Emotion recognition deficits in the differential diagnosis of amnesic mild cognitive impairment: a cognitive marker of the limbic-predominant variant?

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ABSTRACT

Objective: Late onset amnesic mild cognitive impairment (aMCI) with long disease course and slow progression has been recently recognized as a possible phenotypical expression of a limbic-predominant neurodegenerative disorder. Basic emotion recognition ability crucially depending on temporo-limbic integrity is supposed to be impaired in this group of MCI subjects presenting a selective vulnerability of medio-temporal and limbic regions. However, no study specifically investigated this issue. **Methods:** Hereby, we enrolled 30 aMCI with a biomarker-based diagnosis of Alzheimer's disease (i.e., aMCI-AD, n=16) or a biomarker evidence of selective medio-temporal and limbic degeneration (aMCI-mTLD, n=14). Ekman-60 Faces Test (Ek-60F) was administered to each subject, comparing then the performance with that of 20 healthy controls (HC). **Results:** aMCI-mTLD subjects showed significantly lower Ek-60F global scores compared to HC, whose performance was comparable to aMCI-AD. Fear, surprise and anger recognition deficits characterized the aMCI-mTLD performance. Fear recognition scores were significantly lower in aMCI-mTLD compared to aMCI-AD. **Conclusions:** Impaired social cognition, suggested by defective performance in emotion recognition tasks, may be a useful cognitive marker to detect limbic-predominant aMCI subjects among the heterogeneous aMCI population.

Key-words: Mild Cognitive Impairment; Ekman 60 Faces test; Cognitive Marker; Differential Diagnosis; Medial Temporal Lobe Dysfunction; Alzheimer's Disease.

INTRODUCTION

Mild Cognitive Impairment (MCI) is a heterogeneous clinical syndrome due to multiple brain pathologies and conditions (Petersen, 2004). Amnesic MCI (aMCI) subjects with old age, selective episodic memory impairment and relatively stable or very slowly progressing cognitive decline have been described as a phenotypical expression of focal medial temporal lobe dysfunction, possibly due to Alzheimer's disease (AD) pathology (Marra et al., 2012). There is, however, a growing literature suggesting that the aMCI syndrome with dysfunction of the medial temporal lobe (aMCI-mTLD) in aged population is largely associated with non-AD neuropathology (Crary et al., 2014; Ferrer, Santpere, & van Leeuwen, 2008; Nelson et al., 2019). In particular, limbic-predominant age-related TDP-43 encephalopathy (LATE) has been recently described as one of the main pathological substrates of mTLD phenotypes (Nelson et al., 2019).

FDG-PET studies in aMCI-mTLD subjects reported a selective reduction of glucose metabolism in the medial temporal lobe, spreading to fronto-limbic regions, without the typical AD pattern of temporal lateral and parietal hypometabolism (Cerami et al., 2018). Combined FDG- and amyloid-PET evidence in the same cohort suggests comorbid brain pathologies, including amyloid β plaques and tauopathy (Cerami et al., 2018). The clinical-neuropsychological features of this cohort of aMCI-mTLD subjects show several features of confirmed limbic predominant age-related TDP-43 encephalopathy (LATE) cases: advanced age, predominant amnesic syndrome of hippocampal type mimicking AD dementia, selective limbic and temporal lobes neurodegeneration, and low risk of clinical-neuropsychological decline (Nelson et al., 2019).

Even though the temporal and limbic dysfunction is a main feature of the aMCI-mTLD population, no researcher has yet investigated social cognition skills in this clinical syndrome. Social cognition is an ample cognitive domain, including emotion recognition, empathy and theory of mind (ToM) as main components (Frith, 2007). This labyrinth of cognitive processes is orchestrated by a complex array of low- and high-level connections (Frith, 2007; Van Overwalle & Baetens, 2009). Temporo-

limbic regions are main hubs of the “social brain” networks, involved in recognition and processing of socio-emotional information (Daggleish, 2004). While mentalizing relies on a large-scale anterior (i.e., ventromedial prefrontal cortex) - posterior (i.e., temporo-parietal junctions, superior temporal sulcus and precuneus) network, the limbic system (i.e., amygdala, insula and anterior cingulate cortex) is the main processing stream for emotion recognition and empathy.

Deficits of social cognition have been reported in MCI (see for review (Bora & Yener, 2017)) but the emerging picture is heterogeneous, with reports of moderate impairments as well as negative findings. Notably, no attempt to investigate social cognition in MCI with different pathological substrates has been done yet.

