients were compared to those rated by a family member and also to normative data of Italian population (Maddaluno et al., 2022).

2.4. Ekman-60 Faces Test

Facial emotion recognition was assessed by Ekman-60 Faces (EK-60 F) Test, which consists in 60 black and white pictures of the Ekman and Friesen series of Pictures of Facial Affect (Ekman & Friesen, 1976), representing the faces of ten actors (six women and four men), each showing one of the six basic emotions (anger, sadness, happiness, fear, disgust, surprise). A global score (EK-60 F global score) of 60 indicates the best possible performance. Each basic emotion has a sub-score of maximum of 10 points. Images were shown each for 5 sec according to the Ekman and Friesen procedure (Ekman & Friesen, 1976), via power point presentation on a computer. Patients were asked to indicate which of the basic emotions better represented the facial emotion shown on the display (Dodich et al., 2014).

2.5. Collection of AD biomarker and classification according to ATN system

One hundred and thirty-seven patients (22 SCD, 54 MCI and 62 AD-d) underwent CSF biomarker analysis (Aβ1-42, Aβ1-42/1-40 ratio, t-tau, p-tau). The CSF samples were collected by lumbar puncture, then immediately centrifuged and stored at −80 °C until performing the analysis. Aβ1-42, Aβ42/40 ratio, t-tau, and p-tau were measured using a chemiluminescent enzyme immunoassay (CLEIA) analyzer LUMIPULSE G600 [Lumipulse Beta Amyloid1−40, Lumipulse Beta Amyloid1-42, Lumipulse GTotal Tau, and Lumipulse GPhospho Tau (181)]. Cut-offs for normal values were: for Aβ1-42, >670 pg/mL; Aβ42/40 ratio, >.062; t-tau, <400 pg/mL; and p-tau, <60 pg/mL (Alcolea et al., 2019). Reagent kits were obtained from Fujirebio.

Among these patients, 33 (11 SCD, 13 MCI and 9 AD-d) also underwent amyloid PET. Amyloid PET imaging was performed according to national and international standards (Minoshima et al., 2016), with any of the available fluorine18-labelled tracers (18Florbetaben [FBB]-Bayer-Pyramal, 18Flutemetamol [FMM]-General Electric). Images were rated as either positive or negative according to criteria defined by the manufacturers.

Based on biomarker results, patients were classified according to the A/T/N classification (Jack et al., 2018): patients were rated 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. In case of discordant CSF and Amyloid PET results, we considered only the pathologic result. Patients were classified as T+ or T− if CSF p-tau concentrations were higher or lower than cut-off values respectively. Patients were classified as and N+ if CSF t-tau was higher than cut-off values. Patients were further classified as carrier of AD pathology (AP+) when A+ was associated with T+ (regardless of N classification), or non-carriers (AP−) when they were classified as A− (regardless of T and N classification), or A+/T−/N−, or A+/T−/N+.

2.6. Apolipoprotein E (APOE) genotyping

Patients' DNA was extracted from peripheral blood samples using of a standard automated method (QIAcube, QIAGEN Hilden, Germany). APOE genotypes were investigated by HRMA (Sorbi et al., 1994). Two sets of PCR primers were designed to amplify the regions encompassing rs7412 [NC_000019.9:g.45412079C>T] and rs429358 (NC_000019.9:g.45411941T>C). The APOE genotype was coded as APOE ε4− (no APOE ε4 alleles) and APOE ε4+ (presence of one or two APOE ε4 alleles).

2.7. FDG-PET brain imaging

One hundred and eighty-eight patients (36 SCD, 78 MCI, 74 AD-d) underwent brain [18F]FDG-PET. [18]FDG-PET scans acquisition was performed 30−40 min after 18F-FDG administration (3.7 MBq/kg), according to EANM guidelines for brain imaging (Varrone et al., 2009). After the injection, patients were left in a dimly lit, quiet room and told to keep their eyes closed. Images were obtained on a PET/CT scanner (Philips Gemini TF 16 PET/CT), and reconstructions were performed using 3D LOR iterative algorithm reconstruction (FOV, 256; matrix, 128 × 128; voxel dimensions, 2 × 2 × 2 mm). CT acquisitions for attenuation correction were performed on spiral 16 slices CT with a slice thickness of 2 mm. [18F]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) and computing environment R 4.0.3 (R Foundation for Statistical Computing, Vienna, 2013). All *p*-values were two-tailed and significance level for all analyses was set at $\alpha = 5\%$, corresponding to a threshold *p* of .05. All variables were described as mean and standard deviation. Distribution of all variables was assessed through Shapiro−Wilk test. Depending on the distribution of our data, we used *t*-tests or non-parametric Mann−Whitney−U tests for between-groups comparisons and Pearson's r or Spearman's ρ for correlations. We used chi-square tests to compare categorical data. Differences among groups in continuous variables were assessed through one-way ANOVA followed by Bonferroni *post-hoc* test. Differences between T0 and T1 scores were explored through Wilcoxon signed-rank test. Changes in each IRI subscale from before to after the onset of cognitive symptoms were quantified as Delta (Δ T0 − T1): ΔFT, ΔPT, ΔEC and ΔPD. Multiple regression analyses were run to evaluate the influence of demographic, genetic, biological, and neuropsychological factors on IRI subscales and emotion recognition. Multiple-way MANCOVA was used to determine the interaction effect among EK-60 F total and partial scores controlling for demographic and neuropsychological covariates. Bonferroni correction for multiple comparisons was applied. We calculated the size effect by the Cohen's d for normally distributed numeric measures, η^2 for Mann−Whitney−U Test and the Cramer's V for categorical data.

Differences between SCD group and normative Italian population IRI subscales scores were explored through confidence intervals. Confidence intervals were calculated for both groups, and they were compared separately. Z scores for each subject's neuropsychological and IRI subscale values in SCD group have been calculated to perform more accurately correlations.

2.9. SPM analysis

In order to assess the metabolic pattern related to empathy changes in the AD continuum since the early stage, a total of 78 patients were considered (5 SCD, 22 MCI and 51 AD-d). Each SCD or MCI patient was carrier of Alzheimer's Pathology (AP+), presenting both amyloid and tau positive biomarkers. For this analysis, we excluded all patients with a diagnosis of SCD or MCI with amyloid and tau biomarker negativity (AP−), and AD-d patients with atypical presentation (logopenic variant Primary Progressive Aphasia, poster cortical atrophy and cortico-basal syndrome). We included patients who had undergone an [18]FDG-PET scan within a temporal range of 18 months before or after the empathy analysis (Fig. 1). [18]FDG PET data were analysed using Statistical Parametric Mapping (SPM12) on MATLAB (MathWorks Inc, Sherborn, MA, USA). Scans were manually reoriented, setting the origin to the anterior commissure, normalized to dementia-specific [18F]-FDG-PET template, and then smoothed (FWHM 8 mm). Correlation analyses were performed using multiple regression design, with age and MMSE as nuisance variables. The significance threshold was set at $p < .001$, uncorrected, and $p < .05$ FWE small volume corrected. Only clusters containing more than 20 voxels were deemed to be significant.

