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RESEARCH ARTICLE

Exploring motor and visual imagery in Amyotrophic Lateral Sclerosis

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Abstract Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disease characterized by the progressive atrophy of both the first and the second motor neurons. Although the cognitive profile of ALS patients has already been defined by the occurrence of language dysfunctions and frontal deficit symptoms, it is less clear whether the degeneration of upper and lower motor neurons affects motor imagery abilities. Here, we directly investigated motor imagery in ALS patients by means of an established task that allows to examine the presence of the effects of the biomechanical constraints. Twenty-three ALS patients and 23 neurologically unimpaired participants have been administered with the (1) hand laterality task (HLT) in which participants were asked to judge the laterality of a rotated hand and the (2) mirror letter discrimination task (MLD) in which participants were asked to judge whether a rotated alphanumeric character was in its canonical or mirror-reversed form (i.e. control task). Results show that patients present the same pattern of performance as unimpaired participants at the MLD, while at the HLT, they present only partially with the effects of biomechanical constraints. Taken together, our findings provide evidences that motor imagery abilities, related to the mental simulation of an action, are affected by this progressive disease.

Keywords Motor imagery · Mental rotation · Hand recognition · Motor pathways · Grasping and reaching · Amyotrophic Lateral Sclerosis

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Introduction

Knowledge of the location of body parts in space, accomplished through efference copy information and feedbacks from sensory systems, allows the execution of correct movements (Frith et al. 2000; Schwoebel et al. 2001). Imaging a movement and recalling an action are performed through the simulation of the movement itself (Decety et al. 1994; Decety and Jeannerod 1995; Gentilucci et al. 1998a; Parsons 1987; Sekiyama 1982). It has been demonstrated that the time required to mentally simulate a movement is proportional to that needed to perform the corresponding real action (Jeannerod and Decety 1995; Jeannerod 2001; Kosslyn et al. 1995). Motor imagery (MI), the ability to imagine movements, is also characterized by the effects of biomechanical constrains, as shown in the hand laterality task (HLT), in which participants judge the laterality of a visually presented hand stimulus (Parsons 1987, 1994). These effects are associated with the viewing perspective (i.e. palm vs. dorsum at 180°) and with the hand position (i.e. comfortable vs. awkward positions). For instance, it has been demonstrated that reaction times are roughly symmetrical

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at 180° for the dorsum view of the hand, whereas latencies are highly asymmetrical at 180° for the palm view (Brady et al. 2011). In other words, reaction times are considerably higher for away from body postures, than for across body postures (Parsons 1987; Brady et al. 2011). The effect associated with the hand postures consists in slower responses and lower accuracy when participants judge the laterality of a hand presented in a position difficult to reach with a real movement (awkward positions) (Brady et al. 2011; Conson et al. 2010; Parsons 1987, 1994; Parsons et al. 1995, 1998). Similarly, an advantage (faster reaction times and higher accuracy) for hands oriented in executable and comfortable grasping postures (comfortable positions) has been observed (Brady et al. 2011; Conson et al. 2010; Parsons 1994; Sekiyama 1982). The effects of biomechanical constraints are selectively related to MI tasks and indicate that participants mentally simulate the movements of their own body part to match it with the to-be-judged visual stimulus (Gentilucci et al. 1998a, b). Accordingly, if the effects of biomechanical constraints are not observed, MI tasks are not carried out using body parts representation movement but instead by means of general visuo-spatial mental rotation (MR) strategies (Conson et al. 2010; Parsons 1994; Sekiyama 1982).

Finally, the relation between imagined action recall and real movement execution is anatomically supported by the overlap of brain regions involved in MI with those of real action execution, such as the left intraparietal sulcus (Corradi-Dell'Acqua et al. 2009) and the premotor cortex (Ehrsson et al. 2004; Parsons et al. 1995).

This anatomical account and the behavioral results confirm the strong association between being able to perform a movement and being able to imagine it (Jeannerod 1995). Furthermore, recent studies demonstrated that MI abilities may be influenced by the modulation of peripheral factors. Chronic pain patients, who exhibit a partial alteration of proprioceptive and sensory inputs but maintain preserved motor abilities, show MI impairment (Schwoebel et al. 2001). Similarly, it has been demonstrated that in Locked-in Syndrome, characterized by a complete paralysis preventing voluntary motor acts, MI is negatively affected by the disconnection of the descendent motor pathways (Conson et al. 2008, 2010).

Amyotrophic Lateral Sclerosis (ALS) is the most common motor neuron disease, and it is characterized by the progressive atrophy of both the first and second motor neurons (Brooks 1994; Brooks et al. 2000). ALS causes a decrease in the flow of information that is sent through the corticospinal motor tract, due to the degeneration of the descending motor pathways (Chevalier-Larsen and Holzbaur 2006). Consequently, ALS patients suffer from a progressive loss of the ability to move (Brooks 1994; Brooks et al. 2000) and end up in a locked-in state after few years from the onset of the disease (Uccelli et al. 2007). Furthermore, the cognitive profile of ALS patients could be also characterized by various impairments (Tsermentseli et al. 2011; Lomen-Hoerth et al. 2003; Raaphorst et al. 2010).

