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ORIGINAL ARTICLE

Cognitive impairment is associated with gait variability and fall risk in amyotrophic lateral sclerosis

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Abstract

Background: In amyotrophic lateral sclerosis (ALS), gait abnormalities contribute to poor mobility and represent a relevant risk for falls. To date, gait studies in ALS patients have focused on the motor dimension of the disease, underestimating the cognitive aspects.

Methods: Using a wearable gait analysis device, we compared gait patterns in ambulatory ALS patients with mild cognitive impairment (ALS MCI+; $n=18$), and without MCI (ALS MCI−; $n=24$), and healthy subjects (HS; $n=16$) under two conditions: (1) normal gait (single task) and (2) walking while counting backward (dual task). Finally, we examined if the occurrence and number of falls in the 3 months following the baseline test were related to cognition.

Results: In the single task condition, ALS patients, regardless of cognition, displayed higher gait variability than HS, especially for stance and swing time ($p<0.001$). The dual task condition revealed additional differences in gait variability parameters between ALS MCI+ and ALS MCI− for cadence ($p=0.005$), stance time ($p=0.04$), swing time ($p=0.04$) and stability index ($p=0.02$). Moreover, ALS MCI+ showed a higher occurrence ($p=0.001$) and number of falls ($p<0.001$) at the follow-up. Regression analyses demonstrated that MCI condition predicted the occurrence of future falls ($\beta=3.649$; $p=0.01$) and, together with executive dysfunction, was associated with the number of falls (cognitive impairment: $\beta=0.63$; $p<0.001$; executive dysfunction: $\beta=0.39$; $p=0.03$), regardless of motor impairment at clinical examination.

Conclusion: In ALS, MCI is associated with exaggerated gait variability and predicts the occurrence and number of short-term falls.

KEYWORDS
amyotrophic lateral sclerosis, cognition, falls, gait analysis, wearable sensors

INTRODUCTION

Gait is no longer considered a merely motor phenomenon but a process requiring the integrity of attentive and cognitive functions [1–3]. In amyotrophic lateral sclerosis (ALS), walking abnormalities contribute to poor mobility and represent a considerable risk for falls and fractures. Falls are common (33%) in patients with ALS [4] and death related to head-trauma secondary to falls occurs in approximately 1.7% of ambulatory patients with ALS [5]. To date, studies on gait and falls in ALS have focused on the motor aspects of the disease, such as reduced lower limb muscle strength [6, 7], changes in mobility and stance as assessed by the Timed Up and Go test [8], and the impairment of stability and postural reflexes [9], thus underestimating the cognitive dimension of the disease [10–12]. Yet, several studies in healthy elderly individuals as well as in patients with neurological disorders (e.g., Parkinson's disease, Alzheimer's disease) demonstrated the influence of executive functions and attention on gait performance [1, 2, 13–16] and fall risk [17, 18]. This is particularly true in complex gait situations, such as when performing a cognitive task while walking (dual task conditions) [19, 20].

Dual task conditions significantly affect gait variability even more than gait velocity in elderly fallers [21] and in patients with Parkinson's disease (PD) [22, 23] and Alzheimer's disease (AD) [15], likely reflecting executive dysfunctions [21]. Significant deterioration in magnitude and variability of gait parameters has been also described in patients with ALS compared with healthy controls while performing a complex mental task [24], suggesting a link between cognitive impairment and gait performance in ALS. This is particularly relevant from the clinical perspective as gait disturbances, especially in patients with neurological diseases and cognitive impairment, have been associated with an increased risk of falls [25].

Within this context, the present study had two main aims: first, to characterize the effect of a challenging cognitive task on gait variability in patients with ALS with or without cognitive impairment; and second, to assess whether impairment of cognitive functions could predict future falls.

METHODS

Patients and gait analysis

We planned to enrol at least 40 patients in line with sample size of previous studies ranging from 11 [26] to 27 [24] and based on an estimated dropout rate of 30%. Thus, we recruited 42 ambulatory patients with short-disease duration (12 months on average) and mild motor involvement (i.e., walking without assistance) from the ALS Clinic Centre Federico II University Hospital between June 2021 and June 2022, according to the following inclusion criteria: (i) diagnosis of "probable", "probable laboratory-supported" or "definite" ALS, as per the revised El Escorial criteria [27]; (ii) autonomous walk for 5 min; (iii) no use of wheelchair or assistive device for mobility (i.e., cane, walker, ankle foot orthoses); (iv) no use of non-invasive ventilation support (NIV); and (v) no comorbid conditions likely to affect gait [26]. Patients with a diagnosis of dementia [28] were excluded.

A convenience sample of healthy subjects (HS), age and sex-matched to the whole patients' group, and free from medical conditions that could interfere with motor activity (i.e., neurological, or orthopaedic disorders), was also enrolled.

At study entry, we recorded demographics and clinical history. To characterize patients' disease severity, neurological conditions were assessed by: (i) Medical Research Council (MRC) scale [29] (seven muscles for each side for upper limbs: score 0–70 points; and six muscles for each side for lower limb: score 0–60 points); (ii) ALS Functional Rating Scale-revised (ALSFRS-R); [30], by which we also computed the disease progression rate (ΔALSFRS-R: 48 – ALSFRS-R at the study inclusion/disease duration in months); and (iii) Penn Upper Motor Neuron Score (PUMNS) [31], to assess upper motor neuron (UMN) burden by totalling the number of pathological UMN signs at examination (score 0, normal, to maximum of 32, severe UMN involvement) at bulbar (scores 0–4), upper limb (scores 0–14) and lower limb regions (scores 0–14) [31]. Genetic analysis was performed in all patients, exploring *C9orf72* repeat expansion and mutations of *SOD1*, *TARDBP* and *FUS* genes.

