TOWARDS AN EVOLUTIONARY COGNITIVE PERSPECTIVE OF THEORY OF MIND IN AMYOTROPHIC LATERAL SCLEROSIS: EVIDENCE IN NON-DEMENTED PATIENTS USING THE ECAS SCALE

ABSRACT

Objective: Social cognition dysfunction is well-recognized as one of ALS-related cognitive impairments but most of previous studies have associated social cognition subcomponents, including Theory of Mind (ToM), with executive dysfunctions using tasks with high executive demands. The aim of the present study was to investigate dysfunction of affective ToM in a sample of non-demented ALS patients and to evaluate any possible associations with executive and non-executive dysfunction.

Method: Forty-three non-demented ALS patients and 30 healthy controls (HC) were administered the judgment of preference task from the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS), as well as the full ECAS scale. Total score as well as the type of errors ("favorite", "unclassified") were recorded for the affective ToM task.

Results: A significant proportion of ALS patients (31%) were impaired in this ToM task, scoring significantly lower compared to HC. Patients with impaired cognitive status were more impaired in ToM task (45%) compared to those with preserved cognitive status (15%). ALS patients had significantly more errors compared to HC, yet the pattern of errors did not differ and both ALS and HC made significantly much more "unclassified" errors. Within ALS analysis revealed a significant association between ToM score and ECAS language and visuospatial abilities but not executive or memory function.

Conclusion: Our findings provide further evidence regarding impaired affective TOM in a well-characterized group of non-demented ALS patients, revealing that approximately one out of three non-demented patients shows impaired affective TOM, as determined by eye gaze in Judgement of Preference task of the ECAS scale. In our group, this impaired performance was not driven by any executive dysfunction; yet, it was more evident in patients with impaired cognition and was associated with patients' language and visuospatial performance.

INTRODUCTION

Amyotrophic Lateral Sclerosis is a multisystem disorder which affects the upper and lower motor neurons and causes the death of neurons which control voluntary muscles. It is now well accepted that ALS is not a disorder restricted to the motor system since motor symptoms often coexist with cognitive and behavioral deficits, mostly related to frontotemporal dysfunction (Beeldman, et al,.2015; Consonni et al,. 2012; Goldstein & Abrahams,2013). Even though only 5-15% of patients meets criteria for frontotemporal dementia (FTD) (Rascovsky et al.,2011;Piguet et al., 2011 ;Snowden, & Mann, 2000;), approximately 50% or even more show more subtle cognitive impairments with executive dysfunction being the predominant deficit (Abrahams & Goldstein, 2002; Strong et al., 2009). This fact and related neuropathological and neuroimaging evidence have led to the proposal of the spectrum of ALS-FTD cognitive changes (He, & Strong.,2001; Murphy, Henry & Lomen-Hoerth., 2007;Neary et al., 2000). Recently, there has been an interest regarding potential impairments in social cognition in patients with ALS (Bora.,2017) and it has been shown that the social cognition is an inseparable part of the ALS-related cognitive profile (Bieldman et al., 2016).

Social cognition refers to a wide range of cognitive capacities elicited by, about, and directed towards other people. In particular, these skills allow humans to both understand themselves and interact with and understand others, engaging in appropriate goal-directed behaviors. Among several components, social cognition includes the Theory of Mind (ToM), that is the understanding of desires and beliefs of others and the prevision of our future behavior (Mitchell, 1996). ToM is divided into two components. The cognitive component is relevant to the beliefs, thoughts and intentions of others, (Coricelli,2005) and it is mediated by the dorsomedial prefrontal cortex, the dorsal anterior cingulate cortex and the dorsal striatum (Abu-Akel & Shamay-Tsoory, 2011; Gallagher & Frith, 2003). The emotional component is relevant to understanding the emotions of others (Brothers & Ring, 1992) and it is mediated by the ventromedial and orbitofrontal cortex, the ventral anterior cingulate cortex, the amygdala and the ventral striatum (Abu-Akel & Shamay-Tsoory, 2011; Gallagher & Frith, 2003).

