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Differential Impairment of Cognitive and Affective Mentalizing Abilities in Neurodegenerative Dementias: Evidence from Behavioral Variant of Frontotemporal Dementia, Alzheimer's Disease, and Mild Cognitive Impairment

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Abstract.

Cognitive and affective theory of mind (ToM) can be impaired in the course of neurodegenerative dementias. Experimental tests based on different task conditions and/or complexity may fail to capture disease-specific patterns of impairments. In this study, we assessed with a single task both the affective and the cognitive facets of ToM ability in a sample of 47 patients (i.e., 12 AD, 20 bvFTD, and 15 aMCI fulfilling IWG criteria for AD in predementia phase) and 65 healthy controls. Subjects were administered the Story-based Empathy task (SET), a non-verbal task measuring the ability to infer others' intentions (IA) and emotions (EA) compared to a control condition (causal inferences, CI). Global and single sub-condition scores were evaluated with a vectorial method, analyzing the relationship between social abilities and basic cognitive functioning by means of two indices representing the basic ability to perform the task and the balance between basic functions and ToM skills.

Dementia (AD and bvFTD) patients showed impaired performances on all SET sub-conditions, whereas aMCI subjects' performance was not different from healthy controls. Vectorial analysis revealed a specific change in the balance between EA and CI conditions only in the bvFTD group, supporting a disproportionate deficit in mental states attribution based on affective cues. The overall deficit in the task in AD appears to be more general and related to the severity of dementia. This latter finding is further supported by the normal performance of the prodromal AD group.

Keywords: Alzheimer's disease, frontotemporal dementia, mild cognitive impairment, neurodegenerative diseases, theory of mind

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INTRODUCTION

Theory of mind (ToM) has been classically described as the process by which "an individual imputes mental states to himself and others" [1]. It is widely recognized as a multidimensional process [2, 3] requiring the integration of several components. Among them, the ability to attribute emotion (EA) and intention (IA) to others plays a key role in the mentalizing construct [4].

The distinction between affective (i.e., EA) and cognitive (i.e., IA) facets of ToM has been assessed using different tests, with respect to both their cognitive (e.g., reasoning about belief) or affective (e.g., reasoning about feelings) demands. First- and second-order false-beliefs, generally used to assess cognitive ToM ability [5, 6], differ in difficulty, as second-order false-belief tasks require high-level ToM skills [5]. On the contrary, affective ToM is classically investigated with tasks such as the Reading the Mind in the Eyes or the Yoni, which require subjects to mentalize based on eye gaze or facial expression [7–9].

Functional MRI studies on healthy subjects have identified brain correlates of affective and cognitive ToM [10–12], highlighting the engagement of both common and differential brain networks in the attribution of intentions and emotions. In particular, posterior temporo-parietal regions (e.g., temporo-parietal junction, posterior superior temporal sulcus, and precuneus) are key components of mentalizing networks [13, 14], while fronto-limbic regions (e.g., ventromedial prefrontal cortex [11], amygdala [12], inferior frontal gyrus [15, 16], and anterior cingulate cortex [12, 15]) are additionally engaged in tasks requiring inference on other's mental state based on affective cues.

Focal neurological disorders [9, 16, 17] and neurodegenerative conditions (see [18] for a review) may affect mentalizing abilities with specific and differential patterns of deficits, according to the topographical distribution of brain damage. In particular, affective mentalizing deficits have been reported in patients with frontal brain lesions due to the selective damage of the inferior frontal gyrus [16] and the ventromedial prefrontal cortex [9, 17]. Specific involvement of affective ToM has also been reported in amyotrophic lateral sclerosis [19] in association to gray-matter reduction in the inferior frontal gyrus and anterior cingulate cortex.

More widespread ToM deficits may be present in other neurodegenerative diseases such as Alzheimer's disease (AD), primary progressive aphasias or progressive supranuclear palsy [18], and Parkinson's disease [20], as well as in some psychiatric conditions as major depression [21] and schizophrenia [22].

Due to a highly selective pathology-driven disruption of the structures engaged in the ToM-related brain networks [23], mentalizing impairments are among the main features of the behavioral variant of the frontotemporal dementia (bvFTD), the second most common early-onset dementia [24, 25]. The clinical picture of bvFTD is usually characterized by social cognition disorders, particularly loss of empathy and emotion recognition deficits, associated with progressive and insidious behavioral alteration and executive disorders [26, 27].

Many studies explored both intention and emotion attribution deficits in bvFTD patients. Overall, these studies highlighted a widespread deficit in both affective and cognitive ToM [18, 28–30], but EA and IA have been often assessed using different tasks [18, 29], making the results open to alternative interpretation (e.g., task difficulty).