2.10. Data availability and open practices

The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author Dr. Valentina Bessi (valentina.bessi@unifi.it). Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must complete a formal data sharing agreement. No analysis code was used. No part of the study procedures or analyses were pre-registered prior to the research being conducted.

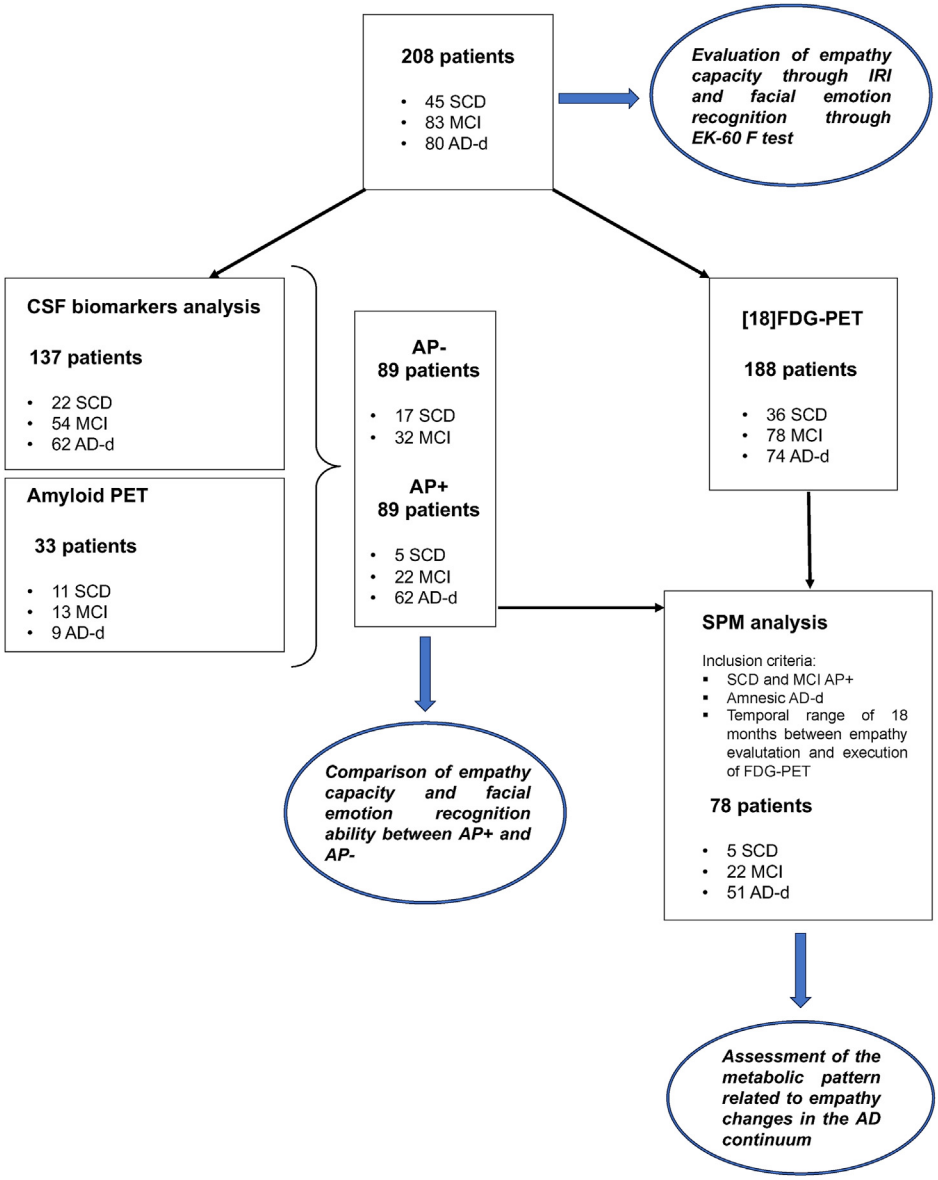

Fig. 1 – Flow chart for patients' inclusion criteria in each analysis.

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

	SCD	MCI	AD-d
	n = 45	n = 83	n = 80
Sex (F/M)	36/9*	50/33	44/36*
Age at onset (years)	55.73 ± 9.46°,ς	64.13 ± 9.67°	66.26 ± 6.56ς
Age at empathy evaluation (years)	64.94 ± 8.40ψ,ϖ	71.36 ± 8.29ψ	70.95 ± 7.01ϖ
Disease duration (years)	8.13 ± 7.32λ,η	6.27 ± 3.64λ	4.01 ± 1.76η
Family history of AD	34/43 (79.06%)	41/74 (55.40%)	37/68 (54.41%)
Years of education	13.56 ± 3.12	11.56 ± 4.48	11.53 ± 4.63
MMSE	28.93 ± 1.33ϒ	26.74 ± 2.36ζ	19.29 ± 5.84ϒ,ζ
APOE ϵ4+	8/32 (25%)	19/55 (34.54%)	29/60 (48.33%)

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. *$\chi^2 = 7.81$, $p = .006$; °$p < .001$; ς$p < .001$; ψ$p < .001$; ϖ$p < .001$; λ$p = .001$; η$p < .001$; ϒ$p < .001$; ζ$p < .001$. Statistical significancy after Bonferroni correction $p = .0062$.

Legal copyright restrictions prevent public archiving of neuropsychological tests (i.e., MMSE, EK-60 F, IRI) which can be obtained from the copyright holders in the cited references.

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

3. Results

3.1. Demographic features

Demographic variables are described in Table 1. Out of 208 patients, 45 were diagnosed with SCD (21.63%), 83 with MCI (39.90%) and 80 with AD-d (38.46%). Considering the whole sample, 130 patients were females and 68 males. Difference in sex distribution was observed among groups, with a higher proportion of females in SCD than in AD-d subgroup (80% *vs* 55%, $\chi^2 = 7.815$, $p = .006$, Cramer's V .250). Both age at onset of cognitive disturbs and age at empathy evaluation were lower in SCD patients (age at onset: 55.73 ± 9.46 years; age at empathy: 64.94 ± 8.40 years) than in MCI (age at onset: 64.13 ± 9.67 years, $p < .001$; age at empathy: 64.94 ± 8.40 years, $p < .001$) and in AD-d (age at onset: 66.26 ± 6.56 years, $p < .001$; age at empathy: 70.95 ± 7.01 years, $p < .001$).

Out of 147 patients who underwent *APOE* genotype analysis, 38.09% were classified as *APOE* ε4 carriers.

3.2. Classification according to ATN biomarkers

One hundred and thirty-seven patients (22 SCD, 53 MCI and 62 AD-d) underwent CSF biomarker analysis (Aβ1-42, Aβ1-42/1-40 ratio, t-tau, p-tau). Thirty-three patients (11 SCD, 13 MCI, 9 AD-d) underwent amyloid PET, which detected amyloid deposition in 22 patients (6 SCD, 8 MCI, 8 AD-d).