The integrity of MI abilities is still a matter of debate in ALS. Anatomical studies suggest that ALS induces a progressive atrophy in the primary motor areas (Brooks et al. 2000), which are involved in MI processes (Parsons et al. 1995). Accordingly, recent neuroimaging studies reported differences between ALS patients and controls during MI performance. In particular, ALS patients show an increased activity outside the primary motor cortex involving the premotor areas (Kew et al. 1993, 1994; Konrad et al. 2002, 2006; Schoenfeld et al. 2005), the contralateral sensorimotor cortex (Schoenfeld et al. 2005; Kew et al. 1993, 1994), the inferior parietal lobule (Kew et al. 1993, 1994; Konrad et al. 2002) and the anterior cingulate cortex (Konrad et al. 2006; Kew et al. 1993; Schoenfeld et al. 2005). On the other hand, reduced cortical activations are also reported in ALS patients during MI tasks in both parietal and medial frontal regions (Stanton et al. 2007). However, it is still unknown whether these activations correspond to an impairment or if they represent a compensatory mechanisms to imagine movements in the absence of motor feedbacks (Lule et al. 2007).

Here, we behaviorally investigate MI integrity in ALS patients, focusing on the effects of biomechanical constraints by means of the HLT, a reliable task (Parsons 1987; Sekiyama 1982), ad hoc adapted to the clinical features of ALS patients. Moreover, we improve existing designs administering patients with an alphanumeric characters rotation task, the mirror letter discrimination task (MLD), in order to separate body related from general MR deficits, having the two tasks strictly the same conditions but different stimuli (Pelgrims et al. 2010). Thus, using the HLT and the MLD, we directly investigated the contribution of the motor system in recognition and mental movement's simulation of body parts in ALS patients.

The hypothesis of the study is that, as MI involves the primary motor area and ALS patients have a deficit in the first and second motor neuron, they could present a selective impairment in MI abilities.

Materials and methods

Participants

Twenty-three right-handed patients with sporadic ALS (19 men; mean age 56.57 ± 12.39 years; mean education 14.51 ± 5.84 years) participated in this study (Table 1). All patients have been diagnosed as defined or probable ALS, with spinal or bulbar onset, according to the El Escorial revised criteria for the diagnosis of ALS (Brooks et al. 2000).

Table 1 Demographical, neuropsychological and clinical features of ALS patients

	Demographic features	
Age	56.57	±12.39
Years of education	14.51	±5.84
Disease duration	19.78	±9.89
	Neuropsychological and clinical features	
RCPM	29.32	±2.53
ALSRS-r	22.83	±10.86
	Pathology onset (%)	
Bulbar	82.60	
Spinal	17.4	
Probable	17.4	
	Diagnosis (%)	
Defined	82.60	
Flail leg	8.69	
	Phenotype (%)	
Bulbar	8.69	
Pyramidal ALS	13.05	
Classic ALS	65.21	
Respiratory	4.35	

For disease duration (in months), years of education, RCPM's corrected scores and ALSRS-r overall score are indicated the mean score and standard deviation of ALS patients group. Whereas for the pathology onset (S = spinal, B = bulbar), diagnosis (P = probable, D = defined) and phenotype (C = classic ALS, P = pyramidal ALS, F = flail leg, R = respiratory, B = bulbar) for each patient are reported the percentage of incidence inside the ALS patients group

RCPM Raven's Colored Progressive Matrices, *ALSRS-r* Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

Each participant was administered with the Raven's Colored Progressive Matrices (RCPM) (Carlesimo et al. 1996; Raven et al. 1996) (average corrected score 29.32 ± 2.53) in order to exclude deficits of mental reasoning, potentially interfering with the experimental study (Conson et al. 2010).

For each patient, we collected information about the pathology onset, the disease duration, the phenotype (Chio et al. 2011) and an index of the global residual motility and functionality (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised—ALSFRS-r) (Cedarbaum and Stambler 1997) (average score 22.83 ± 10.86) (see Table 1). Exclusion criteria for participating in the study were as follows: (1) severe cognitive decline; (2) comorbidity with other neurological diseases; (3) psychiatric disorders or substance abuse; (4) severe secondary pathology, clinically established and (5) somatosensory and/or proprioceptive deficits as evaluated by the objective neurological examination. Twenty-three right-handed control participants (19 males), matched for age (mean age 55.17 ± 12.22 years) and education (mean education 15.15 ± 3.64 years), were also recruited as control group.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and an informed consent was obtained from all participants. The research protocol and the informed consent form have been approved by the Ethics Committee of Niguarda Ca' Granda Hospital, Milan.

Experimental tasks

Hand laterality task

The HLT allows the investigation of specific indexes of MI, such as the effects of stimulus orientation and biomechanical constraints (Conson et al. 2008, 2010; Parsons 1987, 1994; Sekiyama 1982; Nico et al. 2004). When judging 180° oriented hands, participants show a peak in error rates (Cooper and Shepard 1975; Parsons 1987; Sekiyama 1982; Sirigu et al. 1996; Nico et al. 2004). Given that this phenomenon, known as the effect of stimulus orientation, was also observed in a variety of visuo-spatial rotation tasks, using non-body stimuli, such as alphanumeric characters (Booth et al. 2000; Harris et al. 2000; Jordan et al. 2001; Milivojevic et al. 2009; Podzebenko et al. 2002), it may be better ascribed to more general visuo-perceptual processes involved in MR rather than to MI in particular (Shepard and Metzler 1971; Jordan et al. 2001). Therefore, the choice of using the HLT, as it allows to investigate more specific indexes of MI, such as biomechanical constraints effects.

The HLT requires participants to decide whether a picture represents a right or a left hand (Parsons 1987, 1994; Parsons et al. 1995; Conson et al. 2010). In our modified version, participants respond by means of eye-gazes, directed toward one of the two given alternatives presented on a response sheet, instead of giving a verbal response or pressing a button. The task was modified as all of our patients were completely unable to move their hands or to provide a verbal response (Girardi et al. 2011).