Since impairments in basic cognitive abilities (e.g., executive functioning deficits of bvFTD patients [31]) may affect ToM performances, some paradigms included a control condition that matches to the ToM conditions in the general cognitive demands, but can be solved without any mentalistic inference. The control condition performance may thus help in elucidating whether task impairments reflect pure ToM deficits or mirror impairments on other cognitive abilities (e.g., executive functioning, working memory, visuo-spatial abilities). Though evidence of single bvFTD studies are controversial, ranging from selective mentalizing impairments to broadened deficits of both ToM and basic cognitive functioning, results of a recent review supported that the ToM deficits seen in bvFTD do *not* simply reflect a general cognitive impairment [29].

In contrast to bvFTD, global cognitive functioning is considered to influence performances on mentalizing tasks in AD patients [32]. In particular, false-belief tasks with highly demanding cognitive load (i.e., second-order) are more impaired compared to first-order conditions [18, 33]. This evidence strongly suggests a prominent role of global cognitive functioning in the resulting performance on ToM task in AD. Since temporo-parietal regions are selectively damaged in AD dementia [34], posterior components of the mentalizing networks may be affected in this neurodegenerative condition. Moreover, with the progression of the disease and the extension of the pathological process to more anterior brain regions [35, 36], it is likely that also AD patients may present affective ToM deficits. While evidence on cognitive ToM

impairments in AD are consistent [18, 33], reports of affective ToM deficits are sparse and discordant, even with the use of the same ToM paradigm (i.e., the Reading the Mind in the Eye; [37–39]).

In order to assess general or condition-related ToM deficits, we explored affective and cognitive facets of mentalizing abilities in bvFTD and AD patients using a single task (i.e., Story-based Empathy task, SET) [28] in its standardized version [40]. Moreover, as the SET also includes a control condition (i.e., physical causality), we evaluated the weight of basic cognitive functions on the resulting ToM skills. Performances of AD dementia patients are compared with those of a group of amnestic mild cognitive impairment patients (aMCI) fulfilling IWG criteria [41, 42] for AD in predementia phase (i.e., cerebrospinal fluid (CSF) positive for AD), in order to evaluate whether the ToM deficits reported in AD are associated to "AD dementia" or to "AD pathology" condition.

MATERIALS AND METHODS

Subjects

A total of 112 subjects participated in the study, including 65 healthy controls (HC) and 47 neurodegenerative patients (i.e., 20 probable bvFTD [27], 12 AD dementia [42, 43], and 15 aMCI patients [44] fulfilling IWG criteria [41, 42] for AD in predementia phase).

HC subjects were recruited at community centers. Exclusion criteria included a positive history of neuropsychiatric disorders, pathological signs on neurologic examination, Clinical Dementia Rating (CDR) global score >0, and a Mini-Mental State Examination raw score $\leq$28. None of the HC subjects was taking any medication interfering with neurobehavioral functioning.

All patients were consecutively recruited at the Department of Clinical Neurosciences, Vita-Salute University and San Raffaele Scientific Institute (Milan, Italy) and evaluated by a team of experienced behavioral neurologists and neuropsychologists. All patients underwent a standard neurological examination and neuropsychological assessment including main cognitive domains (language, memory, attention and executive functions, and visuo-spatial abilities). Behavioral changes were investigated using caregiver questionnaires (i.e., Neuropsychiatric Inventory [45] and Frontal Behavioral Inventory [46]). Only patients in mild stage of the disease (CDR global score 0.5–1) were included. Patients with severe language verbal comprehension deficits or comorbid medical conditions potentially interfering with cognitive functioning were excluded.

While bvFTD patients showed predominant deficits in executive functions with a relative sparing of episodic memory and visuo-spatial abilities, AD and aMCI had impaired performance on an episodic memory test, suggesting an amnestic syndrome of the hippocampal type. Deficits in short-term and working memory tasks were additionally found in AD dementia patients. In support of the clinical diagnosis, bvFTD patients showed widespread changes involving the core behavioral dimensions (i.e., disinhibition, apathy or inertia, loss of empathy or sympathy, perseverative, stereotyped or compulsive behaviors, and hyperorality or dietary changes). Psychotic symptoms were more frequent in AD. Behavioral profile of AD patients highlighted a prevalence of negative symptoms (i.e., apathy, anxiety, and depression). Apathy was the most frequently reported symptom in both groups. AMCI subjects presented only mild reactive depression and anxiety.

Neuroimaging data (i.e., CT or MRI and FDG-PET) and CSF $A\beta_{1-42}$ and tau levels were collected to support the clinical diagnosis. In particular, all bvFTD patients presented brain atrophy and/or hypometabolism in the frontal and anterior lobe, while AD patients showed medial temporal lobe atrophy on CT/MRI and temporo-parietal hypometabolism on FDG-PET imaging. CSF showed decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in all aMCI patients.

All subjects, or their informants/caregivers, gave informed consent to the experimental procedure that had been approved by the local ethical committee.

Demographic and clinical characteristics of the study participants are presented in Table 1.