Although ToM and social cognition deficits have been well-reported during the last decade in both demented and non-demented patients with ALS (for a review: Bora,2017; Christidi et al,2018), it remains poorly defined how these deficits are related to other cognitive processes which are more or less affected in ALS as well as to patients' clinical characteristics, including disease progression. Specifically, there are conflicting findings regarding the nature of deficits in social cognition which have been mostly attributed to executive dysfunction (Meier et al., 2010; Watermeyer et al., 2016).

Several studies in non-demented ALS patients report significant correlation between executive functions, ToM and other components of social cognition, with the latter being examined using tasks with significant executive load such as the three subtests of the Happé's cartoon task, Written Scenarios tasks and the Reading the Mind in the Eyes task (RME) (Gibbons et al., 2007;Snowden et al.,2003; Watermeyer et al., 2015). On the other hand, this association has also been reported when TOM was also examined using tasks with lower executive load, such as the judgement of preference task based on eye gaze and false belief task (Bertoux et al.,2015; Carluer et al.,2015;Girardi et al., 2011). Furthermore, some studies found that deficits in ToM are not related to executive functions since some of them found a significant correlation with non-executive functions, such as long-term memory (Cavallo et al.,2011; Trojsi et al., 2016). Despite the research on the nature of social cognition in ALS, it has not become clear its relationship to executive functions due to methological issues mostly regarding the tests used for the assessment of social cognition and other cognitive functions. On the other hand, symptoms onset seems to be a predictive factor and bulbar-onset patients seems to more often show often impaired social cognition (Girardi et al., 2011;Gibbons et al., 2007;Trojsi et al., 2016).

The aim of the present study is to describe the profile of affective ToM dysfunction in a sample of non-demented ALS patients and evaluate any possible associations with executive and non-executive dysfunction.

METHOD

Participants

Forty two non-demented ALS patients were included in the present study. All patients underwent clinical assessment, including full neurological and electrophysiological examination, and diagnosed with sporadic ALS according to the modified El Escorial diagnostic criteria for ALS (Brooks et al., 2000). Patients were subsequently referred for neuropsychological assessment as part of their routine clinical care. We also included a group of 30 unrelated healthy volunteer participants, as a healthy control (HC) group with similar demographic characteristics compared to ALS patients. Inclusion criteria for the present study were the following: (a) absence of a history of other neurologic conditions affecting cognition (other than ALS for patients), (b) no serious psychiatric disease (e.g., major depression, schizophrenia), (c) no family history of ALS, (d) absence of psychoactive drugs or other medication that could affect mental status, and (e) absence of dementia (Mini Mental State Examination score >24 preserved activities of daily living, preserved social and personal conduct and insight based on patients' and caregivers' selfreports; preserved discourse speech based on WAIS Vocabulary score and narrative speech .Patients disability level was evaluated using the Revised

Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (Gordon et al. 2010). All participants provided inform consent for the study, which was approved by the ethical committee of our institution. Table 1 displays demographic characteristics for ALS and HC groups, as well as clinical characteristics for the ALS group.

Table 1. Demographic and clinical characteristics of ALS patients and HC

	ALS	HC	p-value
Age (yrs)	60.57 (9.90)	60.67 (7.36)	0.965
Education (yrs)	10.55 (3.68)	11.97 (3.42)	0.102
Gender (M/F)	24/18	13/17	0.255
ALSFRS-R	39.83 (5.377)	-	-
Disease duration (m)	22.11 (32.36)	-	-
Progression rate	0.57 (0.82)	-	-
Cognition (P / Imp)	21 / 21	30 / 0	< 0.001
ECAS total score	89.55 (20.55)	106.53 (9.77)	< 0.001
ECAS ALS-specific score	64.98 (16.97)	78.23 (7.68)	< 0.001
ECAS ALS-nonspecific score	24.57 (5.55)	28.30 (3.23)	0.002
ECAS behavioral score	1.21 (1.28)	0.0 (0.0)	< 0.001

Note. ALS = Amytrophic Lateral Sclerosis; HC = healthy controls; yrs = years; m = months; M / F = male / female; ALSFRS-R = revisited Amyotrophic Lateral Sclerosis Functional Rating Scale; P / Imp = Preserved / Impaired; ECAS = Edinburgh Cognitive and Behavioral ALS Screen.