Our modified HLT consisted of one hundred ninety-two stimuli, divided in two blocks, in which each stimulus appears twelve times in a semi-random order. Stimuli were obtained from photographs of a male hand (one individual only). We purposely did not create an averaged "template hand" as we preferred the most ecological stimulus. Left and right hand images were presented in dorsum and palm viewing conditions. We followed the original distinction proposed by Parsons (1987) between stimuli across and away from the body's midsagittal plane (Parsons 1987). Accordingly to this categorization, stimuli across the body midline are +270° for the right hand and −270° for the left hand, whereas stimuli away from the body midline are +90° for the right hand and −90° for the left hand (Fig. 1). For the purpose of data analyses, we considered the left hand stimuli as mirror-image pairs of the right hands. Consequently, we

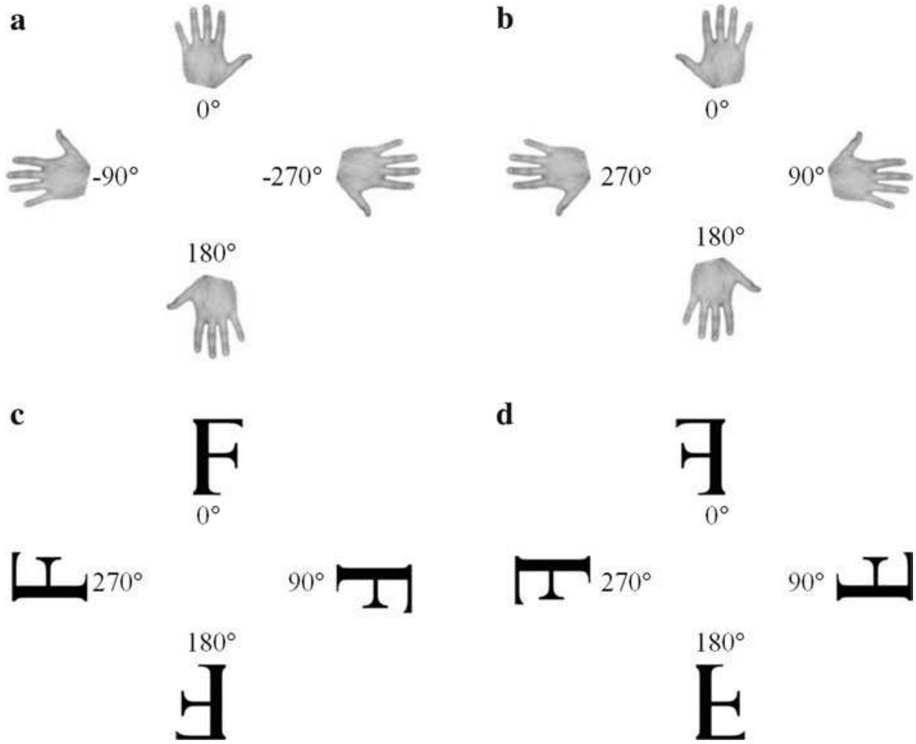

Fig. 1 Schematic presentation of the HLT and MLD tasks stimuli. For the MLD, canonical (**c**) and mirror form (**d**) letters are shown at each orientation (0°, 90°, 180°, 270°). For the HLT stimuli, left hands (**a**) and right hands (**b**) are shown to highlight that left hand images are considered mirror-images of right hands. In detail, we labeled the right hand stimuli from 0°, +90°, 180° and +270° in clockwise direction, whereas the left hand stimuli were labeled from 0°, −90°, 180° and −270° in counter clockwise direction. Adopting this data set allowed to distinguish between stimuli across and away from the body's midsaggital plane: the +270° right hand and −270° left hand were considered across body plane stimuli, whereas the +90° right hand and −90° left hand were considered away body's plane stimuli. Furthermore, this methodology allows also to distinguish easily between comfortable postures (−270° left hand and 270° right hands) and awkward postures (−90° left hand and 90° right hands). **a** Left hand; **b** right hand; **c** F in the canonical form; **d** F in the mirror form

labeled the right hand stimuli as 0°, +90°, 180° and +270° in clockwise direction, whereas the left hand stimuli were labeled as 0°, −90°, 180° and −270° in counter clockwise direction.

Mirror letter discrimination task

We choose, as control task, the MLD, in which participants are requested to indicate whether the displayed alphanumeric characters are in their normal or mirror-reversed orientation (Fig. 1). Previous works have demonstrated that tasks using letters instead of body parts involve general visuo-spatial rotation processes rather than MI (Jordan et al. 2001; Pelgrims et al. 2010; Gogos et al. 2010; Booth et al. 2000; Alivisatos and Petrides 1997), allowing to separate MR from MI deficits. Letters "F" and "J" have been chosen because their asymmetry is comparable to that of hands (Pelgrims et al. 2010) (Fig. 1). The number of stimuli, their order and the response type are the same as in the HLT. Although the 270° and 90° orientations are not essential to compute relevant indexes as in the HLT, we maintained the same experimental conditions in both tasks.

Patients and controls were instructed to mentally rotate the image until the top was up to decide whether the presented stimulus was a letter in the "canonical" or the "mirror" form, as task instructions have been proven to be useful to reduce the inter-individual variance in rotation strategies (Jordan et al. 2001; Hochberg and Gellman 1977) (Fig. 1).

Apparatus and procedure

We developed a tool for bedside testing, composed by a plastic table of presentation (TOP) (Fig. 2a, b) and two transparent response sheets (Fig. 2c, d). The TOP is a rectangular plywood platform, measuring 58 cm × 47 cm, divided in two parts: the bottom part is used for stimuli presentation (Fig. 2a) and the top part contains the response grid appropriate for the trial (Fig. 2c, d). A support, allowing stimuli presentation at 80° of inclination (correct visual angle for bedside patients), is placed on the back of the TOP (Fig. 2b).