Social cognition assessment

All subjects were administered a standardized nonverbal cartoon task, namely the SET [40], consisting of two main experimental conditions (i.e., intention attribution (IA) and emotion attribution (EA)), plus a control condition entailing the comprehension of causality based on knowledge about the physical properties of objects or human bodies (causal inference (CI)). The test lasts 15/20 minute, each condition includes six trials and the subjects' task is to select the correct finale of a comic strip among three different possible endings (see Fig. 1). A global score (GS) of 18 indicates the best possible task performance.

Table 1
Demographic and clinical data for each group. Mean and standard deviation (in brackets) for every variable are reported in each group

	AD ($n=12$)	bvFTD ($n=20$)	aMCI ($n=15$)	HC ($n=65$)	Statistics	*Post-hoc* analysis
F/M	5/7	8/12	5/10	34/31	$X^2(3) = 2.38$	–
Age in years	73.17 (10.05)	66.80 (8.66)	73.07 (6.15)	66.89 (8.66)	F (3,108) = 3.8*	HC < aMCI ($p=0.05$)
Years of education	11.75 (4.49)	11.65 (3.73)	12.33 (4.86)	12.18 (4.49)	F (3,108) = 0.113	–
MMSE adjusted score	21.50 (3.93)	24.77 (3.39)	25.64 (2.29)	28.64 (1.09)	F(3,108) = 54.03***	bvFTD < HC***, AD < HC***, aMCI < HC***, AD < bvFTD***, AD < aMCI***
Disease duration (in months)	38 (23.57)	48.47 (30.4)	28.33 (12.13)	–	F(2, 43) = 3.08	–
CDR sum of boxes	5.59 (2.5)	4.8 (3.0)	2.07 (0.8)	–	–	–
FBI	13.92 (10.1)	24.55(9.84)	6.80 (6.167)	–	F(2,43) = 15.74***	BvFTD > AD**, bvFTD > aMCI***
NPI Global score	20.33 (16.89)	30.15 (15.86)	11.33 (10.90)	–	F(2,43) = 5.23**	BvFTD > aMCI**
Delusions	1.09 (3.62)	0.05 (0.22)	0	–	H(2) = 1.24	–
Hallucinations	1.09 (3.16)	0.20 (0.89)	0	–	H(2) = 1.24	–
Agitation/aggression	1.45 (3.7)	2.25 (3.23)	0.29 (0.76)	–	H(2) = 5.87, $p=0.05$	–
Depression/dysphoria	2 (2.14)	1.65 (2.77)	1.71 (2.94)	–	H(2) = 1.14	–
Anxiety	2.82 (3.97)	3 (3.32)	3.71 (3.33)	–	H(2) = 1.16	–
Elation/euphoria	0.18 (0.6)	0.8 (2.09)	0	–	H(2) = 2.35	–
Apathy/indifference	5 (3.37)	6.85 (4.67)	2.07 (2.30)	–	H(2) = 10.07**	AD > aMCI*, BvFTD > aMCI**
Disinhibition	0	3.05 (4.25)	0	–	H(2) = 13.21**	BvFTD > AD*, BvFTD > aMCI*
Irritability/lability	2.36 (2.33)	2.65 (3.40)	2.79 (3.79)	–	H(2) = 0.91	–
Aberrant motor behavior disorders	1.09 (1.87)	2.50 (4.15)	0	–	H(2) = 6.015*	–
Sleep and night-time behavior disorders	0.82 (1.47)	3.05 (4.5)	0	–	H(2) = 5.75	–
Appetite/eating changes	2.91 (3.47)	3.15 (4.01)	0.7 (2.16)	–	H(2) = 5.52	–
Token task	26.75 (5.80)	28.96 (3.79)	30.86 (2.73)	–	F(2,43) = 2.93	–
Semantic verbal fluency	28.58 (11.96)	27.50 (10.89)	34 (6.49)	–	F(2,43) = 1.74	–
Phonemic verbal fluency	21.75 (12.3)	17.94 (7.72)	29.20 (10.38)	–	F(2,43) = 5.11*	BvFTD < aMCI**
Digit span forward	4.21 (1.71)	4.62 (1.03)	5.61 (0.7)	–	F(2,43) = 5.32**	AD < aMCI*
Raven matrices	28 (3.86)	23.9 (6.57)	29.4 (5.18)	–	F(2,43) = 4.13*	BvFTD < aMCI*
Attentive matrices	39.29 (10.16)	36.47 (9.31)	49.20 (6.94)	–	F(2,43) = 8.68**	BvFTD < aMCI**, AD < aMCI*
Immediate recall deficits (n. of cases)§	10/12	8/20	7/15	–	$X^2(2) = 6.03$*	AD ≠ bvFTD*, AD ≠ aMCI ($p=0.05$)
Delayed recall deficits (n. of cases)§	12/12	7/20	15/15	–	$X^2(2) = 18.08$***	AD ≠ bvFTD**, aMCI ≠ bvFTD**
Rey-Osterrieth complex figure recall	8.32 (5.63)	9.75 (7.37)	9.87 (6.26)	–	F(2,43) = 0.21	–
Rey-Osterrieth complex figure copy	28.86 (8.4)	27.25 (7.17)	33.27 (4.13)	–	F(2,43) = 3.28*	bvFTD < aMCI ($p=0.05$)

AD, Alzheimer's disease; bvFTD, behavioral variant of frontotemporal dementia; aMCI, amnestic mild cognitive impairment; HC, healthy controls; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating scale FBI, Frontal Behavioral Inventory; NPI, Neuropsychiatric Inventory. *$p<0.05$; **$p<0.01$; ***$p<0.001$;§ Since mnestic functions were evaluated in single cases either with the Free and Cued Selective Reminding test or with the Rey Auditory Verbal Learning test, we compared patients' performances by classifying them as normal or impaired/reduced according to the Italian normative standards.

