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Episodic memory and learning rates in amyotrophic lateral sclerosis without dementia

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ABSTRACT

In amyotrophic lateral sclerosis (ALS), memory deficits may be primary or secondary to executive dysfunction. We assessed episodic memory and executive function of non-demented ALS patients, comparing episodic memory profiles and learning rates of ALS patients with those of mild cognitive impairment (MCI) subjects and cognitively healthy controls (HC). In a multidisciplinary tertiary centre for motor neuron disease, 72 non-demented ALS patients, 57 amnestic MCI (aMCI), 89 single non amnestic MCI with compromised executive functions (dysexecutive MCI), and 190 HC were enrolled. They were screened using the Frontal Assessment Battery and Mini Mental State Examination. Episodic memory performances and learning rates were tested using the Rey Auditory Verbal Learning Test (RAVLT). Episodic memory dysfunction (immediate recall) was found in 14 ALS patients (19.4%). The ALS group had lower performance than HC on immediate recall, without differences in learning rate, and better performance than aMCI subjects on all RAVLT measures. Compared to dysexecutive MCI subjects, ALS patients had only better verbal learning abilities. ALS patients with executive dysfunction had a lower score on immediate and delayed recalls, verbal learning, and primacy effect than ALS patients without executive dysfunction. The immediate recall among couples of diagnostic groups differed in a statistically significant way except for the ALS/dysexecutive MCI groups. In ALS patients, episodic memory performances and learning rates appeared to be better than

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in aMCI subjects and similar to those with dysexecutive MCI, suggesting also a secondary functional damage due to executive impairment.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a multisystem disorder with motor and cognitive involvement (Lomen-Hoerth et al., 2003; Phukan, Pender, & Hardiman, 2007). Although ALS is primarily a motor system degeneration, it is now well recognized that motor symptoms might be present in a spectrum of cognitive dysfunction, ranging from mild cognitive impairment (MCI) (35%) to overt dementia (15%), typically frontotemporal dementia (FTD) (Montuschi et al., 2014; Phukan et al., 2012; Strong et al., 2009). The presence of this complex cognitive impairment has implications for clinical decision, patient compliance to medical interventions, and survival (Elamin et al., 2011).

In nondemented ALS patients, the most commonly reported deficits are in the executive domains, in particular on verbal fluency abilities (Abrahams et al., 2000; Phukan et al., 2012; Ringholz et al., 2005; Volpato et al., 2010). There is evidence that cognitive profile in ALS, however, is not characterized exclusively by executive dysfunction, but involves several cognitive domains, including memory (Abrahams, Newton, Niven, Foley, & Bak, 2014; Beeldman et al., 2016; Montuschi et al., 2014; Phukan et al., 2012). Memory deficits can derive from temporal lobe involvement or can be secondary to prefrontal dysfunction. However, the evidences are weak and conflicting (Machts et al., 2014; Mantovan et al., 2003; Raaphorst, de Visser, Linssen, de Haan, & Schmand, 2010; Vellage et al., 2016). While several studies showed that memory deficits are a primary dysfunction, independent from executive impairment (Elamin et al., 2013; Raaphorst et al., 2015), other studies considered memory impairment secondary to executive dysfunction (Consonni et al., 2017; Grossman et al., 2008; Machts et al., 2014; Mantovan et al., 2003). The memory impairment in ALS may be dependent on hippocampal damage as reported in neuropathological and neuroimaging studies (Bede et al., 2013; Brettschneider et al., 2013; Takeda, Uchihara, Arai, Mizutani, & Iwata, 2009). Some reports showed that the memory in ALS patients without dementia showed a correlation between the hippocampal volume loss and severity of memory impairment (Abdulla et al., 2014; Raaphorst et al., 2015). Neuropsychological tests such as the Rey Auditory Verbal Learning Test (RAVLT), commonly used in clinical practice to assess verbal episodic memory in many neurodegenerative disorders including ALS, could be modified by the presence of executive dysfunctions, affecting the slope of the curve of learning (Consonni et al., 2012). The Frontal Assessment Battery (FAB) has shown a good validity as a screening instrument to detect executive dysfunction in ALS (Barulli et al., 2015).