We modified all the tasks to allow patients to respond by means of eye movements (Mulder 1982). The transparent response grid contained in the TOP (Fig. 2c, d) was developed to allow the experimenter to monitor patients'

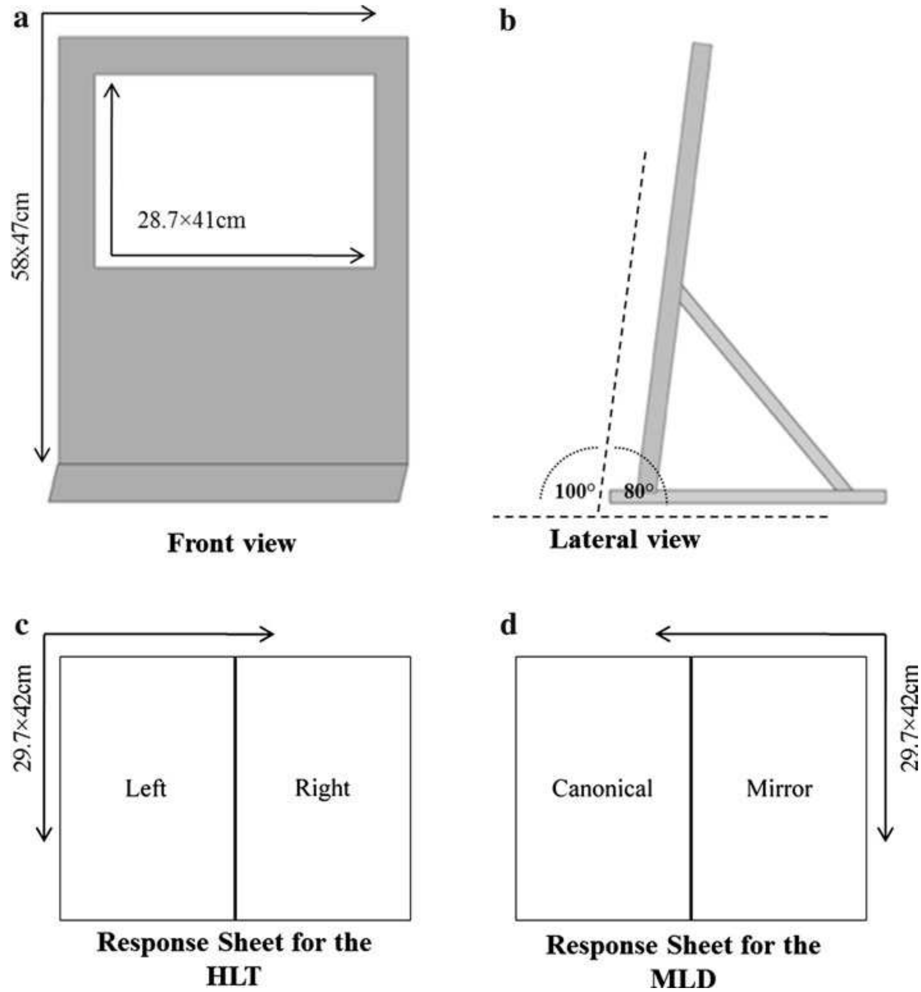

Fig. 2 Details of the tools used to administer the experimental tasks. **a** *Frontal view* of TOP with measures; **b** *lateral view* of TOP; **c** response sheet used for the HLT; and **d** response sheet used for the MLD

eye movements and to register on line the response. Specifically, for the HLT, the answer sheet had two alternatives printed on them: "left" and "right" (Fig. 2c), congruent with the patient left and right perspective; for the MLD task, the two alternatives were "canonical" and "mirror", printed, respectively, on the left and the right side of the response grid (Fig. 2d). An examiner trained to decode eye movements seated in front of the participants (he was blind to which stimulus was displayed to avoid biases) and reported the responses on the grid. The experimental stimuli were displayed on a paper sheet (A3 format, 29.7 × 42 cm), centrally printed on a white background.

Patients and controls were both instructed to answer directing their eye-gaze toward one of the two alternatives presented on a response sheet (Fig. 2c, d), to control for differences in the task administration between groups. Participants familiarized with eye-gaze response modality before the beginning of the task.

The HLT and the MLD were administered to patients and controls in a counterbalanced order. The TOP was located in front of the subject at about 50 cm of distance. In the HLT, patients and controls had both their hands out of sight, laying dorsum.

Data analysis

Data have been analyzed using Statistical Package for Social Sciences (SPSS 13.0©, Chicago, IL, USA). In both tasks, the dependent variable was the percentage of correct answers (accuracy estimates) (Table 2). For all the main analyses, alpha level was set at 0.05.

To control for a general MR impairment, we performed a mixed-effects ANOVA on the MLD data, with Angle of rotation as within-subject factors and Group as between-subject factor. Further, we explored directly the presence of the effect of stimulus orientation. The presence of this effect is demonstrated by a significance of the Angle of rotation factor, more specifically by a significant difference in the performances between stimuli at 0° versus 180°, with an error peak in this last condition (Jordan et al. 2001; Shepard and Metzler 1971). Importantly, this effect would indicate that participants were able to use a cognitive strategy at least based on MR (Jordan et al. 2001; Shepard and Metzler 1971).

