The processing of actions and-action words in Amyotrophic Lateral Sclerosis patients

The Processing of Actions and Action-Words in Amyotrophic Lateral Sclerosis Patients

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Running Head: Action processing in a motor disease

Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with prime consequences on the motor function and concomitant cognitive changes, most frequently in the domain of executive functions. Moreover, poorer performance with action-verbs *versus* object-nouns has been reported in ALS patients, raising the hypothesis that the motor dysfunction deteriorates the semantic representation of actions. Using action-verbs and manipulable-object nouns sharing semantic relationship with the same motor representations, the verb-noun difference was assessed in a group of 21 ALS-patients with severely impaired motor behavior, and compared with a normal sample's performance. ALS-group performed better on nouns than verbs, both in production (action and object naming) and comprehension (word-picture matching). This observation implies that the interpretation of the verb-noun difference in ALS cannot be accounted by the relatedness of verbs to motor representations, but has to consider the role of other semantic and/or morpho-phonological dimensions that distinctively define the two grammatical classes. Moreover, this difference in the ALS-group was not greater than the noun-verb difference in the normal sample. The mental representation of actions also involves an executive-control component to organize, in logical/temporal order, the individual motor events (or sub-goals) that form a purposeful action. We assessed this ability with action sequencing tasks, requiring participants to re-construct a purposeful action from the scrambled presentation of its constitutive motor events, shown in the form of photographs or short sentences. In those tasks, ALS-group's performance was significantly poorer than controls'. Thus, the executive dysfunction manifested in the sequencing deficit –but not the selective verb deficit– is a consistent feature of the cognitive profile associated with ALS. We suggest that ALS can offer a valuable model to study the relationship between (frontal) motor centers and the executive-control machinery housed in the frontal brain, and the implications of executive dysfunctions in tasks such as action processing.

Keywords: Amyotrophic Lateral Sclerosis; action processing; noun-verb dissociations; dysexecutive syndrome; action sequencing.

Abbreviations:

ALS = Amyotrophic Lateral Sclerosis;

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale;

PPT = Pyramids and Palmtrees Test;

KDT = Kissing and Dancing Test

1. Introduction

Amyotrophic lateral sclerosis (ALS), the most common form of Motor Neuron Disease, is a neurodegenerative disorder that primarily implicates the motor system. Motor dysfunction frequently begins with fasciculations or cramps that gradually lead to weakened atrophic limbs, spasticity and bulbar symptoms, often associated with dysarthria (a disorder in the articulation of speech) and respiratory symptoms (Silani, Messina, Poletti *et al.*, 2011). The consequences of this neurological condition are not limited to motor symptoms: the 20-50% of patients exhibit cognitive deficits that, in the 5-15% of the cases, evolve in a full-blown dementia, usually of the frontotemporal type or FTD (Raaphorst, De Visser, Linssen et al., 2010; Silani et al., 2011; Andersen, Abrahams, Borasio et al., 2012). Most frequently, initial cognitive changes impact the executive functions (Abrahams, Leigh, Harvey *et al*., 2000; Elamin, Phukan, Bede *et al.*, 2011; Phukan, Elamin, Bede *et al.*, 2012; Taylor, Brown, Tsermentseli *et al.*, 2013): in effect, pathological performance on executive-function tests is currently regarded as the criterion for a diagnosis of cognitive impairment in ALS (Strong, Grace, Freedman *et al.*, 2009). More recently, attention has been reverted to language impairments, primarily observed in association with executive dysfunction (Phukan *et al*., 2012; Grossman et al., 2008; Taylor *et al*., 2013). For instance, Taylor *et al.* (2013) reported that the 43% of 51 non-demented ALS-patients was likely to have a language impairment, as indexed by a composite score derived from several language tasks.

A number of studies have suggested that the language impairment in ALS is characterized by a selective deficit in processing verbs *vs.* nouns (a summary of these studies is reported in Table 1). Bak and Hodges (1997) described three ALS patients with aphasia and FTD, whose performance was poorer with verbs than nouns, in a word-picture matching task. Moreover, the only patient who could complete the task exhibited significantly poorer performance in action naming than object naming. Bak, O'Donovan, Xuereb *et al.* (2001) extended this observation to six new cases with ALS and signs of dementia. Their patients were overall impaired in syntactic comprehension, as assessed with the Test of the Reception of Grammar (TROG; Bishop, 1989), and showed greater difficulties in naming drawings of actions than drawings of objects, and in matching a spoken verb with the corresponding action (among two options), relative to matching a spoken noun with the corresponding object.

In a subsequent study (Bak and Hodges, 2004), three ALS patients with dementia and aphasia were tested with the Pyramid and Palm trees test (PPT, Howard and Patterson, 1992), a picture-picture matching task involving objects, and with the Kissing and Dancing test (KDT; Bak and Hodges, 2003), a picture-picture matching involving actions. In all three patients, performance on KDT was significantly poorer than performance on PPT. More pronounced difficulties with action-verbs than object-nouns, in the context of a motor disorder such as ALS, have been linked to the deterioration of motor centers, participating in the representation of actions in language and semantics (Bak and Chandran, 2012).