CSF amyloid biomarkers (Aβ1-42 or Aβ1-42/1-40 ratio) and amyloid PET were concordant in 78.78% of cases (8 out of 11 SCD, 10 out of 13 MCI and 8 out of 9 AD-d). Three SCD patients showed discordance between amyloid biomarkers (one with positive CSF, 2 with positive amyloid PET). In MCI subgroup, all 3 discordant cases had positive amyloid PET. Finally, in AD-d subgroup only one patient was discordant, showing positive CSF amyloid Aβ1-42.

Based on the biomarker results, 5 SCD and 22 MCI patients were classified as having AD pathology (AP+), while 17 SCD and 32 MCI patients were classified as non-carriers of AD pathology (AP−). Percentage of AP+ patients were not different between SCD and MCI subgroup (22.72% *vs* 40.74%, $\chi^2 = 2.214$, $p = .188$, Cramer's V .171). Obviously, all AD-d patients were AP+.

3.3. Evaluation of empathy in SCD, MCI and AD-d patients by the caregiver

IRI questionnaire was administered to the caregiver. Considering IRI T1 subscales, PD-T1 scores were significantly different among groups (F [2.191] = 12.709, $p < .001$): in more details, at Bonferroni *post hoc* corrections, SCD presented lower PD-T1 scores than MCI (24.03 ± 5.76, $p = .002$), and AD-d patients (25.82 ± 5.77, $p < .001$). No differences were detected in other IRI subscales (Table 2) (Fig. 2).

Changes in IRI subscales scores from T0 to T1 were evaluated and subsequently quantified as delta (Δ). ΔPT, ΔEC and ΔPD were significantly different among groups (ΔPT F [2,193] = 12.718, $p < .001$; ΔEC F [2,193] = 6.266, $p = .002$; ΔPD F [2,193] = 14.36, $p < .001$). In more details, ΔPT was higher in AD-d than in MCI (5.12 ± 6.11 *vs* 2.05 ± 4.71, $p = .001$) and in SCD (.50 ± 3.50, $p < .001$). Similarly, ΔEC was higher in AD-d than in SCD subgroups (1.08 ± 3.59 *vs* −.90 ± 1.82, $p = .002$). On the other

Table 2 – Comparison of IRI scores rated by caregivers in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI), and Alzheimer's Disease dementia (AD-d).

	SCD	MCI	AD-d	F	*p*	*p* between SCD and AD-d	*p* between SCD and MCI	*p* between MCI and AD-d
IRI total T1	82.90 ± 12.47	87.11 ± 12.83	84.38 ± 14.49	1.561	.222	1.000	.332	.616
FT T1	17.92 ± 4.70	17.53 ± 5.09	17.14 ± 6.62	2.718	.069	.152	1.000	.157
PT T1	18.82 ± 5.70	18.82 ± 5.90	15.82 ± 6.61	1.729	.180	.503	1.000	.271
EC T1	25.82 ± 4.19	26.72 ± 5.37	25.58 ± 5.67	.966	.382	1.000	1.000	.542
PD T1	20.13 ± 5.55	24.03 ± 5.76	25.82 ± 5.77	12.709	**<.001**	**<.001**	**.002**	.160

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**. Statistical significancy after Bonferroni correction $p = .01$.

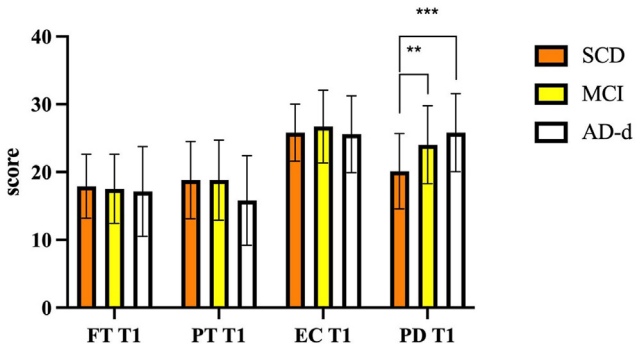

Fig. 2 – Empathy assessed by Interpersonal Reactivity Index (IRI) in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). **$p = .002$; ***$p < .001$.

hand, ΔPD was lower in AD-d than in MCI (−8.17 ± 6.87 *vs* −5.13 ± 5.21, $p = .003$) and in SCD patients (−2.50 ± 3.08, $p < .001$) (Table 3).

Furthermore, we compared IRI scores at T0 and T1 as rated by the caregiver to determine whether there were statistically significant changes in IRI scores before and after the onset of cognitive symptoms. In SCD subgroup, a significant increase of PD scores (PD-T0 17.56 ± 4.66 *vs* PD-T1 20.13 ± 5.55, $z = -4.27$, $p < .001$) and EC scores (EC-T0 24.90 ± 3.85 *vs* EC-T1 25.82, $z = -2.92$, $p = .003$) was found. In MCI subgroup, we detected an increase of PD scores (PD-T0 18.90 ± 5.23 *vs* PD-T1 24.03 ± 5.76, $z = -7.06$, $p < .001$) and a decrease of PT scores (PT-T0 20.87 ± 5.96 *vs* PT-T1 18.82 ± 5.90, $z = -3.82$, $p < .001$). Finally, AD-d patients showed an increase of PD scores (PD-T0 17.36 ± 5.13 *vs* PD-T1 25.82 ± 5.77, $z = -7.14$, $p < .001$), and a significant decrease of PT scores (PT-T0 22.26 ± 6.02 *vs* PT-T1 17.09 ± 6.65, $z = -6.37$, $p < .001$) and of FT scores (FT-T0 17.67 ± 5.38 *vs* FT-T1 15.86 ± 5.73, $z = -3.35$, $p = .001$) (Table 4).

Finally, we compared IRI scores and changes along time in SCD and MCI patients according to the presence of underlying Alzheimer's Pathology (AP status). No differences were detected between AP+ and AP− patients in each IRI T1 subscales, both in SCD and in MCI subgroups. On the other hand, when we evaluated changes in IRI scores, we found that ΔPD was significantly lower in SCD AP+ than in SCD AP− (−7.75 ± 2.63 *vs* −1.81 ± 2.16, $p < .001$, η^2 .49), while no differences were detected between MCI AP+ and MCI AP−. Moreover, comparing T0 and T1 scores, we found an increase of PD scores in both MCI AP+ (PD-T0 17.27 ± 5.07 *vs* PD-T1 23.23 ± 6.89, $z = -3.85$, $p < .001$) and in MCI AP− patients (PD-T0 20.03 ± 5.06 *vs* PD-T1 24.58 ± 4.63, $z = -4.36$, $p < .001$). No differences were detected between PD-T0 and PD-T1 score in SCD AP−. A qualitative difference was found in SCD AP+, with higher PD scores at T1 than in T0, despite it did not reach statistical significance (PD-T0 18.25 ± 3.20 *vs* PD-T1 26.00 ± 4.16, $z = -1.84$, $p = .06$).