Height and weight were measured, and body mass index (BMI) was calculated. Gait was assessed in two conditions: walking at usual speed (single task condition) and walking while performing the serial subtraction task, that is, while audibly counting backward in multiples of 7 from 150 (dual task condition). The serial subtraction task was selected based on previous research showing that it requires executive functions, such as working memory and attention, in older adults [32, 33] and in patients with PD [34, 35], MCI [36] and AD [15]. Each trial consisted of walking back and forth five times along an 8 m straight walkway with a 180 degree turn at the end. The order of the single and dual tasks was randomized.

Within dual task trials, the error rate (%) as well as the stop rate (%) were calculated by dividing the number of errors or stops by the total responses or steps, respectively, and multiplying by 100.

Measurements of gait parameters were obtained using the BTS G-Walk R (G-Sensor 2), that is, a portable, wireless, inertial system with wearable sensors, composed of a triaxial accelerometer (16 bit/axes), gyroscope (16 bit/axes) and magnetometer (13 bit ±1.200 μT). The device was attached with a semi-elastic belt to the L5 spinal segment of the participants; all recorded data were transmitted by Bluetooth to a notebook and processed using the special software program BTS G-Studio (BTS Bioengineering S.p.A., Italy) [37, 38].

Gait analysis included the following spatiotemporal parameters: cadence (steps/min), step velocity (m/s), stride length (m), and the stability index (single/double support time ratio), the averaged value (right and left) for cycle duration (s), step length (% height), stance time (% cycle), swing time (% cycle); asymmetry parameters, defined as the ratio between right and left step, of cycle duration, step length, stance and swing time. We also considered variability of spatiotemporal gait parameters indexed by the standard deviation (SD).

The magnitude of the effect of the cognitive load on gait variability measures was assessed by calculating the dual task cost (DTC%)

with the following formula: [(dual task performance − single task performance)/single task performance] × 100 [39].

Cognitive evaluation

After the clinical and gait assessment, all participants underwent an extensive neuropsychological battery.

To assess cognitive and behavioural profile, a neuropsychologist with specific expertise in ALS assessment (M.S.) administered a multi-domain battery to all participants [40, 41]. For assessing global cognitive functioning, both ALS patients and healthy individuals underwent the Italian versions of the following tests: Mini-Mental State Examination (MMSE) [42]; the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [43], a rapid screening test (15–20 min), including an ALS-specific section (assessing executive functions, social cognition, verbal fluency and language; 0–100 points), and a non-ALS specific section (that assesses memory and visuospatial abilities; 0–36 points). ECAS total score ranges from 0 (worst performance) to 136 (best performance). Moreover, a brief caregiver interview assessed behaviour changes (Behavioural Disinhibition, Apathy/Inertia, Loss of Sympathy/Empathy, Perseverative/Stereotype, Change in Eating Behaviour; from 0 to 10) and psychotic symptoms (from 0 to 3) usually associated with ALS [43].

All participants also underwent a comprehensive neuropsychological battery of tests to assess four cognitive domains: (i) executive functions, evaluated using the Frontal Assessment Battery (FAB) [44], the alternation test of ECAS [43], the phonological and semantic verbal fluency [45], the Wisconsin Card Sorting Test [46] and interference task of Stroop test [47]; (ii) memory, evaluated by means of immediate and delayed recall of 15 Rey-words [45], digit span forward test [48]; (iii) visuospatial functions, evaluated by means of clock drawing test [49], the copying task of the Rey–Osterrieth Complex Figure Test [50] and Raven's coloured progressive matrices [45]; and (iv) language, assessed by object naming, comprehension and spelling tests of ECAS [43]. Consistent with previous gait studies in older adults as well as in patients with neurodegenerative diseases, such as PD [2], ALS patients were classified as having mild cognitive impairment (MCI+) or without MCI (MCI−). MCI was determined by both a cognitive deficit not causing a significant functional decline and an impairment (at least 2 SD below the expected age and education-corrected mean score) in at least two neuropsychological tests belonging to the same cognitive domain or two neuropsychological tests belonging to different cognitive domains [51].

Fall recording

At the end of the assessment, a follow-up control visit was planned in 3 months, and the patients were instructed to report the occurrence and number of falls they experienced within this period. Three months is considered as the ideal time interval to monitor patients to assess progression, adjust care plans, and make recommendations to maximize quality of life [52].

Falls were defined as any change of balance that occurred during normal activities and resulted in the participant's body unintentionally encountering furniture, the ground, a wall or any other surface [53].