Then, we analyzed the HLT data to investigate the presence of MI deficits in ALS patients. We adopted a mixed-effects ANOVA with Stimulus view and Angle of rotation as within-subject factors and Group as between-subject factor. With this analysis, we explored the presence of the effect of the stimulus view, which consists in a difference between dorsum and palm view at 180°. The presence of the effect of stimulus orientation has been also assessed by contrasting the performance at 0° and 180° within each group. Finally, we concentrated on the presence of the effect of hand postures, expressed by a significant advantage in judging comfortable versus awkward hand postures (Parsons 1987). The effects of biomechanical constraints have been analyzed only in the HLT as such indexes are typical of MI use (Parsons 1987).

Finally, we averaged the performance for each angle of rotation in both tasks to obtain an overall performance index and we investigated the influence of pathology-related variables in patients, by means of Spearman's rank correlations.

Results

Mirror letter discrimination task

We obtained the MLD accuracies estimates collapsing the performance for different letters (F and J) and views ("canonical" or the "mirror" form) at each angle of rotation. Levene Test for homogeneity of variances did not show a violation of the homogeneity of variance assumption ($F_{[1,44]} = 0.261$, $p = 0.612$). Nevertheless, we applied the Greenhouse-Geisser correction to be as conservative as possible against Type I Errors. We performed a mixed-effects ANOVA with Angle of rotation (0°, 90°, 180° and 270°) as within-subject factor and Group (Control and ALS) as between-subject factor. This analysis revealed a significant main effect of Angle of rotation ($F_{[1.826,80.336]} = 36.313$, $p < 0.001$) and Group ($F_{[1,44]} = 7.286$, $p = 0.010$) (Fig. 3). No interaction was found between factors (all $p > 0.05$).

We applied t tests (Bonferroni corrected) as post hoc analysis. We explored the main effect of Angle of rotation comparing the accuracies at each angle of rotation. This analysis showed a significantly better performance with alphanumeric stimuli presented at 0° versus 90° ($t_{[45]} = 4.190$, $p < 0.001$), versus 180° ($t_{[45]} = 7.457$, $p < 0.001$) and versus 270° ($t_{[45]} = 3.903$, $p < 0.001$). Similarly, differences were found between letters presented at 180° versus 90° ($t_{[45]} = 6.416$, $p < 0.001$) and versus 270° ($t_{[45]} = -5.716$, $p < 0.001$), with a worse recognition of 180° alphanumeric stimuli. Finally, the analysis of the main effect of Group revealed a worse performance of ALS patients over controls ($t_{[43.165]} = 2.699$, $p = 0.010$).

We assessed the presence of the stimulus orientation within each group by contrasting directly 0° versus 180° orientations accuracies. Results showed that this index was present for both controls ($t_{[22]} = 4.757$, $p < 0.001$) and ALS patients ($t_{[22]} = 6.499$, $p < 0.001$). The found pattern of performances in which controls and ALS patients present the effect of stimulus orientation in the MLD confirms the use of a MR strategy to perform the task.

Table 2 Average percentage of correct answers for control group and ALS patients

Orientations	HLT				MLD			
	Controls		ALS patients		Controls		ALS patients	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
0°	94.44	±1.57	89.40	±3.70	94.18	±2.07	88.37	±2.23
90°	84.96	±2.86	86.99	±1.46	89.84	±2.36	84.43	±2.20
180°	82.99	±2.59	73.92	±3.05	75.07	±4.60	72.71	±3.27
270°	96.74	±0.55	83.21	±1.46	90.71	±2.26	83.54	±1.78

Patients' and controls' average percentage of correct answers (±standard error [SE] of the mean) as a function of stimulus orientation (collapsed between palm/dorsum view and left/right laterality [hands] and F/J and canonical/mirror-reversed view [letters]). For the HLT, we adopted Parsons (1987) original distinction between stimuli across the body midline and stimuli away from the body midline to estimate the accuracies for 90° and 270° rotated hands stimuli (see main text for details)

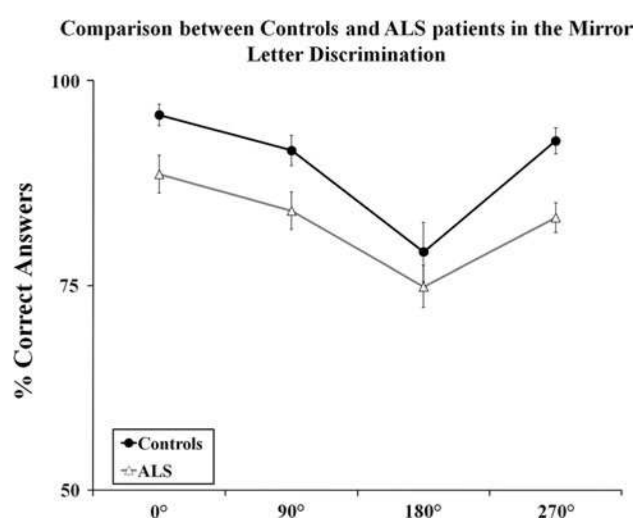

Fig. 3 Percentage of correct answers (*bars* represent standard error of the mean) in control participants (*black line with black circles*) and ALS patients (*gray line with white triangles*), in the MLD, for each degree of rotation stimuli (collapsing accuracies estimates between F/J and canonical/mirror-reversed view). ALS patients and controls showed the same pattern of performance with a greater accuracy for 0° stimuli and the higher error rate for stimuli presented at 180°, suggesting that the effect of stimulus orientation is present for alphanumeric characters

Hand laterality task

We obtained the accuracies estimates for 0° and 180° in dorsum and palm view collapsing left and right hand performances. We followed the original distinction proposed by Parsons (1987) between stimuli across the body midline (or comfortable postures) and stimuli away from the body midline (or awkward postures). Thus, we averaged +90° right hand and −90° left hand performances to obtain the 90° category (awkward postures) and we average accuracies for +270° right hand and −270° left hand to recode the 270° rotated category (comfortable postures) (Fig. 1). We adopted this statistical approach because it allows to explore all the typical effects of the HLT. Levene Test for homogeneity of variances showed a violation of the homogeneity of variance assumption in the HLT data ($F_{[1,44]} = 5.873$, $p = 0.020$). Thus, we applied also in this case the Greenhouse-Geisser correction to the ANOVA.