Memory impairment in subjects with MCI is often in a transition stage between normal age-related decline and the more serious clinical syndromes associated with Alzheimer's disease (AD) pathology. Furthermore, many ALS patients are in the same age range of increased risk of MCI or AD with higher possibility of developing cognitive disorders (Logroscino et al., 2010). Episodic memory tests with multiple learning-test trials are sensitive to detect memory impairment in MCI, involving complex memory processes, such as the learning rate, i.e., the ability to integrate information from trial to trial, which may take different patterns of impairment in AD and in MCI patients (Moulin, James, Freeman, & Jones, 2004). The learning rate can be deduced by the slope of the learning curve (Lezak, 2004). The learning rate has been found impaired in amnestic MCI (aMCI) patients compared to cognitively normal older adults, in particularly with a deceleration of learning in tests using word lists (Moulin et al., 2004). The aims of the present study were to assess episodic memory and executive function in ALS patients without dementia, and to compare episodic memory profiles and learning rates of ALS with cognitively healthy controls (HC) and MCI subjects (amnestic and dysexecutive patterns).

2. Methods

2.1. Participants

The present retrospective observational study was conducted on the basis of the guidelines for Good Clinical Practice, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and was approved by our local Institutional Review Board. In the period between January 2010 and December 2014, we enrolled consecutive ALS patients referred to the Neurodegenerative Disease Unit, University of Bari 'Aldo Moro', Bari, Italy, a tertiary center with referral of the whole spectrum of neurodegenerative diseases. The ALS diagnosis was based on El Escorial Criteria (Brooks, 1994). We excluded subjects with: 1) Mini Mental State Examination (MMSE) score lower than 26 (Magni, Binetti, Bianchetti, Rozzini, & Trabucchi, 1996), 2) with dementia diagnosed using the criteria defined by DSM-5 for dementia syndrome (American Psychiatric Association, 2013). All cases underwent a neurological examination by ALS-expert neurologists with identification of upper motor neuron (UMN) and lower motor neuron (LMN) signs and in their distribution in the four body regions. Site of onset (bulbar/spinal), time to diagnosis (time from the onset of the first symptom and the diagnosis of the disease), and disease duration (time from symptom onset to evaluation) were explored. ALS disease stage was based on the King's clinical staging system (Roche et al., 2012). Functional impairment was evaluated with the ALS Functional Rating Scale-revised (ALSFRS-R) (Cedarbaum et al., 1999) and Manual Muscle

Testing (MMT) (Great Lakes ALS Study Group, 2003). Forced vital capacity (FVC) was chose as indicator of respiratory function assessed with spirometry. In the same period, we enrolled MCI patients and HC with frequency matched by age and sex. MCI patients were diagnosed according to the International Working Group on Mild Cognitive Impairment criteria and subdivided in aMCI if only the memory domain was impaired, and single non-amnestic MCI (naMCI) if the memory domain was not impaired with impairment only in a non-memory domain (in particular, we selected subjects with compromised executive functions, i.e., dysexecutive MCI) (Winblad et al., 2004). A group of HC without a prior history of neurological or psychiatric disorders were enrolled also by General Practitioners from the same geographic area of the center. All subjects provided written informant consent before enrollment.

2.2. Cognitive assessment

For all enrolled subjects, the cognitive assessment encompassed: 1) MMSE for global cognitive functioning (Magni et al., 1996) and 2) FAB for executive functions (Dubois, Slachevsky, Litvan, & Pillon, 2000). Verbal episodic memory performance was tested using the Italian version of RAVLT through 5 consecutive recall trials of a list of 15 unrelated words, followed by an immediate recall trail and a delay trial after 15 min (Carlesimo, Caltagirone, & Gainotti, 1996; Woodard, Dunlosky, & Salthouse, 1999). We examined following measures in RAVLT: immediate recall (sum of trial 1–5); delayed recall (free recall after 15 min); verbal learning (difference between the number of items correctly recalled after trial 5 and trial 1); verbal forgetting (difference between the items correctly recalled after trial 5 and the trial 6); verbal retention (difference between the items correctly recalled after trial 6 and trial 5); primacy effect score (the first 5 words of the list); recency effect (the last 5 words of the list); memory span (capacity to learn information in Trial 1); rate of learning (performance trial-by-trial). MCI subjects were evaluated with MMSE, FAB, and RAVLT and underwent also a comprehensive assessment to define their cognitive profile (aMCI *vs* dysexecutive MCI) using a neuropsychological test battery exploring sustained attention, information processing speed, language production, verbal fluency, visual perception, and visuoconstructional reasoning as detailed elsewhere (Palmer et al., 2014).