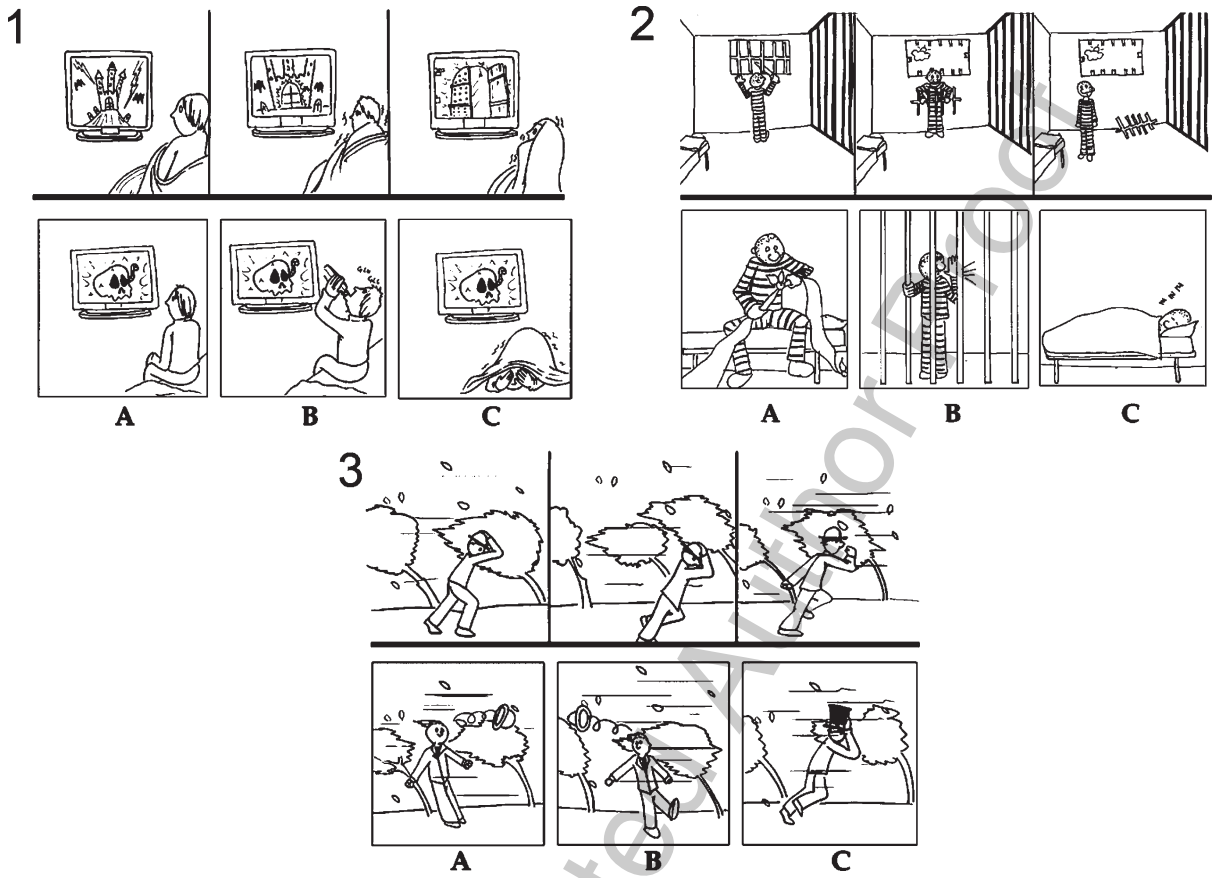

Fig. 1. Comic-strip from the Story-based Empathy Task. 1) Emotion attribution (SET-EA) based on fear, 2) Intention attribution (SET-IA), 3) control condition of causal inference (SET-CI). Possible endings of the story are represented in A, B, and C.

Each condition has a maximum score of 6 points. In order to help subjects to familiarize with the task, they performed a "trial" run, consisting of an example of causal attribution that would not appear in the testing phase. We then verified the adequate comprehension of the instructions asking the subjects to describe each comic strip, formulating a potential story ending before showing them the possible endings. See [40] for further details on the construction of the ToM paradigm and the administration of the task.