This line of research encouraged further analysis of the verb-noun dissociation in ALS, to advance our understanding of the cognitive implications of ALS, and to establish whether ALS can be a valuable model for studying the relationship between motor and language/semantic functions.

Studying the processing of verbs *vs.* nouns in larger groups of patients could inform on whether a selective deficit with action-related stimuli, such as action-verb, is a consistent characteristic of the cognitive changes in ALS, before a full-blown dementia develops.

In doing so, we notice that, in the context of verb-noun dissociation in ALS, grammatical and semantic components of the effect have recurrently been confused. In fact, in all the above studies, verb-noun differences were assessed with action-verbs and object-nouns (i.e. nouns denoting various kinds of concrete objects, such as plants, animals, vegetables, buildings, artifacts, etc.). While the semantic relationship with a motor representation is considered the cause of action-verbs *vs.* object-nouns differences in ALS, these categories of stimuli also differ for other semantic, syntactic and morpho-phonological properties. Thus, performance differences between action-verbs and object-nouns in ALS could reflect differences in action-relatedness or other differences.

To argue that an action-verb deficit results from impaired motor representations, one must show that patients fail with action-verbs (e.g. to eat) but not with non-action verbs (e.g. to wonder), or that the verb-noun difference disappears when both sets of stimuli are semantically related to the same motor representations. This latter control has been implemented in the current study to address the causal relation between semantic relatedness to motor representations and the verb disadvantage in ALS. We reasoned that, if the semantic relatedness to motor representations was the exclusive cause of previously observed noun-verb differences in ALS, such effect should not be found with the current experimental design. Alternatively (i.e., in case such differences persist), we shall refuse an account of verb-noun differences in ALS as exclusively driven by unbalanced semantic relationship of the two word categories with motor representations.

Furthermore, we have mentioned earlier that, in ALS, language deficits co-occur (Phukan *et al*., 2012) and are tightly correlated with frontal-executive dysfunction (Taylor *et al*., 2013). In effect, ALS patients with alleged action-verb deficits most often had executive dysfunction (see Table 1). Neuropsychological investigation has shown that executive functions play a role in tasks involving verbs (Rhee *et al*., 2001; Vigliocco *et al*., 2011) and actions (Cooper and Shallice, 2000). In particular, in action processing, executive functions are critical for retrieving the logical/temporal organization of the individual motor events (or sub-goals) that constitute a coherent, purposeful action (Sirigu, Cohen, Duhamel *et al*., 1995; Sirigu, Duhamel, Cohen *et al*., 1996; Rumiati, Zanini, Vorano *et al*., 2001; Zanini, Rumiati and Shallice, 2002). For instance, Zanini *et al.* (2002) reported that patients with frontal-executive dysfunction systematically failed to retrieve the correct order of motor acts that formed a complete everyday activity (e.g., preparing coffee). The ability for action sequencing is independent from the ability to physically produce action, and may or may not be associated with impaired action recognition (Humphreys and Forde, 1998; Zanini *et al*., 2002). These observations raise the new question that deficits in processing action-related stimuli and action-verb processing could be affected (or even accounted) by the executive dysfunction that most frequently accompanies ALS.

The current study involved 21 non-demented ALS patients and 14 neurologically normal controls, and three sets of experimental tasks. The first set included three motor production tasks: pantomiming on verbal command, object use and imitation. The purpose of these tasks was to assess whether our patients with a diagnosis of ALS showed visibly deteriorated motor performance relative to the normal population.

Moreover, we tested participants' retrieval (naming) and comprehension (word-picture matching) of verbs and nouns. By comparing the performance of ALS-patients *vs.* normal controls on these tasks, we assessed whether the verb-noun dissociation is a consistent characteristic of the cognitive changes associated with ALS. Importantly, in our study, both verbs and nouns were related to the same motor representations. In particular, for each action verb (e.g. "scrivere", *to write*), we selected the manipulable object most consistently involved in the action ("penna", *pen*). The motor representation associated with the action "to write" is held to participate in the representation of the object "pen", as it contributes to define its program for manipulation and its function (Johnson-Frey, 2004; Martin, 2007). Thus, if ALS-patients' disadvantage with verbs (*vs.* nouns) truly reflects damage to the motor representations implicated by action-verbs, this effect should disappear when both verbs and nouns shared motor representations.

Finally, we administered two sequencing tasks, in which participants were instructed to rearrange sets of sentences or photographs in a coherent (verbal or pictorial) description of a purposeful object-directed action. All actions were of the "schema-type" (e.g., brushing one's teeth), namely, simple actions constituted by motor events (or sub-goals) carried out in an effector-specific manner (e.g., in brushing one's teeth, the toothbrush is hold with a whole-hand grip, as opposed to precision grip, and is translate up and down, but not, say, squeezed), to achieve the final action goal (see Zanini *et al*., 2002). This kind of tasks has been proven sensitive to frontal-executive deficits in neurological populations (Rumiati et al., 2001; Sirigu et al., 1996; Zanini et al., 2002).

Thus, with these tasks, we assessed the executive functioning of our patients, and particularly, a component of the executive functioning that could have direct implications for action processing.