We performed a mixed-effects ANOVA with Stimulus view (dorsum and palm view) and Angle of rotation (0°, 90°, 180°and 270°) as within-subject factors and Group (Control and ALS) as between-subject factor. This analysis showed a significant main effect of Angle of rotation ($F_{[2.579,113.484]} = 36.670$, $p < 0.001$) and Group ($F_{[1,44]} = 8.380$, $p = 0.006$). Furthermore, we found a two-way interaction between Angle of rotation and Group ($F_{[2.579,113.484]} = 9.948$, $p < 0.001$) and between Angle of rotation and Stimulus view ($F_{[1.829,113.484]} = 6.522$, $p = 0.003$). No other significances were found (all ps > 0.05).

When exploring the main effect of Angle of rotation, results showed a significantly greater accuracy for hands at 0° versus 90° ($t_{[45]} = 5.349$, $p < 0.001$), versus 180° ($t_{[45]} = 8.407$, $p < 0.001$) and versus 270° ($t_{[45]} = 2.855$, $p = 0.006$). Moreover, we found a significantly worse performance for hands at 180° versus 90° ($t_{[45]} = 4.112$, $p < 0.001$) and versus 270° ($t_{[45]} = -6.595$, $p < 0.001$). Further, when exploring the main effect of the Group, we confirmed that ALS patients are less accurate than controls ($t_{[37.805]} = 2.895$, $p = 0.006$).

We directly compared the performances at 0° versus 180° within each group to explore the presence of the effect of the stimulus orientation. Results showed that also in the HLT, both controls ($t_{[22]} = 4.692$, $p < 0.001$) and ALS patients ($t_{[22]} = 7.782$, $p < 0.001$) present such MR index. Thus, these data confirm our findings from the MLD also in case of body parts stimuli.

Then, we explored the interactions by means of t tests (Bonferroni corrected). For the first interaction between Angle of rotation and Group, we collapsed accuracies for dorsum and palm view. Results showed that this interaction is driven by a significant difference for 270° rotated stimuli (the comfortable postures stimuli), with a better accuracy for controls ($t_{[28.157]} = 8.646$, $p < 0.001$). In this phase, we also assessed if visual recognition (without MR operations) of the stimulus hand is spared in ALS patients by comparing the two groups performances at 0° of rotation. We did not any significant difference ($t_{[43.993]} = 1.208$, $p = 0.234$).

We then explored the second interaction between Angle of rotation and Stimulus view. Results revealed a significant difference between palm and dorsum view conditions at 180° of rotation ($t_{[45]} = -3.195$, $p = 0.003$), being palm hands better recognized (Fig. 4). In other words, our data showed a symmetrical pattern of performance for the dorsum view and asymmetrical accuracies for the palm condition (Fig. 4), strongly in agreement with Brady and colleagues (Brady et al. 2011) findings from reaction times.

Finally, we directly compared performances for 270°, or comfortable postures, versus 90° rotated stimuli, or awkward postures (Parsons 1987), within each group, to assess the presence of the effect of hand posture. Crucially, results showed that controls present this effect ($t_{[22]} = 4.264$, $p < 0.001$). Differently, ALS patients do not show the expected differences between comfortable and awkward postures ($p > 0.05$) (Fig. 5).

Correlation with clinical variables

We were interested in exploring the influence of clinical variables (onset, ALSRS-r scores, disease duration and phenotype) on the HLT and on the MLD performances. Thus, we averaged the performance for each angle of rotation in both tasks to obtain an overall performance measure. Then, we performed Spearman's rank correlations. These analyses showed no significant correlation (all ps > 0.05).

Discussion

Amyotrophic Lateral Sclerosis (ALS) is a degenerative disease characterized by a progressive atrophy of the first and second motor neurons (Brooks 1994; Brooks et al. 2000) and of the descending motor pathways (Chevalier-Larsen and Holzbaur 2006). As a consequence, in this pathology, most of the areas providing the fundamental motor feedbacks used in MI (Parsons et al. 1995, 1998) encounter a progressive deterioration.

Here, we adapted an established task that provides reliable indexes of the use of MI, that is, the effects of biomechanical constraints (Parsons 1987; Sekiyama 1982; Brady et al. 2011), to clarify whether MI abilities are compromised in ALS patients. Moreover, we administered patients with a control task to disentangle body related from general MR deficits (Pelgrims et al. 2010).