In addition, a questionnaire for the evaluation of empathic abilities (i.e., the interpersonal reactivity index-IRI questionnaire) [47] was administered to patients' carers in order to evaluate the relationship between SET performances and patients' empathic aptitude. The IRI is a 28-item questionnaire including four 7-item subscales assessing different aspects of empathy, previously applied in neurodegenerative conditions [48]. Caregivers were asked to rate how well each of 28 statements reflected the current behavior of the participant on a scale of 1 (does not describe at all) to 5 (describes very well). Fantasy ("When I am reading an interesting story or novel I imagine how I would feel if the events in the story were happening to me") and Perspective-Taking ("I sometimes try to understand my friends better by imagining how things looks from their perspective") subscales measure cognitive empathy facet. Emotional empathy is assessed through Empathic Concern ("I often have tender, concerned feelings for people less fortunate than me") and Personal Distress subscales ("Being in a tense emotional situation scares me").

Statistical analysis

Dependent measures were preliminary analyzed to test for normality and heteroscedasticity. Then group comparisons among demographic and experimental variables were analyzed using analysis of variance (ANOVA). *Post-hoc* tests were computed, comparing each diagnostic group to the HC group. In agreement with the different epidemiological features of bvFTD,

AD, and aMCI [25, 49, 50], age was significantly different among groups ($F(3,108) = 3.8$, $p < 0.01$). Since this age unbalance may critically influence the matching with controls, we used SET adjusted scores according to normative data for the Italian population in the analysis of task performances [40].

Additionally, we performed a vectorial analysis using the SET adjusted scores, according to normative data for the Italian population [40], computing two indices, which represent the overall performance (d) and the balance (α) between social abilities (EA and IA) and control capacity of causal inference (CI). We performed the vectorial analysis to address differences across patient groups in ToM performance for two reasons. First, the vectorial analysis differs from ANOVA, covariate, and correlational analyses in focusing on the *balance* or *pattern* of scores across two (or more) variables rather than on the linear outcomes independently for each variable. Second, univariate outcomes can be ambiguous regarding the underlying cause for the differences that are observed using univariate analyses. For instance, if univariate analyses show a difference between a patient group and healthy controls in two variables (e.g., SET-EA & SET-IA), this result is typically interpreted as indicating that the groups are processing one or both tasks differently. This interpretation *may* be correct, but an alternative reason one could secure this pattern of results is that both groups show, e.g., decrements in performance to a differing degree but for the same underlying reason, such as the status of their basic cognitive abilities. In vector mathematics, if the former explanation is correct, then the analyses will show a change in the angle (α) of the vector in two-dimensional Cartesian space (they may also show a difference in the length, *d*, which would provide additional information about performance); if the latter explanation is correct, the angle will *not* differ between the groups but instead *only* the length of the vector (*d*) will differ. Thus, in the vectorial analysis in the present paper, we performed two different vectorial analyses, one for SET-IA and SET-CI and a second for SET-EA and SET-CI. The logic of these analyses is that they provide information about the extent to which the variation in performance on SET-IA (and, independently, SET-EA) could be explained simply in terms of the status of their basic cognitive ability (as indexed by SET-CI). Specifically, considering EA and IA as different dimensions of ToM, each experimental condition can be represented in a two-dimensional Cartesian space in which the x-axis goes from 0 to the maximum of SET-CI score (i.e., 6 points), and the y-axis represents SET-IA (or SET-EA) performance. In this space, a vector can be described in terms of its length (the overall performance) and angle (α), which represents the gradient of this vector and the relative performance on the CI and IA/EA components of ToM as a function of group. For each group, the d values were obtained computing the distance in a two-dimensional Cartesian space between a point with the coordinates (SET-CI adjusted score, SET-IA/EA adjusted score) and the origin. Alpha has been computing through inverse trigonometric functions. As for SET adjusted scores, the statistical analysis were performed using the one-way ANOVA.

The relationship between mentalizing abilities and empathic attitude in patients was then assessed through Pearson's correlation analysis between the different SET conditions and the IRI sub-scales scores. Age in years was also used as covariate for correlation analysis in order to control for this possible confounding factor.

Statistical analyses were performed using SPSS for Windows (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

RESULTS

One-way ANOVA on SET performances highlighted significant differences between groups in all the SET conditions (Table 2). In particular, post-hoc analyses proved significantly lower performances in SET-CI ($F(3,108) = 5.65$, $p < 0.001$, $\eta^2 = 0.136$), IA ($F(3,108) = 17.84$, $p < 0.001$, $\eta^2 = 0.331$), and EA ($F(3,108) = 16.88$, $p < 0.001$, $\eta^2 = 0.319$) conditions in both bvFTD and AD compared to HC (Table 2). No significant difference was found between the two dementia groups. Noteworthy, aMCI patients showed no significant difference in any SET condition compared to HC, but their performances significantly differed from those of AD patients (Table 2).