3.4. *Influence of demographic, biological, genetic and neuropsychological variables on empathy*

No significant correlations were found between age at onset of cognitive symptoms, age at empathy assessment, years of education and each IRI subscales or Δ T0 − T1. Moreover, no differences were detected between women and men in IRI subscale scores, neither in the whole cohort nor in SCD, MCI and AD-d subgroups separately. Considering *APOE* genotyping, no differences were found between APOE ϵ4 carriers and non-

Table 3 – Comparison of changes in IRI scores rated by caregivers from T0 to T1 (Δ) in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI), and Alzheimer's Disease dementia (AD-d).

	SCD	MCI	AD-d	F	*p*	*p* between SCD and AD-d	*p* between SCD and MCI	*p* between MCI and AD-d
ΔFT	−.08 ± 2.37	.65 ± 2.97	1.78 ± 4.48	4.045	.019	.024	.893	.144
ΔPT	.50 ± 3.50	2.05 ± 4.70	5.12 ± 6.11	12.718	**<.001**	**<.001**	.360	**.001**
ΔEC	−.90 ± 1.82	.04 ± 2.71	1.08 ± 3.59	6.266	**.002**	**.002**	.310	.087
ΔPD	−2.50 ± 3.08	−5.13 ± 5.21	−8.17 ± 6.87	14.336	**<.001**	**<.001**	.051	**.003**

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**. Statistical significancy after Bonferroni correction $p = .012$.

Table 4 – Comparison of IRI T0 and T1 scores rated by the caregiver in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD).

	SCD			MCI			AD-d		
	Media ± SD	z	*p*	Media ± SD	z	*p*	Media ± SD	z	*p*
FT 0	17.85 ± 4.18	−.51	.61	18.18 ± 4.69	−1.93	.053	17.66 ± 5.35	−3.35	**.001**
FT 1	17.92 ± 4.70			17.53 ± 5.09			17.14 ± 6.62		
PT 0	19.33 ± 4.98	−1.16	.244	20.87 ± 5.96	−3.28	**<.001**	22.26 ± 5.98	−6.37	**<.001**
PT 1	18.82 ± 5.70			18.82 ± 5.90			15.82 ± 6.6		
EC 0	24.90 ± 3.85	−2.92	**.003**	26.76 ± 5.27	−.11	.911	26.66 ± 4.25	−2.41	.016
EC 1	25.82 ± 4.19			26.72 ± 5.37			25.58 ± 5.67		
PD 0	17.56 ± 4.66	−4.27	**<.001**	18.90 ± 5.23	−7.14	**<.001**	17.31 ± 5. 11	−7.14	**<.001**
PD 1	20.13 ± 5.554			24.03 ± 5.76			25.82 ± 5.77		

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**. Statistical significancy after Bonferroni correction $p = .004$.

Table 5 – Multiple regression models for IRI subscales and changes over time from T0 to T1 (Δ).

	B	95% C.I. per B		β	*p*
		Lower	Upper		
FT-T1					
(Constant)	13.114	11.021	15.207		<.001
Phonemic fluency test	.115	.052	.179	.314	<.001
PT-T1					
(constant)	21.949	18.371	25.526		<.001
Diagnosis	−1.611	−3.054	−.168	−.179	.029
PD-T1					
(Constant)	26.586	24.515	28.658		<.001
Babcock Short story delay recall	−.260	−.448	−.072	−.309	.007
ΔFT					
(Constant)	−1.948	−4.030	.134		.066
Diagnosis	1.241	.401	2.080	.234	.004
ΔPT					
(Constant)	1.343	.264	2.421		.015
Stroop test errors	.390	.142	.638	.312	.002
ΔPD					
(Constant)	−3.596	−5.262	−1.930		<.001
AP status	−3.215	−5.456	−.973	−.270	.005

Unstandardized regression coefficients (B) and 95% Confidence Intervals (95% C.I.), standardized coefficient (β) and *p*-value (*p*), are reported (significant differences at $p < .05$).

carriers in IRI subscales, both in the whole cohort and in each subgroup.

Considering neuropsychological evaluation, we detected correlations between IRI subscales and specific neuropsychological tests (see Supplementary material 1).

Consequently, we ran multiple regression analysis to detect which variables influence each IRI scales. The multiple regression models statistically predicted FT-T1 scores (F [2, 117] = 10.02, $p < .001$, adj. $R^2 = .132$), which were influenced by Phonemic Fluency Test (B = .115 [95% CI .052: .179], $p < .001$). Similarly, the model predicted PT-T1 scores too (F [1, 147] = 4.87, $p = .029$, adj. $R^2 = .025$), and among the covariates, only diagnosis (B = −1.611 [95% CI −3.054:-.168], $p = .029$) was statistically significant. The multiple regression model also predicted PD-T1 score (F [1, 72] = 7.58, $p = .007$, adj. $R^2 = .083$), which were influenced by Babcock Short Story Delayed Recall significantly (B = −.260 [95% CI -.488:-.072], $p = .007$). On the other hand, the model did not predict EC-T1 scores.

Considering variations along time of IRI scales (Δ T0 − T1), the model significantly predicted ΔFT (F [1, 147] = 8.53, $p = .004$, adj. $R^2 = .048$), which was influenced by the diagnosis (B = 1.241 [95% CI .401:2.080], $p = .004$). The regression model also predicted ΔPT (F [1, 90] = 9.73, $p = .002$, adj. $R^2 = .088$), showing that only Stroop Test errors significantly predicted ΔPT (B = .390 [95% CI .142:.638], $p = .002$). Finally, regression model predicted ΔPD (F [1, 103] = 8.08, $p = .005$, adj. $R^2 = .064$), which was significantly influence only by AP status (B = −3.215 [95% CI −5.456:-.973], $p = .005$). On the other hand, none of the correlated variables were associated with ΔEC (Table 5).

3.5. *Self-evaluation of empathy in SCD*

IRI questionnaire was administered to SCD patients to have a self-evaluation of empathy capacity and to compare SCD scores to normative data of Italian population (Maddaluno et al., 2022). Confidence intervals were calculated for the IRI subscales of both the SCD group and the normative sample. FT-T1, PD-T1 and EC-T1 mean scores (FT-T1 23.23, 95% C.I. [21.95–24.50]; PD-T1 19.95, 95% C.I. [18.38–21.52]; EC-T1 26.83, 95% C.I. [25.46–28.21]) were higher in the SCD group than in the normative sample, whereas PT-T1 mean score (14.94, 95% C.I. [13.68–16.20]) was significantly lower than the normative sample (Table 6).

No differences were found in IRI subscales scores between SCD AP+ and SCD AP-. In addition, correlations between IRI subscales scores and neuropsychological test were performed, but no significative results were found (data not shown).

3.6. *Evaluation of facial emotion recognition ability in SCD, MCI and AD-d patients*

Facial emotion recognition ability was assessed by EK-60F test and was compared among SCD, MCI and AD-d patients. Each variable was significantly different among groups (Table 7) (Fig. 3). In more details, EK-60F total score was lower in AD-d (35.03 ± 8.87) than in MCI (43.58 ± 5.91, $p < .001$) and in SCD (47.93 ± 4.78, $p < .001$). Moreover, SCD patients had a better performance than MCI ($p = .003$).