Statistical analysis

Categorical and continuous variables were analysed by means of nonparametric tests. Main effects of the dual task (within factor: single vs. dual task) and cognitive impairment (between factor: ALS MCI+ vs. ALS MCI− vs. HS) on gait parameters and their possible interactions, were assessed by Friedman's ANOVA for repeated measures. The association between clinical and neuropsychological measures (predictors) with the occurrence of future falls (dependent variable) was assessed by two binary logistic regression, whereas the association between clinical and neuropsychological measures (predictors) with the number of falls (dependent variable) was assessed by two multivariable linear regression analyses. In both regression methods, we used forward stepwise selection ($p > 0.05$ for exclusion). Age, disease severity (ALSFRS-R), disease progression rate (ΔALSFRS-R), upper motor-neuron impairment of lower limbs (PUMNS-LL), muscle strength of lower limbs (MRC-LL), presence of cognitive impairment (MCI+ and MCI−) and impaired total score on ECAS were entered as predictors variables (linear regression), or as control variables (logistic regression). Statistical analyses were computed by SPSS version 24.0 (SPSS, Chicago, IL, USA). Further statistical analysis details are provided in Appendix S1.

RESULTS

Clinical and cognitive findings

We evaluated 42 patients with a diagnosis of ALS and 16 HS. Genetic analysis was negative in all patients. Eighteen patients were classified as ALS MCI+ and 24 as ALS MCI−. The three groups did not differ on demographic variables. ALS MCI+ and ALS MCI− patients did not differ in any of the clinical variables (Table 1), but occurrence and number of falls at the follow-up as well as percentage of stops and counting errors during the dual task were significantly higher in MCI+ patients (Table 1). Specifically, MCI+ patients made more counting errors (3.0, IQR 2–3.8) compared to MCI− patients (2.0, IQR 1–3; $p = 0.022$), while the total counting did not differ in the two ALS groups (MCI+: 30.3, IQR 25.2–34.2; MCI−: 28.5, IQR 25.8–36.7; $p = 0.93$). During the dual task condition HS did not stop, and at the follow-up they did not report any falls. Importantly, at the follow-up (Table 1) ALSFRS-R (T0 vs. T1: $F = 20.002$; df = 1; $p < 0.001$; partial Eta-squared = 0.35), MRC-UL (T0 vs. T1: $F = 6.428$; df = 1; $p = 0.01$; partial Eta-squared = 0.13), MRC-LL (T0 vs. T1: $F = 4.609$; df = 1; $p = 0.03$; partial Eta-squared = 0.10), significantly worsened over

TABLE 1 Comparisons of demographic and clinical variables.

Clinical Variable	ALS MCI−	ALS MCI+	HS	*P* value	Effect size
Sample size (*n*)	24	18	16	–	–
Age (years)	55.5 (51–65)	60.5 (57.3–69.8)	56 (52–61)	0.08	0.05
Gender (F/M)	7/17	3/15	6/10	0.388	0.05
Education (years)	10.5 (8–15)	11 (8–13.8)	12.5 (10.8–15)	0.138	0.03
BMI (kg/m^2)	26 (22.8–27.8)	24.8 (23.2–29.4)	26.2 (24.2–28.3)	0.865	0.03
Disease duration (months)	14 (9–19)	10 (5–17)	–	0.217	0.51
Onset region (bulbar/spinal)	6/18	4/14	–	0.834	0.03
ΔALSFRS-R	0.8 (0.3–1.6)	0.8 (0.4–1.5)	–	0.227	0.33
Baseline (T0)					
ALSFRS-R	38 (32–41.3)	39.5 (38.3–41.8)	–	0.393	0.15
PUMNS-UL	3.5 (1–6.3)	2 (2–7)	–	0.690	0.13
PUMNS-LL	7 (4–10)	7.5 (4.5–8)	–	0.877	0.07
MRC-UL	53 (45–69)	58.5 (46–65)	–	0.740	0.06
MRC-LL	56 (50–60)	56.5 (50–58)	–	0.757	0.04
Follow-up (T1)					
ALSFRS-R	36 (31–38.5)	37 (34–40)	–	0.448	0.14
PUMNS-UL	4.0 (1–7.3)	2.5 (2–6.3)	–	0.730	0.18
PUMNS-LL	7 (4.8–9.3)	7.5 (4.5–8)	–	0.928	0.03
MRC-UL	52.5 (43.8–67)	57 (44–64.8)	–	0.769	0.05
MRC-LL	54 (48–60)	56 (48.5–58)	–	0.857	0.13
Occurrence of falls at the follow-up (yes, %)	6 (25)	14 (77.8)	–	**0.001**	1.17
Number of falls at the follow-up	0.0 (0.0–0.25)	1.0 (1.0–1.0)	–	**<0.001**	1.41
Errors rate during dual task (%)	5.9 (3.6–8.0)	10.5 (6.9–13.1)*	4.1 (0.0–8.1)	**0.002**	1.32
Stop rate during dual task (%)	0.0 (0.0–2.3)	2.4 (1.9–4.0)	–	**0.001**	0.76

Note: Values are expressed as median (interquartile range) or as frequencies and percentage. Comparisons between three groups were performed by means of non-parametric Kruskal–Wallis test (the effect size was expressed as Eta-squared coefficient; small effect = 0.02, medium effect = 0.13, large effect = 0.26); comparisons between two groups were performed by means of nonparametric Mann–Whitney *U* test (the effect size was expressed as Eta-squared coefficient; small effect = 0.02, medium effect = 0.13, large effect = 0.26). Frequencies were compared by means of chi-square test (the effect size was expressed as omega squared coefficient; small effect = 0.1, medium effect = 0.3, large effect = 0.5). Values in bold type indicate significance $p < 0.05$.