- Table 1 about here -

2. Materials and methods

2.1. Participants

Patients. Twenty-one patients with diagnosis of ALS took part in the study (9 females, mean age, years ±standard deviation: 63.3 ±14.7, mean education: 9.8 ±5.4). Six patients were recruited from the neurological unit of the "Ospedali Riuniti" of Trieste, and sixteen patients from the neurological unit of the "Azienda Ospedaliero-Universitaria-Santa Maria della Misericordia" of Udine. A neurologist assessed the severity of physical/motor dysfunctions and dysarthria with the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R; Cedarbaum, Stambler, Malta *et al.*, 1999), a questionnaire-based scale that measures the abilities for carrying out daily-life activities (see Table 2).

All patients underwent a neurological evaluation before the experimental sessions. Given that our experimental tasks involved visual stimuli and word production, we recruited patients who were referred by the neurologist as having preserved visual sensory efficiency and no speech production deficits. No one had a presumptive diagnosis of dementia.

As part of the screening, all patients were administered a picture-naming task with line drawings of 50 objects and 50 actions, matched for frequency and age of acquisition of the corresponding word, and picture typicality (Crepaldi, Aggujaro, Arduino *et al*. 2006). The purpose of this test was to assess verb-noun differences with a task analogous to those used in most previous studies on ALS consisting of action and object naming (e.g., Bak and Hodges, 1997; Bak and Hodges, 2004). As in those previous studies, intra-individual differences between object- and action-naming were computed (chi-square statistics), revealing that 18 out of 21 patients performed qualitatively better on object than action naming; in 9 cases this difference was significant (*P*s<0.05; see Table 2). Descriptively, the verb-noun difference was on average 11.62 percentage points (82.8% correct for verbs and 94.4% correct for nouns). This number is within the range of verb-noun differential scores (2-15 percentage points) in previous samples reported in Table 1, except for Bak et al. (2001), who reported a difference of ~30 percentage points averaging across three patients[1]. This analysis demonstrated that our sample was comparable with the samples of previous studies, in showing an overall advantage of object-nouns over action-verbs.

Controls. Fourteen neurologically healthy adults (8 females, age = 65.1 ±16.3, education = 10.3 ±3.3), matched with patients for age and education (age: $t(33)=-0.35$, $P=0.72$; education: $t(33)=-0.26$, $P=0.79$), served as controls. They were clear of signs of cognitive decline, as assessed with the Montreal Cognitive Assessment (Nasreddine, Phillips, Bédirian *et al.*, 2005). The study was approved by the local Ethics Committee. All patients and controls signed the informed consent before taking part in the study.

- Table 2 about here -

2.2. Stimuli

Actions/action-verbs and object/objects-nouns. The following stimuli were taken from Papeo *et al.* (2010): 15 color video clips of pantomimes of manual actions (3 s each), in

[1]Verb-noun differential scores were obtained from the descriptive statistics reported in the studies listed in Table 1 or, where not available, estimated from the plots of action and object naming performances.

which the same actor pantomimed the use of a manipulable object (the object was not shown); 15 real manipulable objects (those implied in the above actions); 15 verbs denoting the above object-use actions; and 15 nouns denoting the above manipulable-objects and matched with verbs for length ($t(14)=-0.63$, $P>0.1$), age of acquisition ($t(14)=-0.31$, $P>0.1$), and frequency (from Bertinetto et al., 2005; $t(14)=1.87$, $P=0.08$). Thus, the sets of actions/action-verbs and objects/objects-nouns shared a semantic relationship with identical motor representations.

We evaluated this relationship empirically, as follows. First, we assessed whether each manipulable object (e.g. a pen) was consistently retrieved upon presentation of a video-clip, where an object-use action (e.g. writing) was pantomimed but the object was not displayed. Twenty-one participants (15 female, age 24 ±2.8; education 16 ±1.7) saw the 15 action pantomimes used in the study and named the "target" object involved. For each item, at least 76% of participants retrieved the correct target-object (mean 92.4% ±8.8). Binomial tests showed that this response was significantly above chance (50%) for each pantomime (Ps<0.02).

In a second study, 20 new participants (14 female, age 25 years ±3.9; education 16 years ±1.7) were presented with the photographs of the same 15 manipulable objects, and were asked to generate an associated action. In response to all objects, the 100% of participants retrieved a verb denoting a manual action. Moreover, for all objects, at least 85% of participants (mean 98% ±4.1) retrieved an item included in the experimental action-verb list. This response was above the chance level for each object-stimulus (binomial tests; Ps<0.01).

The semantic relationship between action-verbs and object-nouns was further evaluated with a rating study involving a panel of 10 new participants (7 female, age 27 years ±2.7; education 18 years ±0.3). We created two lists of stimuli: in one list, each of the verbs denoting the 15 pantomimes was paired with the noun denoting the object involved in the pantomime (matched pairs); in a control ("scrambled") list each noun was randomly assigned to one verb of the list. Participants were randomly presented with the 15 matched and the 15 scrambled pairs; for each pair, they had to rate on a 7-point Likert-scale the extent to which the action-verb and the object-noun were associated. The mean rating for each matching pair was above the neutral mid-point 4 (mean: 6.85 ±0.25 *SD*). These ratings were significantly greater than ratings assigned to the control pairs (mean: 1.5 ±0.77 *SD*; $t(28)=-25.52$, $P<0.0001$), implying that the semantic relationship between action-verbs and object-nouns in our stimulus-set was stronger than the semantic relationship between *any* manual action and *any* manipulable object.