2.3. Statistical analysis

Demographic and cognitive variables were evaluated using summary statistics (mean, standard deviation, median, range, percentage). Demographic characteristics between diagnostic groups were analyzed using Kruskal–Wallis test (age, years of education) and Chi-squared test (sex distribution).

ALS groups subdivided for absence/presence of episodic memory and executive dysfunctions were compared through Mann–Whitney *U* test for quantitative variables and Chi-squared test for qualitative ones. To evaluate differences in cognitive variables between diagnostic groups accounting for demographic characteristics an Analysis of Covariance (ANCOVA) was applied, with the factor groups (ALS, HC, aMCI, and naMCI) and sex (male and female) and the covariates age and education years. Subsequently, post-hoc Tukey's HSD test were applied when appropriate. The Pearson product-moment correlation was conducted to test whether quantitative variables in the ALS group were correlated. A linear regression was used to assess association between episodic memory measures and executive function, adjusting for age and ALSFRS-R in the ALS group. Interaction between age and executive function was also tested. To compare learning rates for item (average change across 5 trials) between diagnostic groups a Linear Mixed effect Model (Random Intercept) was applied, in order to account for confounding and within subject correlation. The threshold for statistical significance was set at $p < .05$. All statistical analyses were conducted using R (v 3.3.1) and Rstudio (v .99.903).

3. Results

We enrolled 72 nondemented ALS patients, 57 aMCI subjects, 89 naMCI with impaired executive functions (dysexecutive MCI), and 190 HC. Demographic and clinical data are summarized in Table 1. Sixteen ALS patients (22.2%) showed executive dysfunction, 14 patients (19.4%) had a memory impairment on RAVLT immediate recall, and 5 ALS patients (6.9%) had a memory impairment on RAVLT delayed recall. The comparisons between demographic and clinical data of AL patients subdivided for presence/absence of memory or executive dysfunctions are showed in Table 2. ALS patients with memory dysfunction showed a worst respiratory function ($p = .02$) than ALS without memory dysfunction. There were no difference between groups on other demographic and clinical variables, including the ALS staging. MMSE and FAB scores were not correlated with disease duration, FVC, MMT and ALSFRS-R. In ALS patients, immediate recall showed a positive correlation with FAB ($r = .44$; $p = .0001$), MMSE ($r = .35$; $p = .0025$), FVC ($r = .36$; $p = .010$) and ALSRFS-R ($r = .38$; $p = .001$). FAB score correlated with recency effect score ($r = .31$; $p = .007$). Among ALS patients, a one point improvement in FAB score was associated with an improvement of 1.20 points in RAVLT immediate recall score ($p < .001$) and an improvement of .44 points in RAVLT delayed recall score ($p < .001$), adjusting for age and ALSRFS-R. These effects of executive function on memory variables did not change in different strata of age.

The unadjusted comparative analyses among different groups on RAVLT measures are showed in Table 3. The ALS group had lower performance than HC on immediate recall ($p = .004$) and the two groups did not differ on others RAVLT measures, adjusting for age, sex and education. ALS patients had better performance on immediate ($p < .0001$) and delayed ($p < .0001$) recalls, verbal learning ($p < .0001$), forgetting ($p < .0001$), and retention ($p < .0001$), primacy (<.0001) and recency effects ($p = .007$) than the aMCI group in the adjusted analysis. ALS group had higher verbal learning score than the naMCI group (dysexecutive MCI) ($p = .02$) adjusting for age, sex and education. The immediate recall among couples of diagnostic groups

Table 1 – Demographic and clinical data of the sample subdivided in amyotrophic lateral sclerosis (ALS) patients, cognitively healthy controls (HC), non amnestic mild cognitive impairment (naMCI, dysexecutive MCI) subject subjects, and amnestic MCI (aMCI).