Abbreviations: ALSFRS-R, ALS Functional Rating Scale-Revised; ΔALSFRS-R, disease progression rate; ALS MCI+, amyotrophic lateral sclerosis patients with mild cognitive impairment; ALS MCI−, amyotrophic lateral sclerosis patients without mild cognitive impairment; BMI, body mass index; F, female; HS, healthy subjects; LL, lower limbs; M, male; MRC, Medical Research Council; PUMNS, Penn Upper Motor Neuron Score; UL, upper limbs.

*Significantly different from the other two groups ($p < 0.05$).

time, without any significant group effect ($p > 0.05$) or time by group interaction ($p > 0.05$). ALS MCI− patients did not significantly differ from HS in the cognitive tests covering the four domains: executive functions, language, memory, and visuospatial ability (Table 2). ALS-MCI+, instead, achieved significantly worse cognitive scores than MCI− in all four domains (Table 2).

Gait parameters and falls risk analysis

During the single task condition, patients with ALS displayed worse gait performances compared with HS, and significantly higher variability of gait parameters such as stance and swing time (Table 3). No significant difference in any gait parameters was evident between ALS MCI− and ALS MCI+ (Table 3).

As expected, the dual task condition magnified differences in variability gait parameters between ALS patients and HS and, more interestingly, between ALS MCI+ and ALS MCI− (Table 4). Indeed, during the dual task walking condition, ALS-MCI+ showed significantly greater variability for cadence, stance time, swing time and stability index (Table 4).

Multivariate test showed main effects of condition (single task vs. dual task) on spatiotemporal parameters such as step velocity ($F = 77.631$; df = 1; $p = < 0.001$; partial Eta-squared = 0.58), cadence ($F = 75.051$; df = 1; $p = < 0.001$; partial Eta-squared = 0.58), stride length ($F = 21.732$; df = 1; $p = < 0.001$; partial Eta-squared = 0.28).

TABLE 2 Group comparisons of neuropsychological scores.

	ALS MCI−	ALS MCI+	HS	Kruskal–Wallis		Post hoc (*p*)		
Neuropsychological test	**median (min–max)**	**median (min–max)**	**median (min–max)**	***p***	**η^2**	**MCI− vs. MCI+**	**MCI− vs. HS**	**MCI+ vs. HS**
Screening scale								
ECAS total	105 (73–120)	83 (44–124)	111 (85–123)	**0.001**	0.238	**0.005**	NS	**<0.001**
ECAS total ALS	79 (57–89)	65 (26–87)	82.5 (63–91)	**0.002**	0.182	**0.009**	NS	**0.001**
ECAS total no ALS	25 (15–33)	19.50 (12–28)	28 (22–32)	**0.001**	0.204	**0.01**	NS	**<0.001**
MMSE	29 (25–30)	28 (25–30)	30 (27–30)	**0.002**	0.199	NS	NS	NS
Verbal memory								
Digit Span Forward test	6 (4–6)	5 (4–6)	6 (5–8)	**0.001**	0.235	NS	NS	**0.001**
RAVLT – immediate recall	41 (28–60)	33.5 (20–50)	52 (28–65)	**<0.001**	0.322	**0.003**	NS	**0.003**
RAVLT – delayed recall	10 (7–15)	6 (3–11)	12.5 (8–15)	**<0.001**	0.483	**<0.001**	NS	**<0.001**
Visuospatial memory								
ROCF – delayed recall	19 (6–33)	8 (6–20)	20 (16–30)	**0.002**	0.186	**0.001**	NS	**0.001**
Executive functions								
FAB	17 (14–18)	15 (11–17)	18 (15–18)	**<0.001**	0.392	**0.001**	NS	**0.001**
Verbal fluency	34.5 (21–70)	28 (10–41)	43 (33–55)	**<0.001**	0.387	**0.002**	**0.02**	**<0.001**
Semantic fluency	22.5 (15–30)	18.6 (12–25)	21 (13–30)	0.408	0.004	–	–	–
Stroop – time	17 (2–47)	24.5 (3–42)	16 (10–26)	0.04	0.002	–	–	–
Stroop – error	0.5 (−1–25)	0.5 (0–6)	0 (0–3)	0.258	0.013	–	–	–
ECAS alternation	12 (1–12)	6.5 (0–12)	12 (10–12)	0.02	0.092	–	–	–
WCST total score	67 (11–128)	107 (74–121)	74 (8–104)	**<0.001**	0.333	**0.002**	NS	**0.001**
Visuospatial ability								
ROCF – copy	34 (20–36)	32.5 (10–36)	36 (32–36)	**0.001**	0.227	**0.01**	NS	**0.001**
RCPM	28.5 (18–36)	26 (11–29)	34 (25–36)	**<0.001**	0.263	NS	NS	**<0.001**
CDT	10 (7–10)	10 (5–10)	10 (10–10)	0.09	0.050	–	–	–
Language evaluation								
ECAS language	25 (18–27)	22 (8–28)	26.5 (10–28)	**0.001**	0.202	**0.006**	NS	**0.002**

Note: Significance was set at $p < 0.0026$, according to Bonferroni correction for multiple comparisons (number of comparisons = 19). $\eta^2 = 0.02$ indicates small effect, $\eta^2 = 0.13$ indicates large effect, $\eta^2 = 0.26$ indicates large effect. Values in bold type indicate significance ($p < 0.0026$).