Considering single emotion, AD-d patients presented lower scores in anger, disgust, happiness, sadness and surprise recognition than MCI and SCD (Table 5). As regard fear

Table 6 – Comparison of IRI subscale scores between SCD self-evaluation and normative sample.

	SCD N = 45			Normative sample N = 456		
	Mean value	95% C.I.		Mean value	95% C.I.	
		Lower	Upper		Lower	Upper
Fantasy FT-T1	23.23 ± 3.99	21.95	24.50	16.23 ± 5.10	15.76	16.70
Perspective taking PT-T1	14.94 ± 3.94	13.68	16.20	17.70 ± 4.36	17.30	18.10
Empathic concern EC-T1	26.83 ± 4.30	25.46	28.21	20.10 ± 4.54	19.59	20.43
Personal distress PD-T1	19.95 ± 4.92	18.38	21.52	11.84 ± 5.03	11.38	12.30

IRI subscales scores are reported as mean, standard deviation and confidence interval for continuous variables. Statistically significant differences between IRI subscales are reported as underlined.

Table 7 – Comparison of facial emotion recognition ability among Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI), and Alzheimer's Disease dementia (AD-d) assessed by Ekman 60 Faces Test (EK-60 F).

	SCD	MCI	AD-d	F	*p*	*p* between SCD and AD-d	*p* between SCD and MCI	*p* between MCI and AD-d
EK-60F total score	47.93 ± 4.78	43.58 ± 5.91	35.03 ± 8.87	54.705	**<.001**	**<.001**	**.003**	**<.001**
Execution time (sec)	303 ± 54.46	377.84 ± 91.14	454.60 ± 138.25	29.169	**<.001**	**<.001**	**.001**	**<.001**
Anger	7.55 ± 1.71	6.59 ± 1.91	5.55 ± 2.21	14.333	**<.001**	**<.001**	.033	**.004**
Disgust	8.27 ± 1.50	7.98 ± 1.96	5.92 ± 2.66	23.340	**<.001**	**<.001**	1.000	**.004**
Fear	5.11 ± 2.66	3.08 ± 2.38	3.11 ± 2.08	12.719	**<.001**	**<.001**	**<.001**	1.000
Happiness	9.75 ± .53	9.57 ± .76	8.70 ± 1.62	16.222	**<.001**	**<.001**	1.000	**<.001**
Sadness	7.86 ± 1.82	7.63 ± 1.89	5.37 ± 2.64	26.750	**<.001**	**<.001**	1.000	**<.001**
Surprise	9.20 ± 1.13	8.82 ± 1.42	6.41 ± 2.67	40.701	**<.001**	**<.001**	.858	**<.001**

Values are reported as mean and standard deviation. Statistically significantly different values between the groups are reported as **bold character**. Statistical significancy after Bonferroni correction $p = .006$.

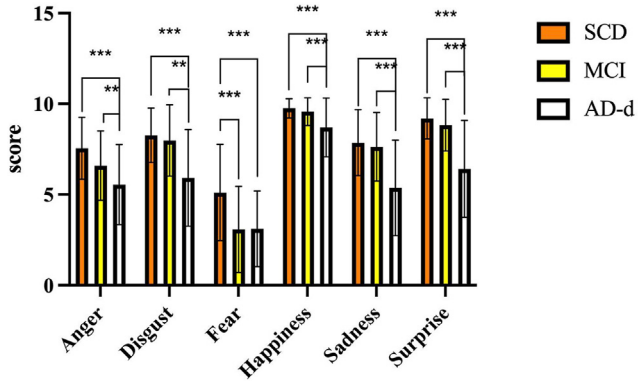

Fig. 3 – Facial emotion recognition ability, assessed by Ekman-60 Faces Test, in Subjective Cognitive Decline (SCD), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD). *$p < .05$; **$p < .01$; ***$p < .001$.

recognition, no differences were detected between AD-d and MCI patients ($p = 1.000$), while SCD performed better than AD-d ($p < .001$). We did not find significant differences in single emotion recognition between SCD and MCI patients, except for recognition of fear, with a better performance in SCD subgroups (5.11 ± 2.66 *vs* 3.08 ± 2.38, $p < .001$).

Finally, when we compared EK-60F scores in SCD and MCI patients according to the presence of underlying Alzheimer's Pathology (AP status), no differences were detected between AP+ and AP− patients.

3.7. *Influence of demographic, biological, genetic and neuropsychological variables on facial emotion recognition ability*

No correlations with age at onset of cognitive symptoms, age at empathy assessment and years of education were found. We also evaluated differences according to sex: in the whole cohort, women performed better than men in the EK-60F global score (42.87 ± 8.22 *vs* 39.05 ± 8.76, $p = .001$) and in surprise recognition (8.31 ± 2.12 *vs* 7.55 ± 2.47, $p < .004$). In SCD subgroups, time of EK-60F test execution was significantly lower in women than in men (289.36 ± 47.62 *vs* 362.00 ± 40.58, $p < .001$), while no differences in EK-60F global score and single emotion scores were found according to sex. In MCI and AD-d subgroup, no differences were detected in facial emotion recognition between women and men. Considering APOE genotyping, no differences were found between *APOE* ϵ4 carriers and non-carriers in EK-60F test score, both in the whole cohort and in each subgroup.

Correlations between neuropsychological tests and emotion recognition ability (both EK-60 F total score and single emotion recognition scores) were explored too (see Supplementary Table 1).

To detect differences in facial emotion recognition ability (EK-60 F total score, single emotion recognition scores and EK-60 F execution time) 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 in emotion recognition ability among the three groups ($F [16, 134] = .999$, $p = .462$, Wilks' $\Lambda = .798$, partial $\eta^2 = .107$). However, among the covariates, age at empathy evaluation was associated to EK-60 F execution time ($p = .005$), Trail Making Test part A was associated to fear recognition ($p = .001$), while Verbal Span Forward influenced sadness recognition ($p = .005$).

3.8. *SPM analysis*

SPM multiple regression analysis showed significant correlations between IRI subscales and brain metabolism in the MCI AP+ and AD-d group, taken separately, and in the whole AD continuum group. No significant correlation in SCD AP+ subgroup was found.

- PT-T1 positively correlated with cerebral metabolic activity:
  - o In the AD continuum group, in left precuneus, right inferior parietal gyrus, right superior and middle frontal gyri and left posterior cingulate gyrus;
  - o In AD-d subgroup, in right middle frontal and right inferior parietal gyri (Fig. 4a).
- PD-T1 negatively correlated with cerebral metabolic activity:
  - o In MCI AP+ subgroup in left inferior parietal gyrus (Fig. 4b).
- ΔPT negatively correlated with cerebral metabolic activity:
  - o In the AD continuum group in bilateral posterior cingulate cortex.