	ALS	HC	naMCI	aMCI	*p* value
	n = 72	n = 190	n = 89	n = 57	
Age, years					
media ± SD	64.38 ± 7.47	65.63 ± 4.61	65.03 ± 6.61	67.02 ± 7.41	.040
Median	63.50	66.00	66.00	69.00	
(Range)	(42.00–82.00)	(42.00–82.00)	(43.00–80.00)	(49.00–79.00)	
Education, years					
media ± SD	9.06 ± 4.09	8.73 ± 3.82	7.62 ± 3.74	8.02 ± 4.07	.014
Median	8.00	8.00	5.00	5.00	
(Range)	(.00–18.00)	(3.00–18.00)	(3.00–18.00)	(2.00–18.00)	
Sex					
Male Number (%)	47 (65.28)	106 (55.79)	41 (46.07)	31 (54.39)	.1117
Female Number (%)	25 (34.72)	84 (44.21)	48 (53.93)	26 (45.61)	
ALS diagnosis					
Number (%)					
Definite	25 (34.72%)				
Probable	23 (31.94%)				
Possible	14 (19.44%)				
Suspect	10 (13.89%)				
Site of onset					
Number (%)					
Spinal	63 (87.50)				
Bulbar	9 (12.50)				
ALS staging					
Number (%)					
1	17 (24.29%)				
2	28 (40%)				
3	17 (24.29%)				
4	8 (11.43%)				
Time to diagnosis					
media ± SD	18.13 ± 20.81				
Median (Range)	12.00 (2.00–132.00)				
Disease duration (months)					
media ± SD	11.45 ± 8.62				
Median	9.00				
(Range)	(.00–36.00)				
ALSFRS-R					
media ± SD	36.41 ± 6.69				
Median	39.00				
(Range)	(20.00–46.00)				
FVC					
media ± SD	88.27 ± 19.82				
Median	92.70				
(Range)	(42.50–124.90)				
MMT					
media ± SD	8.20 ± 1.19				
Median	8.30				
(Range)	(5.00–10.00)				

SD: standard deviation; ALSFRS-R: ALS Functional Rating Scale-revised; FVC: forced vital capacity; MMT: manual muscle testing.

differed in a statistically significant way except for the ALS/naMCI (dysexecutive MCI) groups ($p = .50$) adjusting for age, sex and education.

The comparison of RAVLT measures between ALS patients with and without executive dysfunction are showed in Table 4. ALS group with executive dysfunction had a lower score on immediate recall ($p = .003$), delayed recall ($p = .008$), verbal learning ($p = .02$) and primacy effect ($p = .0001$) than ALS patients without executive dysfunction (Table 4). The adjusted rate of learning in ALS patients was not different than in HC ($p = .0769$). The aMCI and naMCI (dysexecutive MCI) groups had an adjusted learning rate worse than HC (aMCI/HC point estimate difference in slopes = −.67, $p = .0020$; ALS/naMCI point estimate difference in slopes = −.16, $p < .0001$). Unadjusted learning curves from trial 1 to trial 5 are showed in Fig. 1. The adjusted learning rate worsened with increasing age ($p < .0001$) and in male subjects ($p = .0002$). On the contrary, the adjusted learning rate increased with highest educational level ($p < .0001$).

Table 2 – Comparison of demographic and clinical data of amyotrophic lateral sclerosis (ALS) patients subdivided for absence/presence of memory and executive dysfunctions.

	ALS with memory dysfunction	ALS without memory dysfunction	*p* value	ALS with executive dysfunction	ALS without executive dysfunction	*p* value
	n = 14	n = 58		n = 16	n = 56	
Age, years						
media ± SD	64.00 ± 5.87	64.46 ± 7.84	.9	63.81 ± 7.19	64.53 ± 7.59	.6
Median	64.50	63.00		63.50	63.50	
(Range)	(53.00–72.00)	(42.00–82.00)		(53.00–82.00)	(42.00–81.00)	
Education, years						
media ± SD	8.42 ± 3.75	9.20 ± 4.17	.5	7.43 ± 3.70	9.51 ± 4.10	.05
Median	8.00	8.00		6.50	8.00	
(Range)	(4.00–13.00)	(.00–18.00)		(3.00–13.00)	(.00–18.00)	
Sex						
Male, Number (%)	10 (71.43)	37 (63.79)	.8	10 (62.5)	37 (66.07)	1
Female, Number (%)	4 (28.57)	21 (36.21)		6 (37.5)	19 (33.93)	
ALS staging Number (%)						
1	3 (21.43)	14 (25.00)	.63	3 (18.75)	14 (25.93)	.74
2	5 (35.71)	23 (41.07)		6 (37.5)	22 (40.74)	
3	3 (21.43)	14 (25.00)		4 (25.00)	13 (24.07)	
4	3 (21.43)	5 (8.93)		3 (18.75)	5 (9.26)	
ALSFRS-R						
media ± SD	33.33 ± 6.49	37.13 ± 6.58	.08	33.15 ± 7.45	37.26 ± 6.27	.08
Median	33.00	39.00		33.00	39.00	
(Range)	(22.00–42.00)	(20.00–46.00)		(20.00–43.00)	(23.00–46.00)	
FVC						
media ± SD	74.01 ± 21.91	91.83 ± 17.81	.02	85.20 ± 20.95	89.03 ± 19.72	.7
Median	72.55	93.60		89.50	92.70	
(Range)	(43.20–104.40)	(42.50–124.90)		(43.20–106.20)	(42.50–124.90)	
MMT						
media ± SD	7.73 ± 1.09	8.30 ± 1.19	.1	8.27 ± .77	8.18 ± 1.27	1
Median	7.60	8.45		8.60	8.20	
(Range)	(6.30–9.40)	(5.00–10.00)		(6.90–9.40)	(5.00–10.00)	