The effects of biomechanical constraints, such as the effect of hand postures and of the stimulus view, are specific indexes related to MI performance as only the mental

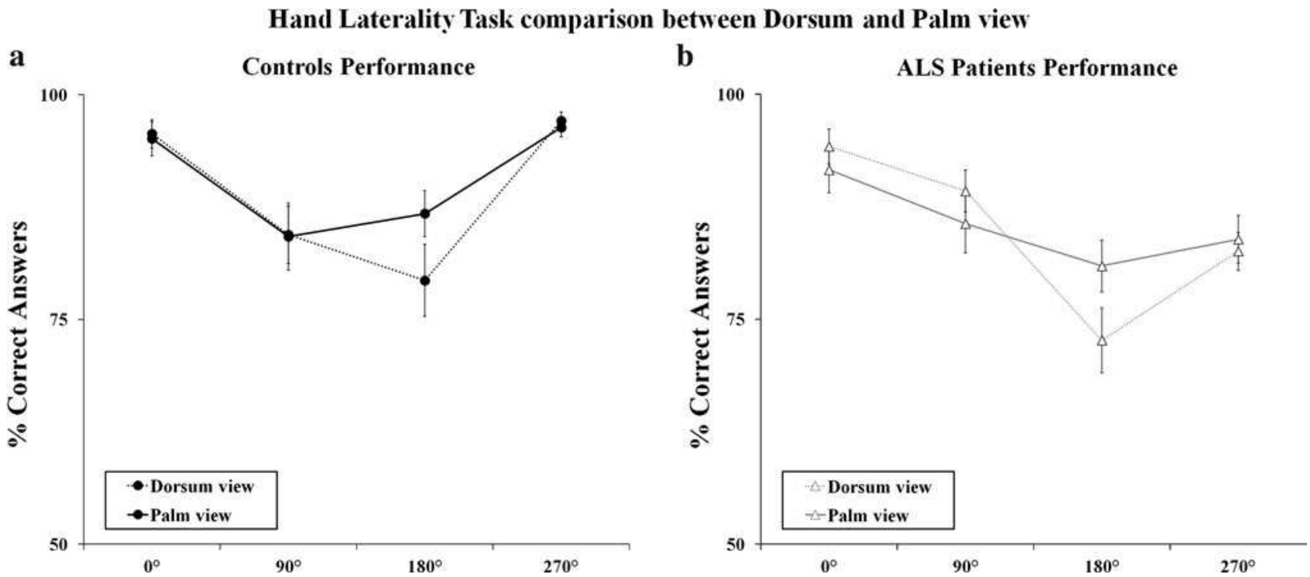

Fig. 4 Percentage of correct answers (*bars* represent standard error of the mean) at the HLT for each degree of rotation. **a** Controls performance is reported in *dotted* (*dorsum view*) and *continuous* (*palm view*) *black lines with blackcircles*. **b** ALS patients accuracies are reported in *dotted* (*dorsum view*) and *continuous* (*palm view*) *gray line with white triangles*. We averaged left and right hand performances for the accuracies estimates at 0° and 180° in *dorsum* and *palm view*. The accuracies for 90° and 270° rotated hands have been estimated according to Parsons (1987) original distinction between stimuli across the body midline and stimuli away from the body midline collapsing left and right hand performances. Thus, for 270° stimuli category, we averaged performance at +270° for the right hand and −270° for the left hand, whereas the 90° stimuli category was obtained by averaging the +90° for the right hand and −90° for the left hand. ALS patients and controls show the same pattern of accuracy, symmetrical about 180° for the *dorsum view* and asymmetrical about 180° in the *palm view*

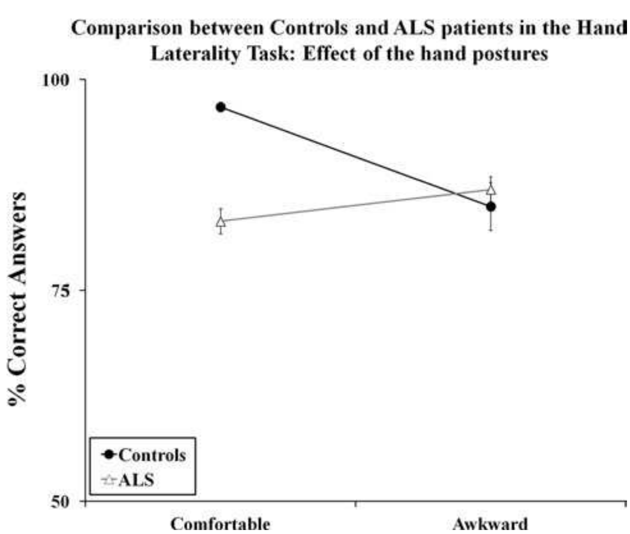

Fig. 5 Percentage of correct answers (*bars* represent standard error of the mean) in control participants (*black line with black circles*) and ALS patients (*gray line with white triangles*), at the HLT for awkward postures (or 90°) and comfortable postures (or 270°). ALS patients, differently from controls, did not show the effect of hand postures

simulation of the movements of one owns body parts to match the stimulus position induces the presence of these effects (Parsons 1994; Gentilucci et al. 1998a, b). The effects of biomechanical constraints are reported in some categories of patients affected by motor dysfunctions. For instance, upper limb amputee patients, affected by peripheral deafferentation of the motor pathways, show the effect of hand postures in MI tasks (Nico et al. 2004). Similarly, the effect of hand postures has been found in patients affected by cortical motor inhibition deficits, as in focal hand dystonia (Fiorio et al. 2006).

Conversely, we did not find a significant advantage in the accuracy for comfortable positions in ALS. In other words, the effect of hand postures was absent in our patients, suggesting that a lesion to the first and second motor neurons affects MI. Our results are consistent with previous studies showing impairments in patients with damage to premotor and parietal cortical areas (Sirigu et al. 1996; Tomasino et al. 2003) and to the cerebellum (Gonzalez et al. 2005). A deficit of MI has been found also in Locked-in Syndrome, demonstrating that a total pontine deafferentation influences MI even when cortical areas are preserved (Conson et al. 2010). However, we also demonstrate that the effect of stimulus view is spared in ALS patients. In other words, our results indicate that not all biomechanical constraints are impaired, but rather we show a dissociation within these effects.