Cognitive Measures

Theory of Mind (ToM): The affective component of ToM was assessed using the Judgment of Preference task (Cohen, et al.,1995 and Snowden et al., 2003), as it is included in the ECAS scale as social cognition test. This task assesses the ability to make a preference judgement based on eye gaze. It is consisted of pre-experimental and experimental condition; in all trials there are six pictures of four objects which belong to the same category (animals, fruits, furniture etc.) and are positioned in each of the four corners (i.e. upper left, upper right, lower left, and lower right). In the pre-

experimental condition, the participants are required to circle their favorite object from each picture. In the experimental condition, the participants are asked to circle the object which a face likes best in each picture. The correct answer is scored with 2 points. The errors are categorized as "favorite'' (in which participants chose their personal favorite object based on the pre-experimental condition) and are scored with 0 points or as "unclassified'' which are scored with 1 point. For the purpose of the present study, the following scores were used: total score; number of total errors; number of "favorite" errors; number of "unclassified" errors.

Other Cognitive Functions: All patients were cognitively examined using the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS) **(**Abrahams et al., 2014), adapted and validated for the Greek speaking population (Kourtesis, 2018). It assesses a range of functions typically affected in ALS (ALS-Specific: Fluency, Executive Functions, Language Functions) and not typically affected in ALS but are common in disorders of older adults (ALS Non-specific: Memory, Visuospatial Functions). An ECAS total score, as well as subscores for ALS-specific and ALS Non-specific domains can be extracted. The ECAS also includes a separate semi-structured behavioral interview which yields a separate behavioral score and is undertaken with an informant/ caregiver separately from the patient and is based on the five key behavioral domains for diagnosing FTD using the most recent diagnostic criteria (Meier SL et al., 2010). For the purpose of the present study, an ECAS Executive Functions score was also calculated without including the social cognition test.

Depression: Patients' depressive symptoms were evaluated using the ALS-Depression Inventory (ADI-12) (Kubler et al., 2005; Ferentinos et al., 2011). It is a self-report screening questionnaire for depressive disorders and is specially designed for ALS patients (Kubler et al., 2005). The scores are ranging from 0 (best possible) to 48 (worst possible) with scores between 22 and 28 indicating mild depression (Kubler et al., 2005).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) while categorical variables are presented as absolute frequencies. Assumptions for normality were initially evaluated (skewness, kurtosis, Kolmogorov-Smirnov test, Q-Q plots) and parametric statistics were then applied. Between-group differences on demographic characteristics were examined using t-test for independent samples (age, education) and chi-square (gender distribution). Between-group differences on ToM scores (total score; number of total errors) and ECAS scores was assessed using t-test for independent samples. Mixed model analysis of variance (ANOVA) was used to evaluate main effect and interaction regarding type of errors and diagnosis. Specifically, we ran two models. In the first model, diagnosis (i.e. ALS ; HC) was used as between-subject factor and type of errors (i.e.

"favorite"; "unclassified") was used as within-subject factor. For the second model, ALS patients were categorized as impaired and non-impaired based on the ECAS total score and a cut-off score of 2SD using available normative data (Kourtesis, 2018). Thus, in this model, three groups (i.e. impaired ALS; non-impaired ALS; HC) were considered in the diagnosis which was used as the between-subject factor while type of errors was the within-subject factor. Post-hoc Bonferroni comparisons between impaired ALS, non-impaired ALS and HC were applied. Correlation analysis between ToM total score and ECAS subscores (ECAS Language; ECAS Verbal Fluency; ECAS Executive Functions (without ECAS social cognition subtest); ECAS Memory; ECAS Visuospatial Functions), as well as clinical variables (disease duration, ALSFRS-R, progression rate) was conducted using Pearson's r. Comparisons on ToM total score between peripheral- and spinal-onset ALS patients was conducted using t-test for independent samples. The level of statistical threshold was set at $p < 0.05$ and all analyses were conducted using IBM SPSS 20.