In the vectorial analysis both AD and bvFTD groups revealed a significant lower performance measured by the d index ($d_{SET\text{-}IA}$ ($F(3,108) = 15.46$, $p < 0.001$, $\eta^2 = 0.3$), and $d_{SET\text{-}EA}$ ($F(3,108) = 13.01$, $p < 0.001$, $\eta^2 = 0.265$) (Table 2 and Fig. 2). A specific imbalance between the affective ToM condition (EA) and the basic abilities (CI) measured by $\alpha_{SET\text{-}EA}$, which was significantly different between bvFTD and HC ($F(3,108) = 5.012$, $p < 0.01$, $\eta^2 = 0.122$), was found only in the bvFTD group. No imbalance between cognitive ToM condition (IA) and the basic abilities (CI) was found in any group. Consistently with the results of the main statistical analysis (see above), the vectorial

Table 2
Social cognition assessment patients and healthy controls. Mean and standard deviation (in brackets) for every variable are reported in each group

	AD ($n = 12$)	bvFTD ($n = 20$)	aMCI ($n = 15$)	HC ($n = 65$)	ANOVA F value (df)	*Post-hoc* analysis
IRI global score	81.67 (10.63)	69.74 (15)	77.60 (15.76)	–	F(2,43) = 3.9*	bvFTD < AD*
IRI emotional empathy	46.33 (5.45)	42.73 (9.74)	44.8 (8.92)	–	F(2,43) = 1.004	–
IRI cognitive empathy	35.3 (8.72)	27.42 (7.02)	32.8 (9.26)	–	F(2,43) = 5.47*	bvFTD < AD*, bvFTD < aMCI ($p = 0.05$)
SET-GS adjusted	9.09 (3.90)	9.64 (3.67)	13.40 (2.66)	14.42 (2.92)	F(3,108) = 18.18***	AD < HC***, AD < aMCI**, bvFTD < HC***, bvFTD < aMCI**
SET-EA adjusted	3.20 (1.32)	2.64 (1.57)	4.22 (1.28)	4.86 (1.25)	F(3,108) = 16.88***	AD < HC**, bvFTD < HC***, bvFTD < aMCI**
SET-IA adjusted	2.82 (1.66)	3.38 (1.67)	5.04 (1.36)	5.08 (0.99)	F(3,108) = 17.84***	AD < HC***, AD < aMCI***, bvFTD < HC***, bvFTD < aMCI*
SET-CI adjusted	3.23 (1.64)	3.71 (1.51)	4.28 (1.13)	4.62 (1.13)	F(3,108) = 5.65***	AD < HC**, bvFTD < HC*
$d_{SET\text{-}IA}$	4.46 (1.95)	5.20 (1.75)	6.74 (1.11)	6.92 (1.23)	F(3,108) = 15.46***	AD<HC***, AD < aMCI***, bvFTD < HC***, bvFTD < aMCI**
$d_{SET\text{-}EA}$	4.68 (1.78)	4.73 (1.75)	6.08 (1.41)	6.77 (1.42)	F(3,108) = 13.01***	AD<HC***, bvFTD < HC***
$\alpha_{SET\text{-}IA}$	41.01 (18.41)	41.67 (16.59)	48.99 (12.94)	47.98 (7.85)	F(3,108) = 2.49	–
$\alpha_{SET\text{-}EA}$	43.77 (19.27)	34.18 (17.86)	44.16 (10.40)	46.22 (8.23)	F(3,108) = 5.012**	bvFTD < HC**

AD, Alzheimer's disease; bvFTD, behavioral variant of frontotemporal dementia; aMCI, amnestic mild cognitive impairment; HC, healthy controls; IRI, Interpersonal Reactivity Index; SET-GS, SET global score; SET-EA, emotion attribution; SET-IA, intention attribution; SET-CI, causal attribution. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