SD: standard deviation; ALSFRS-R: ALS Functional Rating Scale-revised; FVC: forced vital capacity; MMT: manual muscle testing.

4. Discussion

In this observational study from a tertiary center, episodic memory dysfunction (immediate recall) was found in 14 ALS patients (19.4%). The ALS group had lower performance than HC on immediate recall, without differences in the rate of learning. ALS patients had better performance than aMCI subjects on all RAVLT measures. Compared to dysexecutive MCI subjects, ALS patients had similar episodic memory performances with better verbal learning abilities. ALS patients with executive dysfunction had a lower score on immediate and delayed recalls, verbal learning, and primacy effect than ALS patients without executive dysfunction. The immediate recall among couples of diagnostic groups differed in a statistically significant way except for the ALS/dysexecutive MCI groups.

In the present study, approximately 20% of patients with ALS had episodic memory dysfunction characterized by immediate recall deficits. This finding was in line with several other studies identifying a subgroup of ALS patients with prominent episodic memory impairment (Mantovan et al., 2003; Phukan et al., 2012; Ringholz et al., 2005), particularly immediate verbal recall deficits (Consonni et al., 2012, 2017; Raaphorst et al., 2010). Episodic memory was more impaired on immediate recall compared to delayed recall. In the present report, only 7% of ALS patients showed a delayed recall impairment. Delayed recall appears to be a more pure measure of memory, while learning trials and immediate recall included also attentive components (Abdulla et al., 2014). This finding also confirmed studies showing that memory impairment in ALS may be due to attention/executive dysfunction (Consonni et al., 2017; Grossman et al., 2008; Machts et al., 2014; Mantovan et al., 2003). In the present study, the presence of immediate verbal recall deficits in ALS was also confirmed by the comparison of ALS patients with the MCI subtypes. Compared to dysexecutive MCI subjects, ALS patients had similar episodic memory performances with better learning/encoding abilities. ALS patients had higher performance than aMCI subjects on all different RAVLT episodic memory measures. In this latter group, the episodic memory dysfunction was characterized by prominent deficit in delayed recall. Delayed recall deficit in the aMCI group was the main feature and this is consistent with aMCI being a likely early clinical stage of AD (Winblad et al., 2004). Therefore, the episodic memory performances in our ALS patients were distinctly different than those of aMCI subjects. These

Table 3 – Comparative analysis on Rey Auditory Verbal Learning Test (RAVLT) measures and Mini Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores among groups of amyotrophic lateral sclerosis (ALS) patients, cognitively health controls (HC), non amnestic mild cognitive impairment (naMCI, dysexecutive MCI) subjects and amnestic MCI (aMCI).