In view of the above-mentioned evidence, this study aimed at acquiring new data about social cognition disorders in specific MCI subtypes. In details, by using *in vivo* imaging biomarkers for the diagnostic classification of MCI due to AD or with dysfunction of the medial temporal lobe (i.e., suspected for LATE), this study aims at comparing emotion recognition abilities in these two aMCI groups.

MATERIALS AND METHODS

Subjects

The sample included 30 subjects (mean age = 74.5 ± 5.8 years; mean education = 11.0 ± 4.7 years) fulfilling criteria for aMCI (Petersen, 2004) sub-grouped in 16 aMCI due to AD (aMCI-AD) and 14 aMCI with medial temporal lobe dysfunction (aMCI-mTLD). Inclusion criteria for the aMCI-AD group were: amnesic subtype of MCI syndrome; typical AD temporo-parietal hypometabolic pattern at FDG-PET and/or atrophy at MRI imaging. Inclusion criteria for aMCI-mTLD were: amnesic subtype of MCI syndrome; medial temporal lobe and limbic-predominant FDG-PET pattern without the typical AD hypometabolism (Cerami et al., 2015; Cerami et al., 2018). All the included subjects had a three-to-five-year clinical follow-up.

All subjects were evaluated by a team of experienced behavioral neurologists and neuropsychologists and underwent a standard neurological examination and neuropsychological assessment including main cognitive domains (language, memory, attention and executive functions, and visuo-spatial abilities).

Twenty healthy controls (HC) were recruited at community centers for statistical comparisons. Exclusion criteria were a positive history of neuropsychiatric disorders, pathological signs on neurologic examination, Clinical Dementia Rating scale global score > 0 , and a Mini Mental State Examination raw score < 28 . None of the HC subjects was taking any medication interfering with neurobehavioral functioning.

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.

Emotion recognition assessment

Emotion recognition abilities were assessed with the Italian version of the Ekman 60-Faces Test – Ek-60F (Dodich et al., 2014), which includes 60 pictures depicting 10 actors' faces, each one expressing one of the six basic emotions (i.e., surprise, happiness, fear, disgust, anger and sadness). Pictures were serially presented on a computer screen and participants were asked to report verbally the emotion expressed in each of them selecting one out of the six available options (i.e., emotion words) displayed on the bottom of the screen. The scoring procedure resulted in a maximum score of 60 for global performance, and a maximum of 10 for single emotion sub-scores.

Statistical analysis

Subjects were classified as impaired/unimpaired in each basic cognitive domain based on the specific Italian normative data. In addition, according to the standardization of the Italian version of

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the Ek-60F test (Dodich et al., 2014), we calculated the frequencies of globally impaired performances at Ek-60F test and of impaired scores for single emotions in the two aMCI groups.

Group comparisons among demographic and experimental variables were analyzed using either parametric or nonparametric tests, according to data distribution. Demographic and clinical variables were compared between groups using one-way ANOVA (Bonferroni post-hoc test). Due to the non-normal distribution of Ek-60F scores, Kruskal-Wallis test has been used to compare performances between aMCI-mTLD, aMCI-AD and HC. Post-hoc Mann-Whitney tests were used to compare all pairs of groups.

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

RESULTS

Basic cognitive profiles in aMCI-mTLD vs. aMCI-AD

No difference in the demographic and clinical features was found in the two aMCI groups. In particular, MMSE and CDR sum of boxes were comparable between aMCI-AD and aMCI-mTLD subjects. Twenty-one subjects showed a single domain cognitive profile (13 aMCI-AD and 8 aMCI-mTLD), while the rest (i.e., 3 aMCI-AD and 6 aMCI-mTLD) had a multiple domain aMCI syndrome. Cognitive assessment proved severe episodic memory impairments in both aMCI groups, together with visuo-constructive or language deficits in about a quarter of the sample. No subject showed impaired executive performances.

Differential profile of emotion recognition deficits in aMCI-mTLD vs. aMCI-AD

Based on Italian normative values, the Ek-60F global score was impaired in the 29% of aMCI-mTLD subjects and 19% of aMCI-AD. More than 40% of aMCI-mTLD subjects showed impaired fear recognition according to the normative cut-off score.

Kruskall Wallis analysis showed significant differences in the Ek-60F performances of the two aMCI groups compared to HC (Figure 1). Post-hoc analysis proved that aMCI-AD had comparable global scores to HC, whereas they had significantly lower scores in surprise recognition compared to HC. The aMCI-mTLD subjects had significantly lower fear recognition scores compared to both aMCI-AD and HC, and surprise and anger recognition scores compared to HC. Consistently, the Ek-60F global score was reduced in aMCI-mTLD compared to controls.