RESULTS

Between-group differences on ToM

As a group ALS patients scored significantly worse ($p = 0.005$; $|d| = 0.69$) and made significantly more errors on ToM ($p = 0.006$; $|d| = 0.68$). When each patient's performance (total score) was categorized as normal or abnormal based on normative data (Kourtesis, 2018), we found that 31% of patients scored in the impaired range. When patients' cognitive status (ECAS total score) was considered based on normative data (Kourtesis, 2018), we found that 45% of ALS patients with impaired cognition showed impaired ToM while 15% of ALS patients with preserved cognition showed impaired ToM.

With regards to the type of errors (i.e., "favorite" and "unclassified") (Figure 1), we found a significant main effect of diagnosis ($p = 0.006$; $\eta^2 = 0.103$) and type of errors (F = 13.764; $p < 0.001$; $\eta^2 = 0.164$). The interaction effect was not significant ($p = 0.762$; $\eta^2 = 0.001$), as it is shown in Figure 1. ALS patients made significantly more "favorite" ($p = 0.032$; $|d| = 0.52$) and "unclassified" ($p = 0.042$; $|d| = 0.50$) errors compared to HC; yet, both groups made significantly more "unclassified" errors compared to the "favorite" ones.
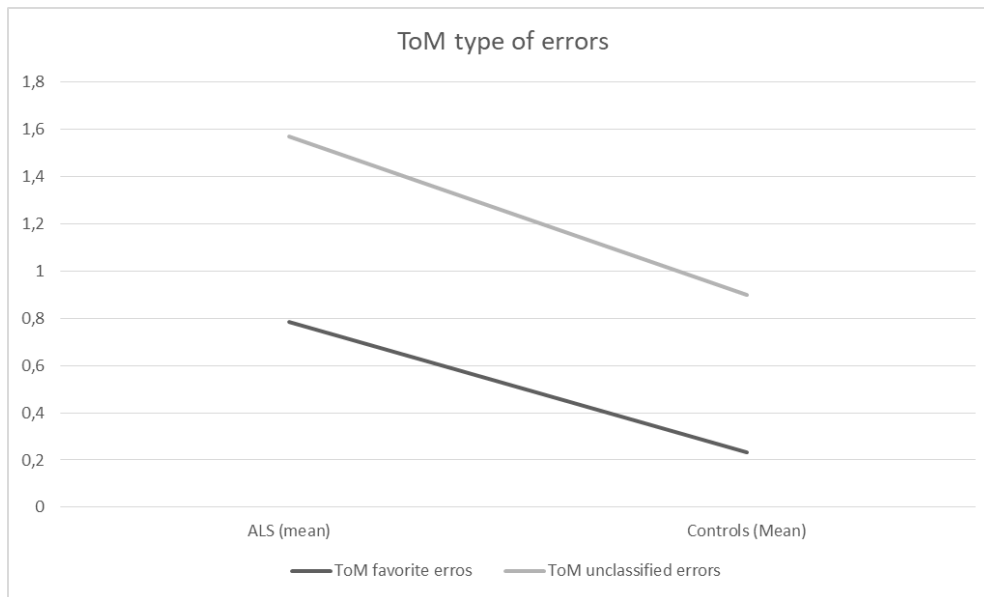
Figure 1 . ToM type of errors (favorite vs. unclassified) in ALS and HC.