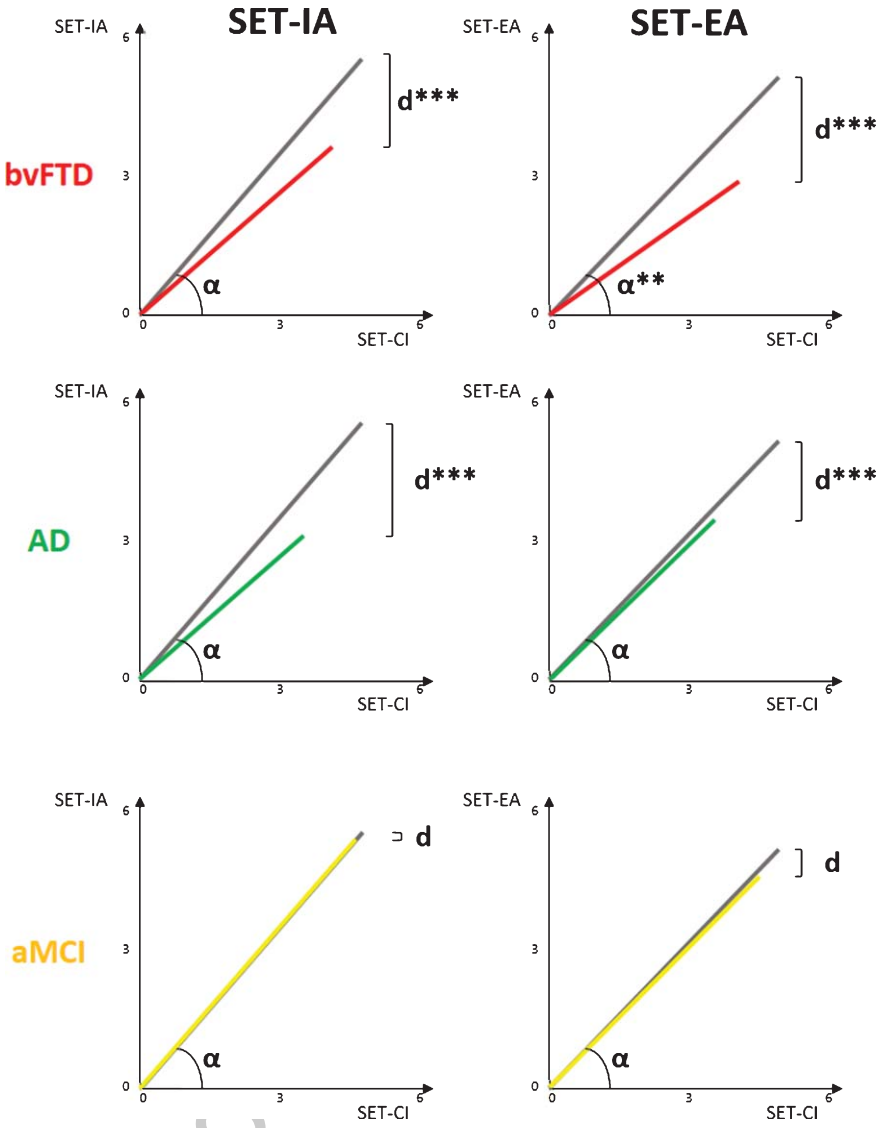

Fig. 2. Two-dimensional Cartesian space for SET-IA and SET-EA conditions in each neurodegenerative sample. The d and α index are depicted in each condition, grey lines represent HC performances. $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.0001$.

analysis showed no differences in d or α index in the aMCI group compared to HC (see Fig. 2). In sum, the vectorial analyses revealed: (1) The aMCI group did not differ from the HC group on overall performance or on the pattern (balance) across IA and CI and across EA and CI—indicating this patient group is "normal" on ToM and on basic cognitive abilities. (2) The AD group, compared to the HC group, performed more poorly on the IA and EA tasks but this impairment in performance on ToM can be explained entirely by a corresponding impairment in basic cognitive ability (as indexed by CI). (3) The bvFTD group, compared to HC group, performed more poorly on the IA and EA tasks, with the diminished performance by the bvFTD group on IA explicable in terms of a corresponding impairment in basic cognitive ability whereas the diminished performance by this group on EA explicable by a specific change in a specific form of social cognition (in contrast to a basic change in cognitive ability).

In order to provide a further confirmation of the imbalance between EA and CI abilities in bvFTD, we performed additional statistical analysis on SET-EA using SET-CI score as covariate. Consistent with the findings of vectorial analysis, we found a significant statistical effect of the group ($F(3,107) = 11.21$, $p < 0.001$). Post-hoc analyses revealed significant

differences between bvFTD and both HC ($p < 0.001$) and aMCI ($p < 0.05$). We then compared the performances at SET conditions within groups. BvFTD was the only group in which we detected a significant effect ($F(2,38) = 4.06$, $p < 0.05$), due to the poorer performance in EA sub-task compared to the control condition ($p < 0.05$).

Correlation analyses showed a positive correlation between EA condition of SET task and both the IRI global score (Pearson $r = 0.451$, $p < 0.05$) and emotional empathy subscales considered together (Pearson $r = 0.378$, $p < 0.05$). No further significant correlation emerged.

DISCUSSION

In the present study, we investigated the ability to attribute mental states using a single task (i.e., Story-based Empathy Task, SET) based on affective and cognitive cues in a sample of neurodegenerative dementia (i.e., bvFTD and AD) and predementia (i.e., aMCI) patients. The use of a single ToM paradigm allowed us to better compare patients' performances in the different facets of mentalizing and to evaluate the weight of basic cognitive functions on the resulting ToM performance through the introduction of a control condition, which equates the ToM task in the general cognitive requirements, but which can be solved without any mentalistic reading. A vectorial analysis was applied to evaluate the selectivity of social functioning deficit by means of the balance between basic functions (SET-CI) and ToM abilities (SET-IA and SET-EA) (see Fig. 2).