RAVLT measures	ALS	HC	naMCI	aMCI	*p* value
	n = 72	n = 190	n = 89	n = 57	
Immediate recall	33.97 ± 9.70	36.51 ± 7.59	32.04 ± 8.34	22.65 ± 6.26	<.0001
	33.00 (10.00–55.00)	36.00 (17.00–62.00)	31.00 (17.00–57.00)	24.00 (9.00–36.00)	
Delayed recall	7.11 ± 2.64	7.47 ± 2.17	6.48 ± 2.06	1.81 ± 1.49	<.0001
	7.00 (2.00–13.00)	7.00 (4.00–14.00)	6.00 (4.00–13.00)	2.00 (.00–5.00)	
Verbal learning	5.39 ± 2.49	4.97 ± 2.17	4.38 ± 2.10	2.39 ± 1.91	<.0001
	6.00 (−1.00–13.00)	5.00 (.00–12.00)	4.00 (.00–10.00)	3.00 (−2.00–8.00)	
Verbal forgetting	1.93 ± 1.92	1.93 ± 2.01	1.78 ± 1.68	3.54 ± 1.56	<.0001
	2.00 (−7.00–6.00)	2.00 (−5.00–7.00)	2.00 (−2.00–8.00)	3.00 (.00–7.00)	
Retention	−1.93 ± 1.92	−1.93 ± 2.01	−1.78 ± 1.68	−3.54 ± 1.56	<.0001
	−2.00 (−6.00–7.00)	−2.00 (−7.00–5.00)	−2.00 (−8.00–2.00)	−3.00 (−7.00–.00)	
Primacy effect	12.61 ± 4.62	13.34 ± 3.78	11.19 ± 4.01	8.36 ± 4.38	<.0001
	13.00 (1.00–22.00)	14.00 (4.00–23.00)	11.00 (2.00–20.00)	9.00 (.00–19.00)	
Recency effect	11.64 ± 3.48	12.47 ± 3.67	11.62 ± 3.67	9.20 ± 4.49	<.0001
	12.00 (5.00–20.00)	13.00 (1.00–22.00)	11.00 (3.00–21.00)	9.00 (.00–22.00)	
MMSE	28.71 ± 1.16	29.15 ± 1.1	28.24 ± 1.6	26.75 ± 2.2	<.0001
	29.00 (26.00–30.00)	30.00 (26.00–30.00)	29.00 (23.00–30.00)	27.00 (18.00–30.00)	
FAB	15.5 ± 2.47	16.16 ± 2.02	13.63 ± 2.87	13.02 ± 3.71	<.0001
	16.00 (6.00–18.00)	17.00 (8.00–18.00)	14.00 (5.00–18.00)	13.00 (7.00–29.00)	

features of episodic memory impairment may be explained in the context of coexisting executive dysfunction in ALS. The qualitative differences in episodic memory between ALS patients and aMCI subjects may depend on processes involving the temporal lobe (Machts et al., 2014). According to recent findings, frontal dysfunction involved energization (preparing the neural system to respond) and we may assume that episodic memory dysfunction in ALS may be secondary to executive dysfunction, a profile that may be indicative of the nature of frontal neurodegeneration in ALS (Gillingham et al., 2017). In fact, episodic memory performance depends on engagement of the executive functions, particularly in the use of recall strategies. The failure of executive functioning during verbal list learning was confirmed by the present findings on inaccurate recall in ALS patients compared to HC. Moreover, the present findings showed that the ALS group had higher primacy and recency effects than aMCI subjects and that FAB score was correlated with recency effect score only.

The present findings also suggested that ALS and aMCI differed on learning rate, i.e., the ability to integrate information trial-by-trial (Lezak, 2004). The learning rate in ALS patients was similar to HC, but it had better performance than in MCI subjects (amnestic and dysexecutive). ALS patients had a highest slope of the learning curve than MCI subjects, particularly than aMCI subjects. Similarly to MCI subjects, ALS patients had a lower initial learning, i.e., the memory span, than HC, but subsequently, in ALS patients

Table 4 – Comparison of Rey Auditory Verbal Learning Test (RAVLT) measures between amyotrophic lateral sclerosis (ALS) with executive dysfunction and ALS without executive dysfunction.

RAVLT measures	ALS with executive dysfunction	ALS without executive dysfunction	*p* value
	n = 16	n = 56	
Immediate recall	27.37 ± 9.25	35.85 ± 9.05	.003
	26.00 (10.00–47.00)	36.00 (14.00–55.00)	
Delayed recall	5.56 ± 1.93	7.55 ± 2.66	.008
	5.00 (2.00–9.00)	7.00 (3.00–13.00)	
Verbal learning	4.12 ± 2.50	5.75 ± 2.39	.02
	4.50 (−1.00–9.00)	6.00 (.00–13.00)	
Verbal forgetting	1.68 ± 2.65	2.00 ± 1.68	1
	2.00 (−7.00–4.00)	2.00 (−2.00–6.00)	
Retention	−1.68 ± 2.65	−2.00 ± 1.68	1
	−2.00 (−4.00–7.00)	−2.00 (−6.00–2.00)	
Primacy effect	9.00 ± 4.14	13.64 ± 4.24	.0001
	8.00 (4.00–20.00)	13.00 (1.00–22.00)	
Recency effect	11.06 ± 3.95	11.80 ± 3.34	.4
	11.00 (5.00–18.00)	12.00 (5.00–20.00)	