When ALS patients were categorized as impaired and non-impaired (Figure 2) based on their ECAS Total score performance and available normative data (Kourtesis, 2018), we found significant differences in social cognition total score (F = 8.600; p < 0.001; η2 = 0.200) and number of total errors (F = 8.086; p < 0.001; η2 = 0.190). Impaired ALS patients scored significantly worse compared to non-impaired ALS patients (p = 0.018) and HC (p < 0.001) and made significantly more errors compared to non-impaired ALS patients (p = 0.025) and HC (p < 0.001). We did not find any difference between non-impaired ALS and HC on social cognition total score and number of total errors (p > 0.05, ns).
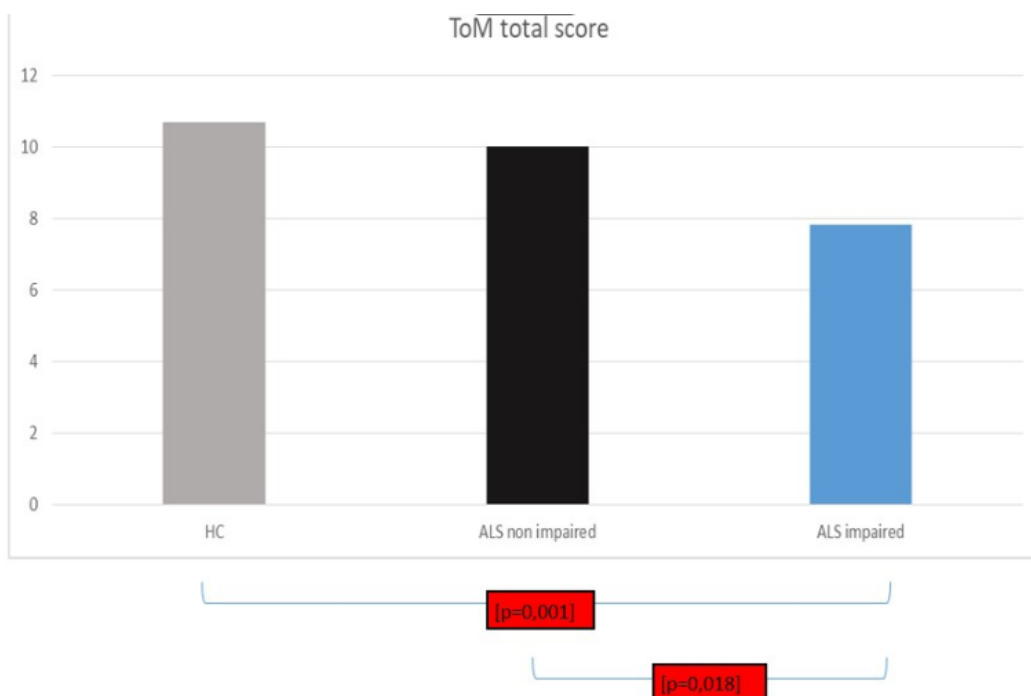
Figure 2. ToM total score in HC and ALS subgroups categorized based on their general cognitive status.

With regards to the type of errors, we found a significant main effect of diagnosis (HC; impaired ALS; non-impaired ALS) ($p < 0.001$; $\eta^2 = 0.190$) and type of errors ($p < 0.001$; $\eta 2 = 0.172$) with the interaction effect being non-significant ($p = 0.954$; $\eta^2 = 0.001$), as it is shown in Figure 3. Post-hoc comparisons on subgroups revealed that impaired ALS patients made significantly more "favorite" ($p = 0.008$) and "unclassified" ($p = 0.027$) errors compared to HC.
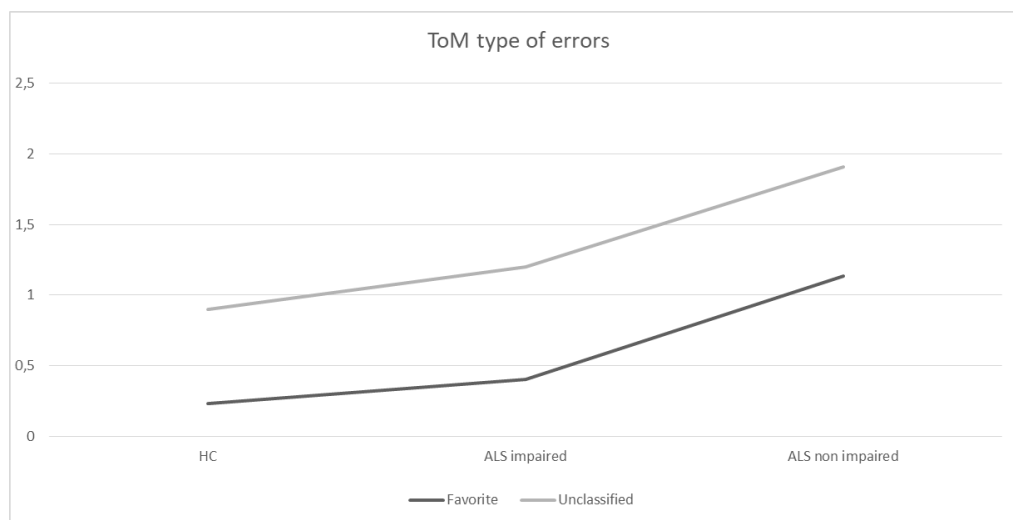

Figure 3. ToM type of errors in HC and ALS subgroups categorized based on their general cognitive status.