The same panel evaluated the semantic relatedness of each individual stimulus in our list (15 action-verbs and 15 object-nouns) to a physical action, on a 7-point Likert-scale. To prevent response-bias, we included 15 control verbs and 15 control nouns, matched with our stimuli for frequency and length but with no obvious motor-action content (verbs: frequency, $t(14)=1.14$, $P=0.27$; length, $t(14)=-1.55$, $P=0.14$; nouns: frequency, $t(14)=-0.62$, $P=0.54$, length, $t(14)=0.21$, $P=0.83$). Although ratings for verbs were on average higher than ratings assigned to nouns ($t(14)=13.51$, $P<0.001$), all items included in the main study obtained ratings above the neutral mid-point 4 (mean rating for verbs: 6.48 ±0.29 *SD*, for nouns: 6.12 ±0.26), which were significantly higher than ratings assigned to control-verbs ($t(14)=13.34$, $P<0.001$) and control-nouns ($t(14)=41.75$, $P<0.001$).

With this series of studies, we ascertained that actions and manipulable objects (and by extension, the corresponding verbs and nouns) in our stimulus-set overlapped for semantic relatedness to motor representations.

Sequences. We created *de novo* 55 color photographs depicting fragments of 15 object-use actions (each action was described by a sequence of 4-5 photographs; the object was shown) and 54 sentences describing the different steps of 15 object-use actions (each action was described by a sequence of 4-5 sentences). In addition, five new sequences were created for control tasks, including shapes (4 circle-, heart-, square-, or triangle-shapes, of four different sizes made in red cardstock) or numbers (10 different numbers of one or two digit, printed in black ink on ten red cards).

2.3. *Tasks and Procedures*

The order of tasks was counterbalanced across participants. Items in each task were presented in a fixed pseudorandom order, except for the object-use task, where items were randomly presented. Patients' testing was carried out in a quiet room of the hospital; controls were tested in a dedicated room at SISSA.

Pantomiming on verbal command. Participants were given a verbal command to produce 15 pantomimes of objects-use actions (e.g., "Show me how you would drink from a glass"). They were instructed to simulate holding and manipulating the object involved in each action. Participants' performance was videotaped for off-line analysis, carried out by one author (C.C.) and two researchers trained for scoring praxis tasks, and blind to the hypotheses of the study and to subjects' classification (patients or controls). Each gesture was scored 2 when at least two raters judged the performance as correct. When the participant produced an error that was acknowledged by at least two raters, we distinguished between cases in which the action was still recognizable (score=1), and cases in which the error was such that the action was no longer recognizable (score=0). The maximum score that a participant could obtain was 30.

Pantomimes imitation. Participants were asked to imitate 15 pantomimes of object use shown in 15 video-clips, on a computer screen. Each gesture was presented once and, if the participant failed to imitate it correctly, it was shown again for a maximum of two times. Participants' performance was videotaped and analyzed offline by the three raters, with criteria identical to those used for the pantomiming-on-verbal-command task.

Manipulable-objects use. The 15 manipulable objects were placed, one at a time, on the table in front of the participant, who was asked to demonstrate how s/he would use it. Participants' performance was videotaped and analyzed offline by the three raters. In evaluating the performance, we distinguished between correct use (score=1) and errors (score=0, when at least two raters judged the performance as incorrect). The maximum score was 15.

Naming of actions and manipulable objects. This task was organized in two subtests. In subtest 1, participants were instructed to produce the verbs describing each of 15 pantomimes of object use, presented as video clips, one at a time, on a computer screen. In subtest 2, participants were instructed to produce the noun denoting each of the 15 manipulable objects depicted in photographs, and presented one at a time on a computer screen. Each response was scored as correct (score=1) or incorrect (score=0).

Self-repairs, dialect forms of the target and phonological errors, in which the target was clearly recognizable, were scored as correct. Semantic paraphasias, circumlocutions, and latencies longer than 5 s were scored as errors. In the event of multiple responses to one item, the first was considered. The maximum score for each subtest was 15.

Verb and noun comprehension. The word-picture matching task was organized in two subtests assessing verb and noun comprehension, respectively. In subtest 1, a verb was spoken aloud by the experimenter, while three color photographs (the target and two distractors) appeared on the computer screen. Each of 15 targets depicted the object-use gesture corresponding to the spoken verb. The two distractors were an action semantically related to target[2], and another visually similar to the target, obtained by modifying a kinematic aspect of the target action. Participants were instructed to point at the photograph depicting the spoken item. In subtest 2, task and procedures were identical to subtest 1, except that a noun, instead of a verb, was spoken and 15 photographs of the above 15 objects were shown together with a semantically related and a visually related object (e.g. target: spoon; semantic distractor: ladle; visual distractor: a round mirror with handle). In both subtests, the relative position of target and distractors (left, center, right of the screen) was counterbalanced across trials. Correct responses were scored 1, and incorrect responses (either distractor) were scored 0. The maximum score for each subtest was 15.