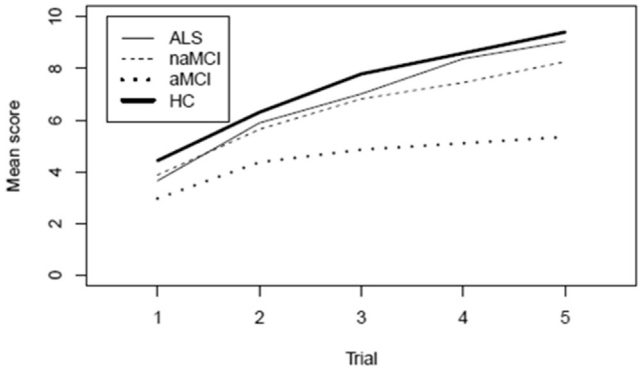

Fig. 1 – Unadjusted learning curves from trial 1 to trial 5 in amyotrophic lateral sclerosis (ALS) patients, non-amnestic mild cognitive impairment (naMCI, dysexecutive MCI) subjects, amnestic MCI (aMCI), and cognitively healthy controls (HC).

there was a learning improvement in contrast with MCI subjects. Therefore, in ALS patients the ability to increase learning was similar to that of HC. The present findings allowed to characterize better the memory profile of ALS patients compared to HC and MCI subjects (amnestic and dysexecutive). The ALS memory pattern was similar to that of dysexecutive MCI subjects on immediate recall, but different on learning increment. These results were consistent with the studies in which the MCI subjects exhibited a deceleration of learning increment, with a shallower slope of the learning curve than controls with an impaired learning memory (Wang, Li, Li, & Zhang, 2013). To the best of our knowledge, the present study was the first to analyze the learning rate in ALS patients compared to MCI subjects and HC.

We must acknowledge that the present study had several limitations. The absence of an extensive evaluation of the executive functions did not allow the correlation of episodic memory profiles with specific executive components in order to further differentiate memory features in ALS and different MCI subtypes. Furthermore, we did not have data collected using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS), a recent and suitable cognitive tool to screen all cognitive domains in ALS (Abrahams et al., 2014), to better detect the profile of cognitive and behavioral changes in our ALS patients. However, the ECAS was not specifically focused on executive functions, evaluating five cognitive (social cognition, language, fluency, memory, and visuospatial functions), and five behavioral domains, characterizing FTD. Again, we did not have genetic data for the whole sample of the present study, in particular for the C9orf72 repeat expansion status that might influence the cognitive profile of these ALS patients (Byrne et al., 2012). Finally, the sample size was relatively small. On the other hand, our evaluation of memory function permitted to evaluate the role of different components of episodic memory extensively. In conclusion, our study showed that in ALS patients an impairment of several cognitive domains including memory was present (Machts et al., 2014), and episodic memory impairment was characterized by a dysfunction of immediate verbal recall. ALS episodic memory performances were better than those in aMCI subjects and more similar to those with dysexecutive MCI. ALS patients with executive dysfunction had a lower score on immediate and delayed recalls, verbal learning, and primacy effect than ALS patients without executive dysfunction. These findings suggested that episodic memory dysfunction in ALS may be secondary to executive impairment.

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Author contributions

Dr. Barulli - study concept and design.

Dr. Piccininni - analysis and interpretation.

Dr. Di Dio - acquisition of data.

Dr. Musarò - acquisition of data.

Dr. Grasso - acquisition of data.

Dr. Tursi - acquisition of data.

Dr. Lozupone - critical revision of the manuscript for important intellectual content.

Dr. Capozzo - critical revision of the manuscript for important intellectual content.

Dr. Tortelli - critical revision of the manuscript for important intellectual content.

Pr Simone - critical revision of the manuscript for important intellectual content.

Dr. Panza - critical revision of the manuscript for important intellectual content and study supervision.

Pr. Logroscino - study concept, design, and supervision.

Supplementary data

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