Abbreviations: ALS MCI+, amyotrophic lateral sclerosis patients with mild cognitive impairment; ALS MCI−, amyotrophic lateral sclerosis patients without mild cognitive impairment; CDT, Clock Drawing Test; ECAS, Edinburgh Cognitive Assessment Scale; FAB, Frontal Assessment Battery; HS, healthy subjects; min–max, minimum–maximum; MMSE, Mini-Mental State Examination; NS, not significant; RAVLT, Rey Auditory Verbal Learning Test; RCPM, Raven's Coloured Progressive Matrices; ROCF, Rey–Osterrieth Complex Figure Test; WCST total score, Wisconsin-Card Sorting-Test.

TABLE 3 Group comparisons of gait parameters during single task.

Single task condition								
	Median (min–max)			Kruskal–Wallis		Post-hoc (*p*)		
Gait variables	ALS MCI−	ALS MCI+	HS	p	η^2	MCI− vs. MCI+	MCI− vs. HS	MCI+ vs. HS
Spatiotemporal parameters								
Cycle duration (s)	1.2 (1–1.7)	1.2 (0.9–1.4)	1.2 (1–1.3)	0.154	0.032	–	–	–
Step velocity (m/s)	0.9 (0.5–1.5)	1.0 (0.6–1.3)	1.1 (0.8–1.3)	0.014	0.118	–	–	–
Step length (% stride length)	65.9 (49–98)	65.7 (45–94)	69.3 (50–84)	0.970	0.035	–	–	–
Cadence (step/min)	98.2 (62–117)	100.9 (81–118)	107.9 (95–122)	0.004	0.168	–	–	–
Stance time (% cycle)	59.9 (57–64)	61.7 (53–64)	60.9 (57–64)	0.067	0.062	–	–	–
Swing time (% cycle)	40.1 (36–43)	38.3 (36–50)	39.1 (36–43)	0.060	0.066	–	–	–
Stride length (m)	1.1 (0.8–1.6)	1.2 (0.9–1.5)	1.2 (0.9–1.4)	0.314	0.006	–	–	–
Stability index	3.8 (1.2–13.2)	3.2 (2.2–4.9)	3.6 (2.6–5.7)	0.066	0.062	–	–	–
Variability parameters (SD)								
Cycle duration	0.06 (0.01–1.3)	0.07 (0.03–1.1)	0.03 (0.02–0.1)	0.009	0.134	–	–	–
Step velocity	0.07 (0.04–0.2)	0.07 (0.04–0.1)	0.08 (0.02–0.2)	0.571	0.016	–	–	–
Step length	3.6 (1.9–7.3)	3.0 (1.2–7.3)	3.7 (1.3–8.2)	0.317	0.005	–	–	–
Cadence	9.2 (0.1–27.7)	10.5 (3.6–21.4)	4.4 (1.9–17.8)	0.014	0.119	–	–	–
Stance time	3.0 (0.9–12.3)	4.3 (1.1–19.4)	1.3 (0.9–3.9)	**<0.001**	0.272	NS	**0.002**	**<0.001**
Swing time	3.0 (1–12.3)	4.0 (1.1–7.2)	1.3 (1–3.9)	**<0.001**	0.260	NS	**0.001**	**<0.001**
Stride length	0.1 (0.04–0.3)	0.1 (0.02–0.12)	0.1 (0.03–0.13)	0.305	0.007	–	–	–
Stability index	1.5 (0.7–2.5)	1.5 (1–2.4)	1.2 (0.7–3.2)	0.157	0.031	–	–	–
Asymmetry parameters								
Step length	1.0 (0.7–1.1)	1.0 (0.7–1.3)	1.0 (0.9–1.2)	0.620	0.008	–	–	–
Cycle duration	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.356	0.005	–	–	–
Stance time	0.9 (0.9–1.1)	1.0 (0.8–1.1)	1.0 (0.9–1.0)	0.334	0.033	–	–	–
Swing time	1.0 (0.9–1.2)	0.9 (0.9–1.5)	1.0 (0.9–1.2)	0.334	0.033	–	–	–

Note: Significance was set at $p < 0.0025$, according to Bonferroni correction for multiple comparisons (number of comparisons = 20). Post-hoc p was set at $p = 0.05$. $\eta^2 = 0.02$ indicates small effect, $\eta^2 = 0.13$ indicates large effect, $\eta^2 = 0.26$ indicates large effect. Values in bold type indicate significance ($p < 0.0025$).

Abbreviations: ALS MCI+, amyotrophic lateral sclerosis patients with mild cognitive impairment; ALS MCI−, amyotrophic lateral sclerosisatients without mild cognitive impairment; HS, healthy subjects; min–max, minimum–maximum; NS, not significant; SD, standard deviation; stability index, single/double support time ratio.

TABLE 4 Group comparisons of gait parameters during dual task.