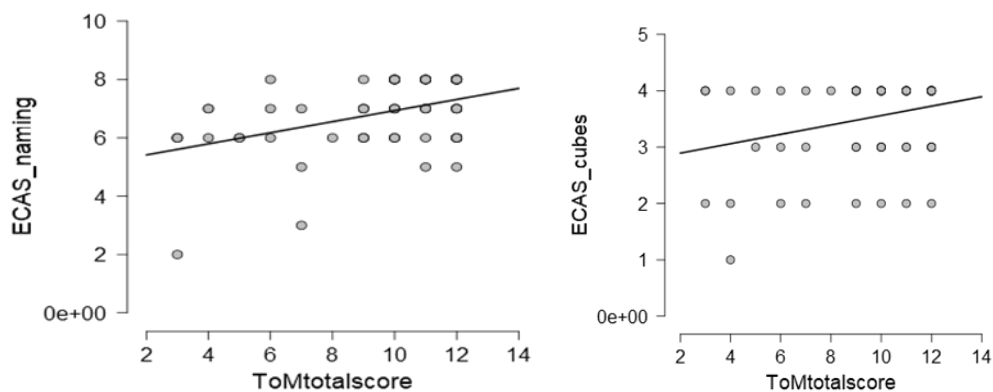**Correlation between ToM and other cognitive functions in ALS**

We found significant correlation between social cognition total score and ECAS Language ($r = 0.047$; $p = 0.003$) and ECAS Visuospatial Functions ($r = 0.455$; $p = 0.002$). We did not find any association between social cognition total score and ECAS Executive Functions ($r = 0.221$; $p = 0.159$), ECAS Verbal Fluency ($r = 0.175$; $p = 0.273$) or ECAS memory ($r = 0.184$; $p = 0.249$).
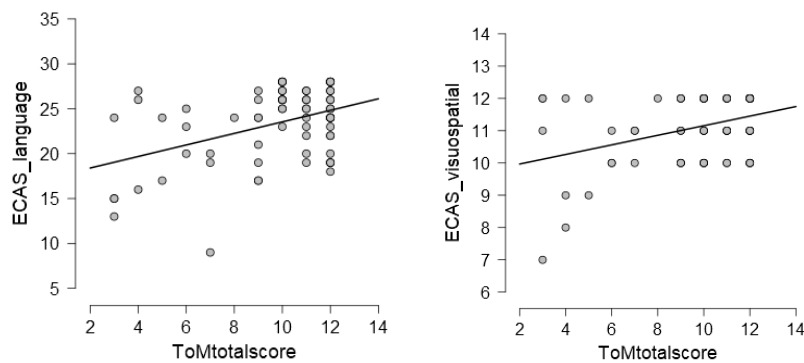
Figure 4. Scatterplot revealing correlation between ToM total score and ECAS language (left panel) and ECAS visuospatial (right panel) performance.

With regards to specific subtests of the above mentioned ECAS subdomains that were associated with social cognition (i.e. language and visuospatial functions), we found that social cognition was significantly associated with ECAS Naming (r = 0.435; p = 0.004) and ECAS Cubes (r = 0.413; p = 0.007) subtests.

Figure 5.Scatterplot revealing correlation between ToM total score and ECAS naming subtest from language domain (left panel) and ECAS cubes subtest from visuospatial domain (right panel).

Correlation between ToM and clinical parameters in ALS

There was no significant correlation between social cognition total score and patients' clinical parameters (disease duration, ALSFRS-R, progression rate). We did not find any significant difference between peripheral and bulbar onset subgroups.