Sequencing tasks. In the sequencing tasks, participants were instructed to rearrange photographs or sentences describing the different steps involved in the use of 15 manipulable objects. This section was organized in two subtests, in which participants

[2] The semantic distance between targets and semantic distractors was rated by a panel of 10 subjects (5 female; mean age =26.6 years ±3.1; mean educational level= 16.9 years ±1.6). For a detailed description of this rating study we refer Papeo et al. (2010).

had to organize 4-5 sentences and 4-5 photographs, to form a coherent purposeful action. The 4-5 sentences or photographs were presented in scrambled order on the table in front of the participant. One point was assigned to each sentence or photograph assigned to the correct position in the sequence. The maximum score was 54 for the sentence sequencing and 55 for the photograph sequencing.

To make sure that participants did understand the task instructions and to evaluate their general ability to order items based on a given criterion, additional sequencing tasks were administered (see Humphreys and Forde, 1998; Zanini *et al.*, 2002). In those tasks, participants had to rearrange 5 items with same geometrical shape and different size, according to the size. Four series of shapes (i.e., hearts, circles, squares, and triangles) were included. One point was given for each shape correctly sequenced. In the last task, participants were required to order ten numbers. One point was given for each number assigned to the correct position in the sequence.

2.4. Analyses

We carried out a group level analysis on the individuals' percentages of correct responses obtained in each experimental task. As data from patients and controls were not normally distributed (Shapiro Wilk's test, $P<0.05$), they were normalized with arcsine transformation.

To compare motor-production performances in patients *vs.* controls a repeated-measures ANOVA was performed with factors, 2 Group (patients and controls) and 3 Task (pantomiming to verbal command, manipulable-object use and imitation). Patients' and controls' performances on verbal tasks were compared in a repeated-measure

ANOVA with factors, 2 Group (patients and controls), 2 Task (naming and comprehension) and 2 Word-category (nouns and verbs). Finally, patients' and controls' performances on sequencing tasks were compared in a repeated-measure ANOVA with factors 2 Group (patients and controls) and 2 Task (sequencing of sentences and sequencing of photographs).

3. Results

Motor-production tasks (Fig. 1). The ANOVA revealed a significant effect of Group, $F(2,66)=12.48$, $P=0.001$, with patients being more impaired than controls in all three motor tasks. The effect of Task, $F(2,66)=0.56$, $P=0.57$, and the interaction $F(2,66)=0.46$, $P=0.63$, were not significant.

The errors made by patients across the motor tasks were analyzed by applying the error classification used for praxis tasks (see Tessari *et al.*, 2007). The majority of errors (66.24%) were spatial (misorientation of hand/arm); in 28.57% of cases gestures were unrecognizable; a minor percentage of errors (5.19%) were semantic, consisting of the "body part as a tool" error (i.e. the participant does not include the object in the gesture and uses the arm/hand/finger as if it were the object). We remark that, although we used tasks and error classification proper of apraxia studies, patients' motor difficulties, primarily affecting the spatial aspects of the gestures, should be intended as a consequence of the ALS at the peripheral level. Presumption of apraxia can only be considered when motor production deficits cannot be accounted for by impaired physical (peripheral) abilities. This was not the case for our patients.

Language-semantic tasks (Fig. 2). The ANOVA yielded a main effect of Word-category, $F(1,33)= 41.75$, $P<0.001$: both patients and controls were less accurate with verbs than with noun in production (i.e., naming) ($P=0.001$ and $P=0.019$, respectively) and comprehension ($P<0.001$ and $P=0.042$, respectively). There was no significant effect of Group, $F(1,33)=1.06$, $P=0.31$, and no interaction between Group and Word-category $F(1,33)=1.28$, $P=0.26$, or between Group and Task, $F(1,33)=0.3$, $P=0.58$.

Sequencing tasks (Fig. 3). The effect of Task was significant, $F(1,33)=5.57$, $P=0.024$: both patients and controls were more accurate with sentences than with photographs. The effect of Group was significant, $F(1,33)=12.55$, $P=0.001$. However, the two factors did not interact, $F(1,33)=0.25$, $P=0.62$, showing that patients' performance was poorer that controls' in sequencing both sentences and photographs.

Both patients and controls performed at ceiling on shape and number sequencing tasks. The patients' successful performance on these tasks ensured that the impaired action sequencing did not reflect a general inability in organizing sequences of items according to a given criterion, or inability to comprehend task instructions.

Our study considered the possibility that executive dysfunctions in ALS, measured here with action sequencing tasks, could affect action processing. Using Pearson's correlations, however, we did not find significant correlation between patients' performance on action sequencing tasks and their performance on language-semantic tasks assessing action recognition (all Ps>.15)[3]. The lack of correlation, together with the finding that ALS patients performed within the normal range in naming and word-picture

[3] Pearson correlation coefficients between action sequencing (verbal version) vs. 1) action naming (r=0.09; $P=0.6$); 2) object naming (r=0.30; $P=0.1$); 3) verb-picture matching (r=0.26; $P=0.2$); 4) noun-picture matching (r=0.33; $P=0.1$). Pearson correlation coefficients between action sequencing (pictorial version) vs. 1) action naming (r=0.22; $P=0.3$); 2) object naming (r=0.002; $P=0.9$); 3) verb-picture matching (r=0.02; $P=0.9$); 4) noun-picture matching (r=0.001; $P=0.9$).

matching, but pathologically in action sequencing tasks, suggests functional independence between the ability to recognize a given action and to mentally organize its constitutive motor events.