Dual task condition								
	Median (min–max)			Kruskal–Wallis		Post-hoc (*p*)		
Gait variables	ALS MCI−	ALS MCI+	HS	p	η^2	MCI− vs. MCI+	MCI− vs. HS	MCI+ vs. HS
Spatiotemporal parameters								
Cycle duration (s)	1.2 (1.1–1.8)	1.2 (1.1–1.5)	1.2 (1–1.9)	0.474	0.009	–	–	–
Step velocity (m/s)	0.8 (0.4–1.2)	0.9 (0.6–1.1)	1.0 (0.8–1.3)	0.007	0.142	–	–	–
Step length (% stride length)	63.1 (43–84)	67.4 (50–79)	70.7 (50–81)	0.156	0.031	–	–	–
Cadence (step/min)	90.4 (56–107)	96.1 (71–108)	103.0 (89–120)	**0.001**	0.231	NS	**<0.001**	**0.003**
Stance time (% cycle)	60.2 (56–65)	61.3 (58–64)	60.3 (59–65)	0.271	0.011	–	–	–
Swing Time (% cycle)	39.8 (35–44)	39.0 (36–49)	39.7 (35–41)	0.546	0.014	–	–	–
Stride length (m)	1.1 (0.8–1.4)	1.2 (0.9–1.4)	1.2 (0.9–1.4)	0.186	0.025	–	–	–
Stability index	4.0 (2.3–7.6)	3.6 (2.5–5.4)	3.8 (2.3–4.7)	0.262	0.012	–	–	–
Variability parameters (SD)								
Cycle duration	0.08 (0.03–0.4)	0.1 (0.04–0.3)	0.05 (0.02–0.12)	**0.002**	0.184	NS	**0.02**	**0.001**
Step velocity	0.08 (0.05–0.2)	0.09 (0.06–0.2)	0.08 (0.04–0.2)	0.036	0.085	–	–	–
Step length	3.9 (2.6–8.6)	4.1 (2.6–9.9)	4.0 (2.4–6.3)	0.420	0.005	–	–	–
Cadence	9.2 (3–20.4)	13.9 (4–22)	5.1 (2.2–14.2)	**<0.001**	0.258	**0.005**	**0.05**	**<0.001**
Stance time	3.0 (0.7–11.4)	4.6 (1.2–7.9)	1.5 (0.4–3.5)	**<0.001**	0.307	**0.040**	**0.002**	**<0.001**
Swing time	3.0 (0.8–11.3)	4.5 (1.3–8.1)	1.5 (0.4–4)	**<0.001**	0.307	**0.040**	**0.002**	**<0.001**
Stride length	0.1 (0.05–0.14)	0.1 (0.5–0.2)	0.07 (0.04–0.1)	0.096	0.049	–	–	–
Stability index	1.4 (0.9–4.4)	1.6 (1.1–5.9)	1.3 (0.5–3.8)	**0.002**	0.107	**0.02**	**NS**	**0.01**
Asymmetry parameters								
Step length	1.0 (0.7–1.2)	1.0 (0.7–1.4)	1.0 (0.9–1.4)	0.354	0.083	–	–	–
Cycle duration	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.832	0.021	–	–	–
Stance time	1.0 (0.8–1.1)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.921	0.011	–	–	–
Swing time	1.0 (0.9–1.3)	1.0 (0.6–1.3)	1.0 (0.8–1.2)	0.919	0.015	–	–	–

Note: Significance was set at $p < 0.0025$, according to Bonferroni correction for multiple comparisons (number of comparisons = 20). Post-hoc p was set at $p = 0.05$. $\eta^2 = 0.02$ indicates small effect, $\eta^2 = 0.13$ indicates large effect, $\eta^2 = 0.26$ indicates large effect. Values in bold type indicate significance ($p < 0.0025$).

Abbreviations: ALS MCI+, amyotrophic lateral sclerosis patients with mild cognitive impairment; ALS MCI−, amyotrophic lateral sclerosis patients without mild cognitive impairment; HS, healthy subjects; min–max, minimum–maximum; NS, not significant; SD, standard deviation; stability index, single/double support time ratio.

The effect of group (ALS MCI+ vs. ALS MCI− vs. HS) was observed on step velocity ($F=4.854$; df = 2; $p=0.02$; partial Eta-squared = 0.15), cadence ($F=7.694$; df = 2; $p=0.001$; partial Eta-squared = 0.22), cadence variability ($F=7.808$; df = 2; $p=0.001$; partial Eta-squared = 0.22), cycle duration variability ($F=4.695$; df = 2; $p=0.01$; partial Eta-squared = 0.15), stance time variability ($F=7.780$; df = 2; $p=0.001$; partial Eta-squared = 0.22), swing time variability ($F=8.498$; df = 2; $p=0.001$; partial Eta-squared = 0.24) and on stability index ($F=8.462$; df = 2; $p=0.001$; partial Eta-squared = 0.23). Significant interaction effects (group × condition) were observed on step velocity variability ($F=3.731$; df = 2; $p=0.03$; partial Eta-squared = 0.12) and for cadence variability ($F=3.778$; df = 2; $p=0.02$; partial Eta-squared = 0.12).

Dual task cost significantly differed across groups for several gait parameters: step velocity ($p=0.005$; Eta-squared = 0.22), step length ($p=0.005$; Eta-squared = 0.26) and stride length ($p=0.001$; Eta-squared = 0.33) (Figure 1). Post-hoc comparisons disclosed that dual task cost in ALS MCI+ was significantly higher than in HS for all the above parameters (step velocity: $p=0.009$; step length: $p=0.004$; stride length $p=0.014$), whereas it was higher than in ALS MCI− for step length ($p=0.03$) and stride length ($p=0.02$) only.