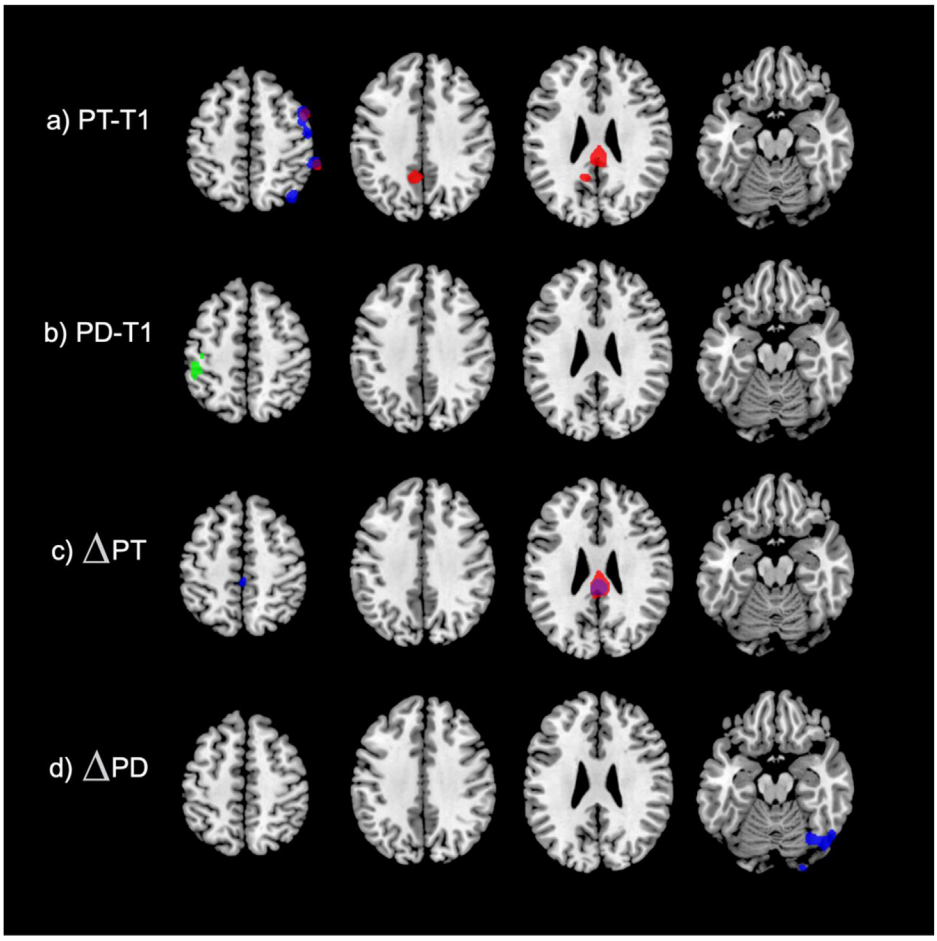

Fig. 4 – a) Clusters of significant positive correlation between PT and cerebral metabolic activity in the AD continuum subgroup (SCD AP+, MCI AP+ and AD-d, red) and AD-d subgroup (blue); b) Clusters of significant negative correlation between PD and cerebral metabolic activity in MCI subgroup (green); c) Clusters of significant negative correlation between ΔPT and cerebral metabolic activity in AD continuum subgroup (SCD AP+, MCI AP+ and AD-d, red) and AD-d subgroup (blue); d) Clusters of significant positive correlation between ΔPD and cerebral metabolic activity in AD-d subgroup (blue).

  - In AD-d subgroup in bilateral precuneus and posterior cingulate cortices (Fig. 4c).
- ΔPD positively correlated with cerebral metabolic activity:
  - In AD-d subgroup in right fusiform gyrus (Fig. 4d).

4. Discussion

Beyond memory and other well-defined cognitive functions such as language and praxis, empathy seems to also be impaired in Alzheimer's Disease. Therefore, current research is trying to define AD-specific empathy deficits and to determine whether empathy begin to be compromised since the early stages of the disease.

Our study fits into this research landscape aiming to better explore empathy in AD and to detect its potential changes in empathy since the very early stage of the disease continuum.

First of all, we wanted to explore empathy capacity using the IRI questionnaire, which was administered to the caregiver, due to the impairment of self-awareness in AD, which makes self-evaluation of empathy difficult and unreliable (Ávila-Villanueva et al., 2021).

Our findings showed a dissociation between cognitive and affective empathy in Alzheimer's Disease: indeed, we found an impairment of cognitive empathy together with a preservation of the empathic concern, part of the affective domain. Nevertheless, we also detected a heightening of emotional contagion, which is the most primitive structure of affective empathy (de Waal & Preston, 2017). Our results are in line with previous works, reporting differences in empathy impairment between FTD and AD dementia. In fact, it has been widely demonstrated that FTD is featured by a comprehensive empathy deficit in both cognitive and affective domain, with lower PT and EC scores as compared to healthy controls (Rankin et al., 2006). On the other hand, current research has recently stated that more complex parts of affective empathy, like empathic concern, seem to be spared in AD dementia, which in featured by a more prominent impairment of perspective taking ability, thus of cognitive domain of empathy (Dermody et al., 2016; Fischer et al., 2019).

Moreover, we found that empathy changes follow a peculiar progressive trend along the AD continuum: indeed, according to caregivers' evaluation, while the impairment of cognitive empathy starts at MCI stage, the amplification of

emotional contagion seems to begin in an even earlier stage of AD continuum, that is SCD.

First, we found a significant increase of PD scores from SCD to AD dementia. Personal Distress is the IRI subscale which better describes emotional contagion, which expresses the tendency to automatically adopt the behaviour of another person (Bernhardt & Singer, 2012). This result is in line with previous works which have already described that emotional contagion might increase along the AD continuum (Fischer et al., 2019; Giacomucci et al., 2022; Sturm et al., 2013).

We also evaluated changes of IRI subscale scores from before to after cognitive symptoms' onset to explore empathy changes from premorbid state in SCD, MCI and AD-d patients. Interestingly, we found a significant increase of PD from before to after the onset of cognitive disturbs in SCD, MCI and AD-d groups, while a decrease of PT scores was found only in MCI and AD-d. These results are in line with current research (Demichelis et al., 2020; Giacomucci et al., 2022; McCade et al., 2013; Weiss et al., 2008), and may suggest that, while a significant change in perspective taking ability (part of cognitive empathy) from premorbid condition starts to be highlightable at MCI stage, the increase of personal distress seems to be detected by the caregiver since SCD stage (Giacomucci et al., 2022).

To further explore empathy changes along time, we quantified as Delta (Δ T0 − T1) the entity of score changes of each IRI subscales. Indeed, ΔPT was higher in AD-d than in MCI and in SCD, thus suggesting the progressive decline of perspective taking ability. On the other hand, ΔPD was lower in AD-d than in MCI and in SCD patients, indicating that the entity of the amplification of emotional contagion becomes higher along the AD continuum.

Taking together all these evidence, according to caregivers' evaluation, empathy changes along the AD continuum seem to depict a peculiar trend with a progressive heightening of emotional contagion starting at SCD stage and with a progressive decline of cognitive empathy which begins at a later time, that is the MCI stage (Bond et al., 2016; Dermody et al., 2016; Fischer et al., 2019; Giacomucci et al., 2022; Narme et al., 2013; Pernigo et al., 2015).