See Table 1 and Figure 1 for the rate of subjects below the normative cut-off scores and details on statistical comparisons.

DISCUSSION

Recent clinical-neuropathological evidences support the need for a revision in the study of cognitive neurodegenerative disorders in the elderly population. The high prevalence of non-AD brain diseases, including α -synucleinopathies, non-AD tauopathies, hippocampal sclerosis, and cerebrovascular disease, that can all mimic AD clinically, may account for discrepancies between clinical and pathology-based AD diagnoses, especially in older people (Nelson et al., 2016). The prevalence of AD pathology decreases in advanced old age, and approximately 25% of MCI from large case series shows cognitive impairments almost exclusively resulting from non-AD pathology (Nelson et al., 2016). Given that subjects of advanced age constitute a rapidly growing demographic group in many countries, old-aged aMCI with non-AD pathology (e.g., age-related TDP-43 proteinopathy) can be expected to have an expanding but probably under-recognized impact on clinical neurology. Despite no treatment is currently available for AD and non-AD neurodegenerative

processes, their differential diagnosis at clinical level might have important implications in terms of prognosis, patient management and clinical trial participation. Grey zones in diagnostics resulting from mixed pathologies that are typical in advanced old age reflect the biologic complexity of such individuals and increase the difficulties in identifying appropriate patient groups for clinical trials.

Observational neurocognitive studies investigating the neuropsychological profile combined with biomarker evidence in aMCI-mTLD subjects may represent a chance to better characterize in vivo the phenotype of suspected non-AD pathology MCI cases. Standard neuropsychological assessment in suspected MCI subjects is generally focused on the identification of the amnesic syndrome of hippocampal type in order to early detect prodromal AD (Dubois et al., 2014). However, growing evidence shows that subjects affected by non-AD pathology (e.g. LATE, argyrophilic grain disease or primary age-related tauopathy (Crary et al., 2014; Ferrer et al., 2008; Nelson et al., 2019)) may also be characterized by mild cognitive deficits with a predominant amnesic phenotype. Accordingly, misdiagnosis is very frequent and, as reported in LATE case series, a high number of subjects (i.e. 70%) receives in vivo a clinical diagnosis of AD (Besser, Teylan, & Nelson, 2020).

Our findings suggest that, while the standard neuropsychological assessment may fail in successfully distinguishing non-AD aMCI subjects from aMCI due to AD pathology, social cognition deficits, such as the one reported through Ek-60F, may represent useful cognitive markers able to add decisive information for the early differential diagnosis of aMCI-mTLD subjects. Basic emotion recognition crucially depends on temporo-limbic integrity, as previously demonstrated in neurological conditions specifically affecting these brain regions (Adams, Gordon, Baird, Ambady, & Kleck, 2003; Dodich et al., 2016). Despite the processing of emotional faces engages a widely distributed brain network (Fusar-Poli et al., 2009; Phan, Wager, Taylor, & Liberzon, 2002), functional imaging studies on emotion recognition consistently found a pivotal role of the amygdala in the detection and generation of fear-related emotions (see (Phan et al., 2002) for review). On the other hand, anger recognition has been associated to a broader network of paralimbic and frontal regions

(Fusar-Poli et al., 2009). In particular, human amygdala is believed to track the valence of external cues, classifying the level of emotional arousal of a given emotion, and to distinguish among specific emotion categories (Fusar-Poli et al., 2009). Since amygdala is generally involved in the processing of salient and aversive stimuli (Fusar-Poli et al., 2009) and both fear and anger signal an increase in the probable presence of a threat, it is not unexpected that the recognition of these basic emotions is particularly affected in aMCI-mTLD subjects, presenting with a selective medio-temporal hypometabolism extended to limbic structures (Cerami et al., 2018). This result is consistent with a solid literature on neurological patients affected by amygdala damage, who systematically showed impaired recognition for both emotions (e.g., (Adams et al., 2003)).

While the majority of functional studies on emotion recognition focused on investigating the neural correlates of negative emotions and happiness (Fusar-Poli et al., 2009; Phan et al., 2002), the presence of a specific brain network specialized in the detection of surprise is still a matter of debate. In our sample a common pattern of surprise recognition deficit in aMCI compared to HC emerged. Since literature supports a broad neural system including amygdala and insula, as well as parahippocampal, fusiform and postcentral gyri to mediate the recognition of surprise (Zhao, Zhao, Zhang, Cui, & Fu, 2017), different neural substrates may underlie this result. In particular, 19% of aMCI-AD subjects showed a deficit in surprise recognition. All of them had an impaired global performance at the task. On the contrary, aMCI-mTLD subjects showed lower global scores compared to HC, with performances in fear recognition significantly lower than those observed in aMCI-AD. This may be a selective marker of early temporo-limbic neurodegeneration, helping in distinguishing the two aMCI subtypes. Further studies exploring possible distinctive neural correlates of basic emotion recognition deficits in aMCI-mTLD and aMCI-AD groups are certainly needed to clarify the issue.