Both real and imagined movements require the activation of an internal model, which transforms a desired action into a specific motor command (Frith et al. 2000; Schwoebel et al. 2001; Shenton et al. 2004). Parsons (1987) demonstrated that healthy subjects mentally rotate their own hand representation to match it with the visual stimulus when judging laterality (Parsons 1987). Current models of hand laterality recognition (Sekiyama 1982; Parsons 1987, 1994; Parsons et al. 1995; Gentilucci et al. 1998a, b) postulate that, in a first stage, an implicit recognition of the stimulus "hand" takes place via a visual analysis, in an action-independent manner. On a second stage, the internal representation of the hand is mentally rotated to reach the position of the target and to judge the laterality of the stimulus. This second level depends on action-related knowledge, in other words is affected by the hand angle of viewing and by its postures (Sekiyama 1982; Parsons 1987, 1994; Parsons et al. 1995; Gentilucci et al. 1998a, b).

We directly assessed the integrity of patients' ability to recognize hands at 0°, accordingly we can hypothesize that the first stage of the MI model, the visual recognition of the stimulus hand, is intact in ALS patients. Conversely, the lack of an advantage in judging hands in comfortable postures (the effect of hand postures) suggests compromised MI abilities and in particular a deficit in the second stage of the hand recognition model (Parsons 1987), in which movement of one owns hand image is performed. Nevertheless, this model does not fully account for our data, as we found a dissociation between biomechanical constraints effects. Postulating that the second stage of hand recognition is globally responsible for these effects, the prediction would be a lack of all biomechanical constraints effects.

Alternatively, our results could be explained considering a broader theoretical frame, namely that of reach-to-grasp actions. These movements are distinguishable into a transport component related to the proximal arm muscles and a grip component related to the distal hand muscles (Arbib 1981; Jeannerod 1999). This subdivision has been recently confirmed by neuroimaging studies (Cavina-Pratesi et al. 2010) that demonstrated a clear division of labor between two sub-streams inside the dorsal stream: a dorsolateral stream devoted to the grasp planning and execution (encompassing aAIP and the vPM), and a dorsomedial substream related to the transport component (comprising SPOC and dPM) (Cavina-Pratesi et al. 2010). The movement required to obtain a hand rotated in a palm or dorsum view is based on the action of distal muscles. Conversely, comfortable versus awkward postures are obtained activating the entire arm, in other words using also the proximal musculature. Paralleling these real constraints, it can be hypothesized that also the correspondent mental simulations are governed by the same rules, presenting biomechanical constraints that are divided into "proximal"- and "distal"-related effects. In fact, while the control group present both the effects, our patients show only the one related to the distal musculature (palm/dorsum view), while the effect related to the proximal muscles (comfortable/awkward postures) is compromised. These findings suggest that MI abilities related to the mental simulation of a motor act are compromised by the disease, although with a progression.

Importantly, our results show that the effect of stimulus orientation is spared in ALS, both when considering body parts and when considering alphanumeric characters. These findings suggest that patients' performance cannot be attributable to a merely impairment of MR processes, but rather is strictly related to body parts.

One possible critique to our study is the measure we employed. In a large number of papers looking at biomechanical constraints (Parsons 1994; Gentilucci et al. 1998a, b; ter Horst et al. 2010), reaction times (and not error rates) are used to demonstrate these constraints. However, our work is not the first making use of accuracy estimates. For instance, Ionta et al. (2007) demonstrated in unimpaired subjects that both reaction times and accuracy are influenced by hand postures, even tough to a less degree for the last measure (Ionta et al. 2007). Further, Ionta et al. (2007) find that the different stimulus view influences these two measures (Ionta et al. 2007). In the same direction, Ni Choisdealbha and colleagues, exploring the effect of hand dominance when judging the laterality of a body part (Ni Choisdealbha et al. 2011), find that accuracies and reaction times are sensitive to the effect of hand orientation and evidenced for both these measures the effects of the biomechanical constraint (Ni Choisdealbha et al. 2011). On the other side, reports in populations with severe motor impairments or limb absence also made use of accuracy to compute alterations of biomechanical constraints effects, in association with response latencies (Nico et al. 2004; Conson et al. 2010). Conson et al. (2010) directly analyzed the relationship between reaction times and accuracy in locked-in patients, highlighting a negative correlation between these two measures. This result seems to further suggest a quite reliable correlation (or mimic) between reaction times and accuracy.

Interestingly, our data did not show significant associations between clinical variables and MI. However, this lack of significance could be due to the numerousness of subjects in the clinical categories, which are not homogeneous. Future studies could better address the influence of clinical factors including a greater number of patients in each category (i.e. phenotype and onset). Exploring the link between the clinical and cognitive profile might be of interest: for instance, different ALS' phenotypes are known to carry distinctive and distinguishable physical prognostic characteristics, while less is known in the cognitive domain (Chio et al. 2011).

We, finally, speculate that our findings might provide evidence that cognitive impairments of ALS also selectively involve body representations. Since the historical work of Head and Holmes, it has been shown that dynamic proprioceptive, somatosensory and motor information serve to guide not only real but also imagined actions (Reed and Farah 1995; Schwoebel et al. 2001; Head and Holms 1911). This information is used to develop the body schema, which is a dynamic and unaware representation of body parts in space, continuously updated during movements (Berlucchi and Aglioti 2010; de Vignemont 2010). Our results, showing that the absence of motor feedbacks and proprioceptive and somatosensory information affect MI, are also suggestive of a possible compromising of the body schema. Future studies, using different tasks investigating directly body schema, could possibly confirm this speculation.

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Conflict of interest The authors declare that they have no conflict of interest.

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