Furthermore, we tried to evaluate a possible difference in SCD and MCI patients, according to the underlying pathology (i.e., the presence or absence of Alzheimer's Pathology). To the best of our knowledge, no other works aimed to assess empathy in SCD and MCI according to biomarker status, considering both amyloid and tau positivity together. Analysing the variation of PD scores before and after the onset of cognitive impairment, a significant increase was observed in both MCI AP+ and MCI AP−, indicating that the amplification of emotional contagion may be detected in the MCI phase regardless of the underlying pathology. However, only a qualitative (but not significant) increase in PD scores was found in SCD AP+. On the other hand, the entity of the variation in PD scores over time (ΔPD) was significantly greater in SCD AP+ patients compared to SCD AP−. Conversely, ΔPD was substantially similar between MCI AP+ and MCI AP−.

It has been previous shown that the increase in PD over time was present in both MCI with positive amyloid biomarkers and also in those with negative amyloid biomarkers (Giacomucci et al., 2022). This result could be explained by the fact that MCI represents a pathological condition with potential several diverse etiologies. Consequently, we could hypothesize that changes in emotional contagion might be related not only to Alzheimer's Disease but also to other conditions that could lead to MCI (Albert et al., 2011; Tangalos & Petersen, 2018).

With regard to SCD, the lack of statistical significance in the differences in PD scores from before to after the onset of cognitive symptoms in the AP+ subgroup could be due to the small sample size. In fact, a previous study demonstrated that the increase in PD over time was significant only in SCD patients with positive amyloid biomarkers but not in those with negative biomarkers (Giacomucci et al., 2022). Moreover, in our study the increase of PD score over time (ΔPD) in SCD AP+ was markedly higher than in AP−. Considering these results, we might hypothesize that the variation in PD, and hence the increase of emotional contagion over time, could be a potential neuropsychological marker suggestive of Alzheimer's Disease, particularly in the preclinical stages of the disease, that is SCD.

To further support our theory, we performed multiple regression analysis to evaluate which factors might be associated to ΔPD. Interestingly, we found that the entity of PD changes over time was significantly influenced only by the AP status, in other word by the underlying Alzheimer's Pathology.

As we previously stated, one of the main limitations of empathy evaluation in neurodegenerative diseases is IRI administration to the caregiver (Rankin et al., 2006), due to the patients' impairment of cognitive functions and self-awareness. However, the IRI was developed as a self-report questionnaire (Davis, 1983). Nevertheless, due to their "objectively normal" cognitive performances, SCD patients may be the ideal group to complete the IRI for a self-evaluation of empathy capacity. For this reason, IRI questionnaire was administer to SCD patients themselves, to compare self-evaluated empathy with the recently collected Italian normative data (Maddaluno et al., 2022). No previous works investigated this topic before.

We found that FT, EC and PD scores were higher in SCD group than in the normative sample, whereas PT scores were significantly lower. Our result about higher PD scores in SCD as compared to normative data agrees with the finding from the caregiver's assessment, reporting an amplification of emotional contagion over time. On the other hand, although the caregiver's assessment didn't show a change in PT over time, self-reported PT scores in SCD were significantly lower than in the general population. In this scenario, it has been recently hypothesized that perspective taking ability starts to be impaired since MCI stage (Giacomucci et al., 2022; McCade et al., 2013; Weiss et al., 2008). However, this result allowed us to hypothesize that a subtle impairment of cognitive empathy abilities may already be present in the preclinical phase of the AD continuum, thus representing a first objective neuropsychological marker.

Despite no differences being found in IRI subscales scores between SCD AP+ and SCD AP−, SCD AP+ qualitatively showed lower PT scores than AP−. Further studies are needed to better explore this point. However, we might suggest that this decline of PT could be suggestive of an underlying Alzheimer's Pathology. This impairment of perspective taking

ability is probably too subtle to be detectable by the caregiver point of view and may be highlighted only through comparison with normative data.

Considering these results about self-evaluation of empathy in SCD and the comparison with normative data, the trend of empathy impairment in AD continuum may be different from what suggested by the caregiver's evaluation. Indeed, caregiver's assessment leads to the hypothesis that amplification of emotional contagion comes first, followed by the impairment of perspective taking. However, considering SCD self-evaluation, we might speculate that perspective taking ability may be subtly involved since the preclinical phase of AD continuum.

We also explored facial emotion recognition by the EK-60 F test. Our results showed that facial emotion recognition ability progressively decreases along the AD continuum, with higher score in SCD and worse performance in MCI and in AD-d. Our findings are in line with previous works reporting difficulties in facial emotions recognition in AD-d and with the few works exploring this ability in MCI and SCD too (Giacomucci et al., 2022; Pernigo et al., 2015; Spoletini et al., 2008; Weiss et al., 2008). In more details, SCD presented higher scores in recognition of single facial emotion as compared to AD-d patients; similarly, MCI performed better than AD-d in recognition of all facial emotions, while no differences were detected between SCD and MCI. The only exception is represented by fear recognition, with higher scores in SCD than in MCI, while the performance in MCI and in AD-d was found similar. These results lead us to hypothesize that facial emotion recognition impairment may begin after MCI stage, with a significant decline in dementia phase, in line with previous findings (Giacomucci et al., 2022). The reduction of fear detection between SCD and MCI has been previously described, suggesting that this earlier difficulty might be due to the fact that fear is a subtle expression, more difficult to be recognized (Giacomucci et al., 2022; Spoletini et al., 2008; Weiss et al., 2008).

We also performed a multivariate analysis of covariance in order to assess which variables might influence facial emotion recognition. Interestingly, we detected an influence of attentive function in fear recognition and of short-term memory in sadness recognition. It's important to stress that previous studies have already reported correlations between cognitive functions and emotion recognition, particularly for negatively valued emotions. In fact, it has been suggested that the difficulties in maintaining an adequate level of attention to extract necessary information from a face could be responsible for the impairment of negative emotion recognition (Pernigo et al., 2015; Torres Mendonça De Melo Fádel et al., 2019; Virtanen et al., 2017).

As a second aim of the study, we wanted to explore neural correlates of empathy deficits in the AD continuum, specifically in AD demented patients, in MCI and in SCD patients carrying Alzheimer's Pathology. To the best of our knowledge, this is the only study that tried to define neural basis of empathy in prodromal and preclinical phases of AD, considering the positivity of both amyloid and tau biomarkers. Only one previous work tried to explore neural basis of empathy deficit in AD and MCI with positive amyloid biomarkers (Giacomucci et al., 2022). Moreover, no studies have previously been conducted considering SCD patients carrying AD pathology too.

Interestingly, cognitive empathy deficits (represented by PT scale and ΔPT) were correlated with the involvement of specific brain empathy-related regions. In more details, perspective taking impairment showed a correlation with involvement of right middle frontal gyrus in AD demented patients. Beside right middle frontal gyrus, left posterior cingulate cortex was correlated with perspective taking impairment in the whole AD continuum group. Moreover, the decrease of perspective taking ability along time was correlated with the involvement of bilateral posterior cingulate cortices in both AD demented patients and in the whole AD continuum group.