- Fig. 1, 2 and 3 about here –

Additional analyses. Acknowledging the cognitive variability of the ALS population (Consonni *et al.*, 2013; Taylor et al., 2012), we considered a broad distinction within our sample, based on the results of the action-object naming test used in the patients' screening (Crepaldi *et al*. 2006). We recall that this test revealed a general advantage in our ALS sample for noun *vs.* verb retrieval, which was statistical significant in 9 cases (chi-square tests; see Table 1). We performed additional ANOVAs over the patients' data, including a categorical predictor that distinguished between two groups: cases with and without a statistically significant verb-noun difference.

There was no difference between the two groups in any of the motor tasks (Effect of Group: $F(1,19)=0.26$, $P=0.61$; Effect of Task: $F(2,38)=0.7$, $P=0.46$; Interaction: $F(2,38)=1.40$, $P=0.26$). In the naming and word-picture matching tasks, the advantage for nouns over verbs independently from the group, remained the only significant effect (Word-category effect: $F(1,19)=27.81$, $P<0.0001$). All other effects were far from significance (Group: $F(1,19)<1$; Task: $F(1,19)<1$; Task*Group: $F(1,19)<1$; Word-category*Group: $F(1,19)<1$; Task*Word-Category: $F(1,19)<1$; Task*Word-category*Group: $F(1,19)=1.4510$, $P=0.24$). Finally, no difference between groups was found in either action sequencing task (Group: $F(1,19)<1$; Task: $F(1,19)=2.21$, $P=0.15$; Group*Task: $F(1,19)<1$). The lack of Group effect confirmed that the verb disadvantage was a general feature in our sample irrespective of whether, at individual level, the verb-noun difference was statistically significance. The lack of Group effect in praxis tasks and action sequencing tasks confirmed the independence of motor and sequencing abilities from the lexical-semantic processing of action-related stimuli.

Finally, we carried out a by-item analysis in which possible effects of processing the same items across different tasks were addressed. Having the same items in different tasks minimized the effect of differences at the stimulus-level on the participants' behavior in different tasks. However, processing an item in a given task might affect (e.g. facilitate) the processing of the same item in the following tasks. If this were the case, the performance on individual items across tasks should correlate. To assess this possibility, we derived rankings of item difficultly across praxis and lexical-semantic tasks involving identical items (the same actions for naming, word-picture matching, pantomiming on verbal command, and imitation; the same manipulable-objects for naming, word-picture matching and object use). Rank order values of item difficulty were defined according to the number of subjects who hit the target in each task. We computed Spearman's rank correlation coefficients to evaluate the relationship between the ranked series of items. Two sets of analysis, considering respectively patients' performances alone and patients' and controls' performance in the same model, gave identical results. No rank correlation was significant (all *P*s>0.05), except for a trend for pantomiming on verbal command *vs.* imitation (*P*=0.053)[4]. Thus, although items repeated across language-semantic and praxis

[4] Spearman's rank correlation coefficients for tasks involving the same action-stimuli: 1) naming vs. word-picture matching: N=15, Spearman R=0.38, P=0.15; 2) pantomiming on verbal command vs. imitation, N=15, Spearman R=0.51, P=0.053; 3) naming vs. pantomiming on verbal command, N=15, Spearman R=-0.03, P=0.92; 4) naming vs. imitation, N=15, Spearman R=-0.04, P=0.89; 5) word-picture matching vs. pantomiming on verbal command, N=15, Spearman R=0.03, P=0.92; 6) word-picture matching vs. imitation, N=15, Spearman R=-0.04, P=0.97. Spearman's rank correlation coefficients for tasks involving the same manipulable objects: 1) naming vs. word-picture matching, N=15, Spearman R=-0.16, P=0.56; 2) naming vs. object use, N=15, Spearman R=-0.28, P=0.30; 3) word-picture matching vs. object use, N=15,

tasks; performance on a given item in a task was independent from performance on the same item in the other tasks.

4. Discussion

The present study assessed the performance of patients with amyotrophic lateral sclerosis (ALS) in three motor production tasks (imitation, pantomiming on verbal command, and object use), in verbal tasks involving action-related verbs and nouns (naming action and manipulable objects, and understanding action verbs and manipulable-object nouns), and in the executive control over action-related information (action-picture and action-sentence sequencing tasks). The general goal of the study was to assess whether a selective impairment in action-verb processing is a consistent, defining characteristic of the cognitive change associated with a motor neuron disorder such as ALS. This analysis, in a group of 21 ALS patients, can inform on whether this population can provide a valuable model for studying the relationship between motor dysfunction and cognitive abilities such as language and semantics. Moreover, given the frequent executive dysfunction in ALS, we assessed whether patients' difficulties concerned aspects of action processing, which rely on executive control over action-related information. In the following, we discuss the findings of the study and their implications.