As expected, dementia patients showed decreased ToM performances ($d_{SET\text{-}EA}$ and $d_{SET\text{-}IA}$). In particular, both AD and bvFTD patients showed reduced scores in all the SET conditions. The evidence of a reduced performance on the control condition suggests the presence of basic cognitive dysfunctions in such patients that may also account for reduced ToM scores [51]. Since neurodegenerative dementia patients usually present simultaneous impairments of different cognitive abilities, mentalizing deficits may be coexistent with dysfunctions on other cognitive domains. These latter deficits may crucially influence performances on cognitive highly demanding task such as ToM paradigms [51, 52].

The analyses on the overall performance (i.e., d index) in AD patients suggest that defective performance in affective and cognitive metalizing may be at least partially explained by basic cognitive deficits. In particular, according to Castelli and colleagues [37], AD ToM deficits may be secondary to other cognitive impairments, with high-level ToM abilities (both affective and cognitive) being the first to be affected, followed then by skills that are more basic in the advanced stages of the disease. Cortical atrophy in AD involves temporal posterior regions as the posterior cingulate cortex, the precuneus and the superior temporal sulcus [36], which underpin cognitive functions related to social abilities, such as mental imagery [53], representation of complex goals [14], and perspective-taking [54]. Damage to these regions may thus elicit, in AD, a deficit in the basic processes underlying the performance of ToM tasks.

On the contrary, socio-emotional processing disorders are core features of bvFTD clinical picture and usually represent key symptoms for the diagnosis [24, 26, 55, 56], suggesting a selective damage of mentalizing and other social cognition networks in this neurodegenerative condition [57]. In particular, bvFTD patients appear to be impaired in other-oriented emotional reactions, which, conversely to intentionality comprehension, are independent from executive functioning or to the general cognitive status [58].

In agreement with this, our data showed a reduced $\alpha_{SET\text{-}EA}$ index compared to HC only in the bvFTD group, proving an imbalance between emotion attribution and causal inference abilities. The introduction of a control condition is highly recommended in ToM tasks to improve the interpretation of defective performance [29]. In particular, the vectorial analysis provides the first evidence of the fact that, in contrast to AD, bvFTD patients present a mentalizing impairment in addition to global cognitive deficits. This evidence is in line with the specific degeneration of fronto-limbic networks in bvFTD [59] that disrupts critical hubs within the so-called "social brain" [60] and results in a severe breakdown of the affective facets of mentalizing ability.

Since the ability to attribute affective states to others (i.e., affective ToM) requires the integration of both cognitive and affective aspects of empathy, with the involvement to some extent of emotional empathy (e.g., emotional contagion, empathic concern, personal distress) [4], which is well known to be impaired in bvFTD patients [27, 58, 61], we tested the relationship between EA performances and empathic attitude. In line with this hypothesis, we found a positive correlation between $\alpha_{SET\text{-}EA}$ index and the IRI global and emotional empathy scores in demented patients. Although this finding suggests low EA performance as good index of impaired affective empathy reflecting the social skills of subjects in daily life [62], the

lack of correlation between EA and IRI sub-scales in our bvFTD sample are not in line with this finding. Further studies are thus needed to better determine the relationship between impaired performances in social tasks and altered social behaviors in daily life.

Unlike dementia patients, the aMCI group did not show any impairment either in the SET or in the vectorial analysis, compared with controls. Significant lower performances on SET emerged in AD compared to prodromal AD/aMCI patients. This result suggests that ToM deficits in AD highly depend on the degree of global cognitive impairments rather than being a signature of the AD pathology. Indeed, although previous reports provided evidence of ToM deficits in aMCI patients [63–65], this result may be due to the use of cognitively demanding tasks [64]. Different from AD, in which ToM deficits seem to be related to the dementia stage, bvFTD patients showed markedly diminished ToM performances, particularly in the affective component, even in the mild disease stages [66], when daily functioning is not impaired and no other cognitive deficits are present. This finding supports the concept that mentalizing dysfunction based on affective cues is a core signature of social cognition disorders in bvFTD patients.

Noteworthy, we did not find an imbalance between cognitive ToM condition and basic control abilities (i.e., $\alpha_{\text{SET-IA}}$) either in AD or in bvFTD patients. This result may be due to the limitations of the study (e.g., small sample size) or to the specific design of the SET-IA condition. Thus, large studies are needed to clarify whether EA is the only component selectively impaired in bvFTD patients and to better analyze the weight of specific cognitive functions in emotion and intention attribution tasks.

In conclusion, the results of our study provide the first direct evidence of a disproportion in affective and cognitive ToM deficits between bvFTD and AD. Even though EA and IA deficits are related to basic cognitive dysfunctions in both dementia conditions, the results of the vectorial analysis suggest that these groups experienced ToM difficulties for different reasons. In particular, AD-related ToM deficits are secondary to more general cognitive difficulties typical of AD dementia. Affective ToM difficulties instead are a core disturbance of bvFTD that may not only be attributed to general cognitive demands. Finally, our data underline the importance of introducing validated tasks exploring affective ToM component in the neuropsychological assessment of patients suspected for bvFTD, in order to provide an early and more accurate differential diagnosis.

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