Previous studies have already reported the involvement of middle frontal gyrus in cognitive empathy deficits in AD (Giacomucci et al., 2022, 2023). As part of dorsolateral prefrontal cortex (DLPFC), middle frontal gyrus is involved in abstract reasoning, perspective taking tasks, inhibition of self-perspective in order to allow the other's perspective to be considered, and evaluation of emotional stimuli (de Waal & Preston, 2017; Nejati et al., 2021; Rankin et al., 2006). Posterior cingulate cortex hypometabolism has been widely described as an early feature of Alzheimer's Disease and a key area of the default mode network (DMN). Several works previously described that the DMN participates broadly in advanced forms of thought and inferences that depend on internal mentation. Indeed, while attention-demanding tasks lead to deactivation, DMN shows an increased activity during tasks that rely on internally constructed representations, including remembering, envisioning the future, making social inferences, taking the perspective of another individuals, considering feelings of others, processing affective stimuli (Buckner & DiNicola, 2019; Bzdok et al., 2012; Smallwood et al., 2021). Considering specifically the posterior cingulate cortex, this brain area seems to have a key role in several functions. In particular, it has been suggested that posterior cingulate cortex is involved in self/other emotion attributions (Ochsner et al., 2004) and in detecting and responding to environmental events that may require a change in behaviour (an important task in cognitive empathy) (Leech & Sharp, 2014). This evidence might explain the correlation between loss of perspective taking ability and the involvement of middle frontal gyrus and posterior cingulate cortex in AD and in AD continuum.

Our results showed an amplification of emotional contagion along the AD continuum. Considering SPM analysis, we found a correlation between personal distress and involvement of left inferior parietal gyrus in MCI patients and between increase of personal distress along time with fusiform gyrus in AD-d patients. The involvement of parietal regions in MCI has been previously described and might be explained by the already known presence of neurons belonging to Mirror Neurons System (MNS) in these areas (Giacomucci et al., 2022). According to the Perception-Action Model, mirror neurons are involved in the conversion of other's behaviour representations into one's own representations, leading to the comprehension of actions of others (Rizzolatti et al., 2009). As previously hypothesized, the heightening of emotional contagion in prodromal stage of AD might be due to a

derangement of MNS network (Farina et al., 2017; Fischer et al., 2019; Moretti, 2016).

The involvement of fusiform gyrus in AD-d patients is more difficult to discuss since it has not been previously described as correlated with personal distress. Indeed, Rankin et al. found a correlation between atrophy of fusiform gyrus and a composite score which was the sum of PT + EC scores of IRI, not including PD (Rankin et al., 2006). This specific brain region has been described as involved in facial perception and recognition (Hadjikhani & de Gelder, 2003). Further studies are obviously needed to better explore this correlation between fusiform gyrus and emotional contagion which might be partially explained by the fact that facial perception and recognition are skills likely related to empathy.

Despite these interesting results, we did not find any significant correlation between IRI subscales and brain metabolism in SCD patients carrying Alzheimer's Pathology. This might be due to the small sample size. However, we might also hypothesize that SCD patients did not present a marked brain hypometabolism since they represent the very early stage of cognitive decline. Indeed, according to the model proposed by Jack et al., AD biomarkers present a progressive dynamic trend and FDG-PET might start showing neurodegeneration later than amyloid and tau biomarkers become positive (Jack et al., 2010). This could be the reason why no correlations with brain metabolism might be detected at this very early stage of AD.

Our study presents some limitation. First, the small size of SCD patients carrying Alzheimer's Pathology (AP+), which might be the cause of the absence of correlations with brain metabolism at SMP analysis. Another limitation is the lack of corrections for multiples comparisons in the correlation analysis between empathy deficits and hypometabolism in FDG PET analysis: we chose this more exploratory approach to explore neural basis of empathy deficit also considering separately SCD and MCI patients. Another limitation of the study is the use of a caregiver-report questionnaire for MCI and AD-d patients, despite the IRI being the most used validated instrument for the evaluation of empathy. In fact, even if observer-based scores have yielded valuable data in previous works (Rankin et al., 2005), they depend on informants varying reliability (Shany-Ur et al., 2012). Another intrinsic limitation of the IRI is, moreover, due to the fact that it does not allow a comprehensive exploration of each component of empathy, only including 7 questions per scale. In the future, we aimed to use other complimentary scales or tests to better analyse cognitive and affective components of empathy and to explore other component of social cognition, such as theory of mind.

Further limitations include the absence of healthy controls and the need to use SCD to compare the behavioural data: however, as previously stated, we compared self-reported SCD scores with normative data from the Italian population (Maddaluno et al., 2022).

On the other hand, our study has some remarkable strengths. First of all, to the best of our knowledge, this is one the first studies analysing empathy changes along the AD continuum in a relatively large cohort of well characterized patients who underwent biomarkers analysis. In more details, empathy changes and emotion recognition were widely and deeply analysed in SCD population, considering both caregiver and self-reported IRI scores. Moreover, SCD self-reported IRI scores were compared with normative data of Italian population, in order to objectively define empathy in this specific population. Another strength is the use of biomarkers not only in prodromal but also in preclinical stages. Moreover, to define carriers of Alzheimer's Pathology, we did not consider amyloid positivity alone but also the tau positivity. This approach will increase the probability that patients with mild objective or subjective cognitive decline are real carriers of Alzheimer's pathology. Another strength is the use of FDG-PET instead of MRI and voxel based morphometry (VBM), since hypometabolism seems to come before atrophy occurs (Jack et al., 2010).

In conclusion, this study highlights the dynamic changes of empathy capacity across different stages of the AD continuum and provides insights into the potential neural substrates.

Empathy changes are detected from the very early stages of Alzheimer's Disease. In particularly perspective taking ability seems to be subtly impaired since SCD and this could be the first "objectively" detectable deficit in this particular population. On the other hand, the increase of emotional contagion over time might be selectively influenced by the underlying Alzheimer's pathology, thus being a potential neuropsychological marker of AD. Despite further studies being needed to confirm our hypothesis, our findings underline the potential role of empathy-related measures as AD markers and the importance of considering social cognition for the early detection and diagnosis of Alzheimer's Disease.

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Authors' contributions

Giulia Giacomucci: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – Original Draft, Writing – Review & Editing. **Valentina Moschini**: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – Original Draft. **Sonia Padiglioni**: Data Curation, Validation, Visualisation. **Diletta Piazzesi**: Data Curation, Validation, Visualisation. **Cecilia Caruso**: Data Curation, Validation, Visualisation. **Claudia Nuti**: Data Curation, Validation, Visualisation. **Alice Munarin**: Data Curation, Validation, Visualisation. **Salvatore Mazzeo**: Data Curation, Validation, Visualisation. **Giulia Galdo**: Data Curation, Investigation, Validation, Visualisation. **Cristina Polito**: Data Curation, Validation, Visualisation. **Carmen Morinelli**: Data Curation, Validation, Visualisation. **Silvia**

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Declaration of competing interest

The authors have nothing to disclose.

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Supplementary data

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