4.1. Verbs and nouns in ALS

Theoretical and empirical work emphasizes a necessary, functional relationship between motor representations for action execution and the representations of actions in language

Spearman R=0.03, P=0.90. These results consider the performances of both patients and controls. Statistically identical results were found considering only patients' performances.

and semantics (Bak and Chandran, 2012). Our patients provided a sensitive model for assessing this hypothesis, as they all had a diagnosis of a fatal motor neuron degeneration (ALS) with visible consequences on their motor behavior. We found that, relative to normal controls, ALS patients were significantly impaired in motor production tasks, but not in language-semantic tasks. In particular, their performance in tasks involving action-verbs and manipulable object-nouns provides insight on two questions.

First, what is the cause of the verb-noun difference? In the current study, while both categories implied motor representations, our patients performed better on nouns than verbs. In previous studies (see Table 1), the semantic relatedness to motor representations was not balanced across verbs and nouns, and might have exaggerated the difference in performance with the two word categories. However, if the verbs disadvantage reflected exclusively motor relations in the verbs' meaning, no difference would have been found here. Instead, the persistence of the verb-noun difference demonstrates that the interpretation of such difference in ALS, as well as in the normal population, has to consider the role of other semantic and/or morpho-phonological dimensions that define – and differ between – the two categories.

Second, is a motor dysfunction necessarily associated with selective deficit in verb processing? We found that the verb-noun difference in ALS-patients was not disproportionate relative to the difference in the normal population. This result shows that the verb deficit is not a specific feature of a motor disorder such as ALS. More generally, it adds to previous observations on populations with pathological (Garcea *et al.*, 2013; Negri, Rumiati, Zadini *et al.*, 2007; Papeo *et al.*, 2010; Papeo and Rumiati, 2013; for a review see Papeo and Hochmann, 2012) or abnormal (Vannuscorps, Andres and Pillon,

2013) motor abilities, demonstrating that motor representations for action execution are not *constitutive* of action representations in language and semantics.

How do the current results relate to previous studies on verb-noun differences in ALS? First, we shall observe that in others' studies (Bak *et al.* 2001; Hillis *et al.* 2006; Grossman *et al.,* 2008), ALS patients had significantly poorer language performance than controls; while in ours they performed within the normal range on language-semantic tasks. This difference across experimental samples might reflect the large variability within the ALS population, and/or the circumstance that we purposefully excluded patients with signs or diagnosis of dementia. As also observed elsewhere (Bak and Chandran, 2012; Bak and Hodges, 2004), research on less cognitively impaired patients is crucial to isolate the relationship between damage to motor function and the lexical-semantic processing of action. Thus, on the assumption that our sample was on average less cognitively impaired than previous samples, the current results show that a motor dysfunction is not sufficient on its own to deteriorate action processing in language and semantic tasks[5].

Then, if a verb deficit can only be seen in cases of concurrent aphasia and/or widespread, severe cognitive loss, the causes of that deficit can be various. In effect, verbs are generally more susceptible to cognitive loss than nouns; but this is the case of many neurological conditions, not limited to those that impact the motor function (e.g. Crepaldi *et al*., 2006; De Bleser and Kauschke, 2003; Vigliocco *et al.,* 2011). Moreover,

[5] With this respect, we also refer to the recent study by Consonni *et al*. (2013). The authors distinguished between ALS cases with cognitive (i.e. executive dysfunction) and/or behavioral symptoms (e.g., apathy, disinhibition and poor social monitoring), and ALS cases without either type of symptoms ("unimpaired"). Although both groups suffered from a motor disorder, only the group of patients with cognitive/behavioral symptoms performed pathologically in action naming. "Unimpaired" patients performed significantly better than the other group and comparably to controls. This study shows that the motor degeneration on its own does not impact language-semantic performance with action-stimuli.

a stable and consistent advantage of nouns over verbs is also typical of the normal population (see De Bleser and Kauschke, 2003; see also the results of the current control sample). Similar observations in neuropsychological research have highlighted the importance of relating patients' performance to normal performance. This approach can ensure that a noun-verb difference in a group of patients, or in a single-case, is significantly greater than the difference that could be found in the normal population (Crawford, Garthwaite and Gray, 2003; Laws, 2005).

This methodological note is particularly relevant in the current context, where evidence of verb-noun dissociations in ALS mostly relies on intra-individual comparisons between a patient's performance in task A (noun processing) and the same patient's performance in task B (verb processing) (Bak and Hodges, 1997; Bak and Hodges, 2004; Bak *et al.*, 2001), or between ALS-group's performance in task A and the same group's performance in Task B (Hillis *et al.*, 2006; Grossman *et al.*, 2008).

Note that, based on mere intra-individual comparisons, we found that 18 out of 21 patients showed an advantage with nouns over verbs (the difference was significant in 9 cases) in the action and object naming screening-tests (Crepaldi *et al.*, 2006). The group-level analysis of ALS-patients' performance in the experimental tasks on action-related verbs and nouns confirmed this effect (nouns > verbs). However, when the ALS-group performance was compared with the controls', no interaction was found. This observation is entirely compatible with previous studies, which failed to report an interaction between group (patients and controls) and word-category (verbs and nouns), i.e. relative to controls, ALS-patients were comparably impaired with nouns and verbs (Bak *et al.*, 2001; Grossman, Anderson, Khan *et al.*, 2008). The relevance of this interaction (or lack of interaction) in deriving conclusions on ALS, however, has surprisingly been downplayed.