Discussion

The present study provided further evidence regarding impaired affective TOM in a well-characterized group of non-demented ALS patients, revealing that approximately one out of three non-demented patients shows impaired affective TOM, as determined by eye gaze in Judgement of Preference task of the ECAS scale. In our group, this impaired performance was unrelated to patients' clinical status and was not driven by any executive dysfunction; yet, it was more evident in patients with impaired cognition in general and was associated with patients' language and visuospatial performance.

ToM and type of errors in ALS

The fact that 31% of patients had impaired performance on affective T0M based on normative data was reflected in the overall significant differences between ALS patients and HC on this simple task which assesses the emotional component of ToM. Our findings are in line with previous studies as reviewed in recent meta-analysis and review papers (Bieldman et al., 2016; Bora, 2017; Christidi et al., 2018) and further signify the importance of measuring social cognition in ALS even with a brief task such the one provided by the ECAS scale. This importance is addressed by the inclusion of social cognition domain in revised Strong's criteria for ALS-FTD spectrum (Strong et al., 2017). A significant proportion of cognitively impaired ALS patients were also impaired in ToM (45% vs. 15% in cognitively non-impaired ALS patients), indicating that the worse the cognitive state of ALS patients the more likely the impairment in ToM.

With regards to the type of errors, we found that ALS patients produced much more "unclassified" than "favorite" errors (a pattern which was also observed in HC) and made significantly more errors of both types compared to HC. This may suggest that our non-demented ALS patients did not have significant difficulties in inhibiting egocentric processing, a deficit which is prominent in patients with the behavioral variant of FTD (bvFTD). Of note, secondary analysis did not show any significant association between ECAS Behavioral score and social cognition measures in our group. It is worth mentioning that all patients complied with tasks instructions when asked for their personal preference in pre-experimental task condition and we thus assume that failures in the experimental condition are unlikely to be secondary to comprehension impairment. In the literature, there are conflicting findings regarding the type of errors. Girardi and colleagues (2011) in non-demented ALS patients found equal number of "favorite" and "unclassified" errors (Girardi et al.,2011). On the other hand, there are studies which found a higher number of "favorite" errors. These findings might underlie difficulties related to egocentric process and inability to shift attention which might be associated with the executive component of social cognition (Van der Hulst et al., 2014). FTD patients

produce a higher number of "favorite" errors than patients with other neurodegenerative diseases (i.e. Huntington's disease), being no longer able to inhibit their favorite preference, a deficit which is consistent with frontal lobe dysfunction (Snowden et al., 2003). Due to these conflicting findings and considering that the type of errors has not been thoroughly studied in ALS specifically without dementia, further investigation is definitely needed in larger sample sizes with additional neuroimaging techniques to identify the anatomical substrate of each type of errors.

ToM and clinical features in ALS

Previous studies identified a significant correlation between symptoms onset and social cognition performance; patients with bulbar onset scored worse than patients with spinal onset as determined by Eye Task (Burke et al.,2016a; Trojsi et al.,2016). However, we did not find any association between patients' clinical status and their performance in ToM.

ToM and other cognitive functions in ALS

There is still a debate about cognitive correlates of ToM and other social cognition compoments; some studies indicate an association between social cognition and executive functions (e.g. Gibbons et al., 2007; Watermeyer et al., 2015) and verbal fluency in particular as a part of executive functions (Cavallo et al., 2011;Meier et al.,2010) in non-demented ALS patients while others have failed to find such an association (e.g Trojsi et al., 2016). Our observation regarding significant correlation between a task with low executive demands and language and visuospatial function may suggest the independence between executive abilities and ToM performance, at least in our sample of non-demented ALS patients with the current methodological approach. Similar findings has led to the conclusion that the affective component of ToM involves medial prefrontal networks (Bertoux et al.,2016;Shamay-Tsoory et ., 2005) in contrast to executive dysfunction which is related to dorsolateral prefrontal networks (Roca et al,. 2011). Trojsi and colleagues (2016) recently found significant correlation between ToM and memory function, suggesting the participation of hippocampus volume in ALS cognitive profile and ToM. These conflicting findings indicate that anatomical background has not been found yet. It has been suggested that ToM is not a single cognitive ability grounded in a single set of brain regions, in favor of the possible existence of a distributed brain network (Schaafsma et al., 2015). In line with this suggestion, recent evidence from axonal stimulation mapping studies suggests that at least two white matter tracts in the right hemisphere may be involved in face-based mentalizing (i.e. a component of social cognition), that is the inferior fronto-occipital fasciculus and superior longitudinal/arcuate fasciculus (Nakajima et al.,2017).