There is ample evidence (Bora & Yener, 2017) that MCI performances significantly vary according inclusion criteria, and cognitive profile (i.e., single or multiple domain MCI), with subjects

Dodich - Emotion deficits in limbic predominant MCI with multiple-domain and visuo-spatial impairments showing worse performance. Nevertheless, previous MCI studies mainly include heterogeneous samples classified according to clinical criteria (Bora & Yener, 2017) without information about *in vivo* AD biomarkers. Thus, no conclusive findings on the impairment of emotion recognition ability can be drawn in MCI without classifying subjects according to *in vivo* biomarker evidence of pathology or neurodegeneration. Comprehensive studies of social cognition in MCI may thus help in clarifying the relationship between possible underlying pathology and inter-individual phenotypical variation. The advancement of clinical research in this field may also increase awareness of this neuropathological condition and improve the definition of disease-specific biomarkers, a necessary step for clinical trials of new targeted drugs.

In conclusion, although the small sample size and the lack of homogeneous data on basic cognitive domains (memory, language and visuo-spatial skills) do not allow a generalization of our results, this study suggests that social cognition impairments significantly characterize limbic-predominant aMCI subjects, possibly representing a useful cognitive marker for their early clinical identification.

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Table 1. Demographic and clinical features of the sample

	<i>aMCI-mTLD</i> (n=14)	<i>aMCI-AD</i> (n=16)	<i>Controls</i> (n=20)	Statistics
F/M	3/11	6/8	11/9	$\chi^2(2)=4.1, p=0.13$
Age in years	75.4±5.1	73.7±6.5	73.6±4.7	$F(2,47)=0.53, p=0.59$
Years of education	10.6±4.8	11.4±4.8	11.0±4.6	$F(2,47)=0.11, p=0.90$
Condition duration in months	43.2±25.9	34.6±19.9	-	$t(28)=1.02, p=0.31$
MMSE at baseline	25.15±3.8 ^a	26.3±1.8 ^b	29.7±0.5	$F(2,47)=18.3, p<0.001$
CDR sum of boxes	2 [1.5, 2.63]	2.75 [1.13-3.5]	-	$U=135, p=0.35$
Standard neuropsychological assesment				
Impairment in language production	14%	20%	-	$\chi^2(2)=0.16, p=0.68$
Impairment in language comprehension	7%	14%	-	$\chi^2(2)=0.37, p=0.54$
Impairment in episodic memory – immediate recall	93%	73%	-	$\chi^2(2)=1.93, p=0.16$
Impairment in episodic memory – delayed recall	100%	86%	-	$\chi^2(2)=2.15, p=0.14$
Impairment in attention and in executive functions	0%	0%	-	-
Impairment in visuo-constructional praxis	38%	21%	-	$\chi^2(2)=0.94, p=0.33$
Ekman 60-Faces Test				
Impairment in global score (borderline performance)	29% (14%)	19% (6%)	0 (10%)	-
Impairment in surprise recognition (borderline performance)	29% (7%)	19% (0%)	0 (0%)	-
Impairment in happiness recognition (borderline performance)	0% (29%)	25% (19%)	10% (10%)	-
Impairment in fear recognition (borderline performance)	43% (7%)	13% (6%)	20% (5%)	-
Impairment in disgust recognition (borderline performance)	0% (7%)	6% (0%)	10% (0%)	-
Impairment in anger recognition (borderline performance)	43% (14%)	31% (19%)	10% (5%)	-
Impairment in sadness recognition (borderline performance)	14% (36%)	13% (25%)	10% (5%)	-
<i>aMCI-AD = amnesic mild cognitive impairment due to Alzheimer's disease; aMCI-mTLD = amnesic mild cognitive impairment with medio-temporal lobe dysfunction; HC = healthy controls; CDR = clinical dementia rating scale; MMSE = mini mental state examination; ^a aMCI-mTLD<HC, $p<0.001$; ^b aMCI-mTLD<HC, $p<0.001$</i>				

Figure legends

Figure 1. Differences at Ekman-60Faces test between aMCI-AD, aMCI-mTLD, and controls. Median and [interquartile range] are indicated for each group and emotion. * $p < 0.05$, ** $p < 0.01$.

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