Few significant differences were found in gait parameters as a function of groups classified by means of Strong (Strong+ vs. Strong−) classification criteria ($p>0.05$) (Table S1 and S2). No difference was found between patients classified as Strong− and Strong+ on dual task cost for each gait variability measure ($p>0.05$).

The binary logistic regression analysis to assess which clinical measure, including presence of MCI, was associated with the occurrence of falls at follow-up provided a significant model (percentage of correct prediction = 78.4%) in which MCI was the best predictor of short-term falls ($\beta=3.649$; $p=0.01$; df = 1; OR = 3.84; CI = 1.8–8.4), followed by lower limbs muscle strength (MRC-LL; $\beta=0.205$; $p=0.04$; df = 1; OR = 1.22; CI = 1.1–1.5). No significant contribution of cognitive impairments to fall occurrence was observed ($p>0.05$).

The hierarchical multiple regression evaluating whether mild cognitive impairment was associated with number of falls at follow-up provided a significant model (explaining 31% of variance), showing that presence of MCI was the global measure of cognitive impairment significantly associated ($\beta=0.63$; $p<0.001$; CI = 0.5–1.3) with the number of falls at the follow-up. A second regression model (explaining 12.3% of variance) showed that executive function impairment was the only domain significantly associated ($\beta=0.39$; $p=0.02$; CI = 0.2–1.4) with the dependent variable.

DISCUSSION

In this study, ALS patients had significantly higher gait variability compared with healthy controls, and the magnitude of variability was greater during the cognitive dual task condition. Interestingly, we also found that the dual task condition selectively affected several walking parameters in ALS MCI+, especially those related to

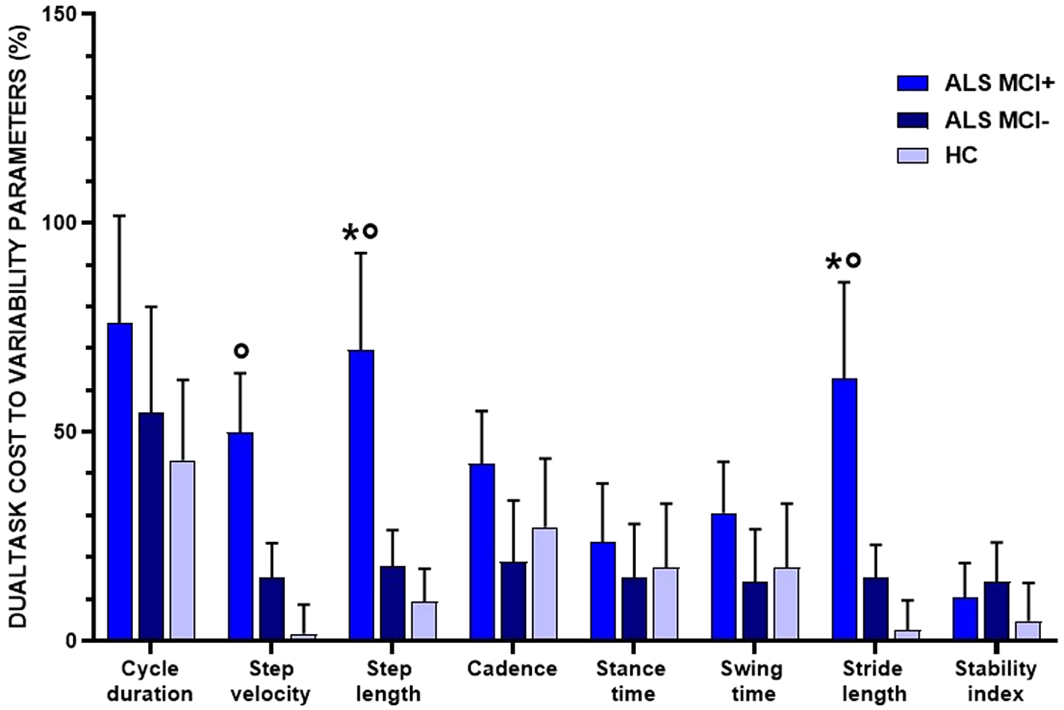

FIGURE 1 In the amyotrophic lateral sclerosis without mild cognitive impairment (ALS MCI+) group the dual task cost was significantly higher compared with the amyotrophic lateral sclerosis with mild cognitive impairment (ALS MCI−) group and healthy subjects (HS) for the step velocity variability, step length variability and stride length variability. The group effect was tested by the Kruskal–Wallis test, while post-hoc comparisons were performed by means of Mann–Whitney *U* test. *MCI+ versus MCI−; °MCI+ versus HS. Significance was set at $p<0.006$, according to Bonferroni correction for multiple comparisons (number of comparisons = 8). Post-hoc *p* was set at $p=0.05$.

the variability of cadence, stance time, swing time and the stability index. These findings support evidence that cognitive load exerts a detrimental effect on gait performance in ALS patients. Analogously, ALS MCI+ also showed a higher occurrence and number of falls at 3 months of follow-up, even if they did not differ from ALS MCI− in motor worsening over time. MCI significantly predicted occurrence of future falls and, together with executive impairment, was independently associated with the numbers of falls.