Our study highlights the involvement of language and visuospatial functions in one component of social cognition, i.e. affective ToM. From a developmental point of view, social cognition is required for children to acquire language, deduce word meanings and communicate pragmatically (Clark, 1987; Macnamara, 1972). In addition, language is necessary for people to share their thoughts and emotions and provides a powerful tool for social cognition, one that is at the center of human culture (Fitch, 2010). Also, our findings support a significant correlation between social cognition and visuospatial abilities. Thakkar & Park (2010) provide similar findings in healthy participants suggesting a common link between the ability of visuospatial transformation and the internal representations and interactions with the physical world. In addition, the role of visuospatial abilities in ToM has been reported in patients with Parkinson's disease, supporting that visuospatial deficits are associated with patients' social interaction and activities in daily living (McKinlay et al ., 2013).

Our correlation findings regarding ToM, language and visuospatial functions might imply not only the common origins and evolution between ToM, language and spatial perception but also that our ability to communicate to each other or to represent an abstract figure of thought are very important in order to feel the emotions of others people and to understand the difference with our feelings (Dehaene and Cohen, 2007; Gallese and Lakoff, 2005; Seyfath et al., 2014;). It has been suggested that three sorts of cognition which all involve discrete elements and rule-governed computations, might represent precursors of language (Hauser et al., 2002), i.e. orientation and navigation (Menzel , 2011), number (Cantlon & Brannon, 2007) and social cognition (Worden, 1998; Cheney & Seyfarth, 1990), and that social cognition might be the most likely candidate as a language precursor (Seyfath et al., 2014). An explanatory framework has recently gained attention in the study of ToM and visuospatial abilities (Gallese and Lakoff, 2005; Dehaene and Cohen, 2007). It has been supposed that new cognitive capacities may have emerged over the course of evolution when brain regions originally devoted to specific functions were repurposed and recombined in novel ways to process additional kinds of information. In this line, the ability to observed special relationships, to represent an abstract relation until to understand how a person feels may share common pathways, although to what extent this overlap is a results of evolution remains an open question. On the other hand, relatively recent evidence in the study of ALS and its neurodegenerative spectrum in FTD have interlinked functional complexes which have their origins in evolutionary adaptations (Eisen et al.,2013) and interpret patients' motor and extra-motor deficits based on the progressive degeneration over distributed interlinked networks (Bede et al., 2016; Bede et al., 2018; Henderson et al., 2018; Martin & Swash, 2015; Trojsi et al., 2012;).

Limitations

Limitations of the present study includes the evaluation of only one subcomponent of social cognition, which is the affective ToM requiring preference judgement based on eye gaze from a picture and inferences regarding one's emotions. Future studies are warranted to include more sophisticated measures to test the type of errors and also addresses the issue of impaired ToM and other social cognition components both in experimental environments (such the ones related to neuropsychological evaluation) and patients' everyday life. To this point, the evaluation of patients' social cognition impairment in association to their quality of life and their caregivers' burden is also important.

Conclusion

This study demonstrated evidence of affective ToM dysfunction in non-demented ALS using a task with low executive demand and highlighted a significant association between affective ToM, language and visuospatial dexterities, which might possibly taps onto common evolutionary patterns of these functions and ALS-related hypothesis regarding evolutionary perspective of motor and extra-motor symptoms based on degeneration across corresponding networks. From a clinical point of view, our findings should be considered even when patients are examined using brief screening measurements since this abnormal behavior might contribute to patients' social interaction with their careers, problems using social cues to understand the emotions of others and difficulty in attributing to others a mental state that differs from their own. A cognitive/behavioral intervention for patients and their caregivers towards social cognition dysfunction is warranted.

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