Gait variability is higher in ALS patients and is influenced by cognition

The dual task effect is larger in individuals with cognitive impairment than in controls [1, 2], and an increase in the dual task complexity further worsens the gait measures [1, 2]. A dual task condition might interfere with gait metrics by increasing gait variability, which is a measure of stability and cognitive cortical dysfunction [22]. Furthermore, when comparing different grades of cognitive impairment (e.g., MCI vs. AD), the more severe the cognitive impairment the more detrimental the observed effects on gait variability [54]. Consistent with these observations, in our study MCI+ patients showed higher gait variability especially for stance, swing time, and cadence during dual task protocol than the other groups. These findings would suggest the evaluation of gait variability parameters, together with neuropsychological tests such as verbal fluency, as part of the standard clinical assessment to detect early functional impairment in ALS patients.

Importantly, it is worth recalling that classification of patients as MCI+ and MCI−, according to established international criteria [51], seems to capture the aspects correlated with gait variability better than the classification frameworks specific for ALS (e.g., Strong criteria [28]). A possible reason for this discrepancy is that the Strong classification [28] seems to be less sensitive than the Litvan criteria [51] in identifying patients with subtle cognitive dysfunctions especially in memory and visuospatial domains. Interestingly, our data in patients with ALS further support the link between cognition and gait performance, as only during the dual task condition MCI+ patients displayed significantly greater variability parameters compared with MCI− patients.

Previous studies demonstrated that ALS patients display increased and highly variable gait cycle time and reduced stride length compared with healthy controls [6, 26]. Importantly, Hausdorff and colleagues [26] also demonstrated that stride-to-stride variability in ALS was present since early walking phases (i.e., the initial 60 strides of the walk), before the possible appearance of fatigue, suggesting that muscle weakness by itself would not necessarily alter the gait rhythm and the stride-to stride control of walking [26]. A significant deterioration of gait parameters including those related to variability has been also described in ALS patients while performing a complex mental task [24], suggesting a possible link between the cognitive dimension and gait abnormalities in the disease. Most studies that assessed the relationship between impairment of specific cognitive domains and poorer gait components consistently showed that high gait variability could be related to dysfunction in the frontal cortical control of walking, in older adults, in Alzheimer's disease, and in PD [13, 22]. Therefore, given the documented impairments in executive function specific to patients with ALS, our data further support the interplay between gait variability and cognitive function. Perhaps more interestingly, the motor impairment apparently did not affect these results as both groups, MCI+ versus MCI−, differed only with respect to cognitive variables.

Cognitive dysfunction predicts the risk of future falls in ALS patients

Our longitudinal data showed that the MCI condition strongly predicted the occurrence and number of falls. Interestingly, analysing the contribution of each cognitive domain, we found that executive dysfunction was strongly associated with fall risk. Our findings are consistent with studies in older adults [17, 33] and in patients with PD [13] identifying impairment of executive functions as a risk factor for falls. Falls are common in patients with ALS [4], including those who are ambulatory, and might have severe consequences, resulting in increased morbidity and mortality [5]. So far, muscle weakness such as reduced lower limb muscle strength [6, 7], alterations in the Timed Up and Go test [8] and the impairment of stability and postural reflexes [9, 55] have been reported to be associated with gait abnormalities and to predict future falls among patients with ALS. In this context, our study suggests that cognitive impairment also has a detrimental effect on gait variability and is independently associated with the fall risk.

Study limitations

We acknowledge that number of falls recording could have been influenced by the cognitive impairment of patients; however, we performed our interview with a caregiver who was present for most of patients' falls and could reliably record occurrence of falls.

Moreover, it would have been interesting to compare the effect of two different cognitive tasks, such as verbal fluency versus subtraction task, to assess the different degree of cognitive–motor interference.

Lastly, the cross-sectional study design and the number of subjects should also be kept in mind when considering follow-up studies.

CONCLUSIONS

Dual task walking increases gait variability more than spatiotemporal and asymmetry gait measures in ALS patients, and especially in those with MCI. This finding suggests that impairment in cognitive

control abilities plays a harmful role in gait variability in ALS patients, regardless of motor impairment. The present results have two main clinical implications. First, clinicians should be aware of cognitive impairment in ALS patients, since, regardless of motor impairment, executive dysfunction can increase the risk of falls and their possible consequences (e.g., immobilization). Therefore, detecting cognitive impairments may help in identifying patients with ALS at risk of falls and in developing prevention strategies and interventions.

Second, incorporating dual task walking conditions with mobility training may be useful in the rehabilitation of patients with ALS. Novel rehabilitative approaches should apply exercises jointly addressing both the specific cognitive and mobility challenges of people with ALS.

AUTHOR CONTRIBUTIONS

All authors listed contributed to the study conception and design, with the main leads being Raffaele Dubbioso and Pasquale Moretta. Material preparation, data collection and analysis were performed by Jeffrey M. Hausdorff, Gabriella Aceto, Valentina Virginia Iuzzolino, Gianmaria Senerchia, Stefania De Marco, Laura Marcuccio, Cinzia Femiano, Rosa Iodice, Elena Salvatore, and Gabriella Santangelo. The first draft of the manuscript was written by Pasquale Moretta, Raffaele Dubbioso, and Luigi Trojano, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of the manuscript will be made available by the authors, to any qualified researcher, without breaching participant confidentiality.

ETHICS APPROVAL

The study was approved by the ethics committee of the University Federico II of Naples (N. 100/17). Written informed consent was obtained from each patient or their guardian.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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