The current set of results does not support the claim that the verb-disadvantage is a genuine, specific feature of ALS; it rather suggests that the verb-noun difference in ALS-patients reflects the typical, *normal* trend that is often preserved, even when the language function is generally impaired (i.e., in the event of aphasic syndromes).

4.2. Action sequencing deficit in ALS

Relative to controls, ALS patients were significantly impaired in action sequencing tasks (verbal and pictorial). These tasks involved the ability to operate on representations of the individual motor events (or sub-goals), to reproduce their logical and temporal order for achieving a coherent, purposeful action. Extensive research has ascribed this ability to the domain of frontal executive-functions (Cooper and Shallice, 2000; Rumiati *et al.*, 2001; Sirigu *et al*., 1996; Zanini *et al*., 2002), which are frequently affected in ALS (Elamin *et al*., 2011; Phukan *et al*., 2012; Strong *et al*., 2009; Taylor *et al.*, 2013). The same research has shown that this ability is independent from the ability to physically realize actions and to recognize actions. This latter dissociation was replicated in our ALS-group, where impaired action sequencing occurred with intact action recognition, as indexed by patients' performance in naming and word-picture matching.

What does the ALS impairment in action sequencing imply? Action sequencing tasks were included to assess the frontal-executive functioning in our patients, and particularly an executive component with direct implications for action processing. The actions included in the tasks were of the "schema-type" (e.g., brushing one's teeth), whereby each step, or sub-goal, is carried out in an effector-specific manner to achieve the final action goal (Cooper and Shallice, 2000; Zanini *et al.*, 2002). With these tasks, we measured the ability to organize the steps that recur in an action, by encoding the concrete sensorimotor relations (or immediate consequences) of each step to determine *what comes next*.

We can exclude that the failure of ALS-patients in action sequencing was due to a general inability to organize items according to a give criterion, or to compute sequences based on perceptual relations, as ALS-patients performed successfully in sequencing tasks relying on this kind of relations (e.g. shape and number sequencing). At the same time, based on our data, we cannot exclude that the action sequencing deficit extends beyond the processing of "schema-type" actions, to any task that involves retrieving temporal/causal relations among stimuli or events[6]. In anticipation of further research, we shall regard the action sequencing deficit as a generic expression of the executive dysfunction characterizing the cognitive change in ALS.

Finally, we lack data to make claims about the neural correlates of action sequencing. However, we note that the link between action sequencing and frontal "executive" regions, based on prior research, does not leave out a possible contribution of the motor aspects of the frontal lobe (i.e., in the precentral gyrus). Models of frontal-lobe functioning acknowledge the involvement of precentral cortex in executive control (Koechlin and Summerfield, 2007); and neuroimaging research has specifically related precentral cortex activity to sequencing tasks (Fiebach and Schubotz, 2006; Schubotz,

[6] Note that the characterization of action sequencing as a test for evaluating the retrieval of temporal and/or logical (or causal) relations across the steps of an action, acknowledges the difficulty of teasing apart this two aspects of the task (i.e. the temporal and the causal/logical one). In effect, whether they can be separated at all remains an open issue, as the temporal relation (or contiguity) among events is part of the definition, and is pivotal in perception of causality (e.g. Scholl and Tremoulet, 2000).

2007). Under the assumption that precentral cortex is affected in ALS (see Bak *et al.*, 2001; Grossman *et al.*, 2008), our results promote the view that implicates this brain structure in the executive-control machinery hosted in the frontal brain.

What is the relationship between action sequencing and action recognition? We have gathered three pieces of information suggesting functional independence between the two abilities: 1) ALS-patients performed normally in naming and word-picture matching (assessing action recognition) but pathologically in action sequencing; 2) their performances in the two sets of tasks were not correlated; 3) patients with quantitatively different noun-verb effect, as indexed by Crepaldi *et al*.'s screening test, did not behave differently in action sequencing. These observations are in line with previous neuropsychological reports of dissociation between the ability for action sequencing and the ability to recognize actions (Rumiati *et al*., 2002; Zanini *et al*., 2002).

Yet, one might conjecture that the progressive loss of executive functions eventually impacts cognitive operations relevant for proper action recognition. In effect, executive dysfunction and lexical-semantic disorders appear tightly related in ALS population; in particular, the latter primarily – or exclusively – occurs in patients with executive dysfunction (Consonni *et al*., 2013; Phukan *et al*., 2012), and is at least partly accounted by it (Taylor *et al*., 2013). Finally, it remains possible that an interaction between action sequencing and the conceptual processing of action can be highlighted with finer-grained tasks, others than naming and word-picture matching, which only assess the global recognition of actions. Understanding in which task-conditions the ability to compute action sequences interacts with conceptual processing of actions is a goal for future research.

4.3. Conclusions

We found that, in a group of 21 patients with a motor neuron disorder diagnosed as ALS, lexical-semantic processing was better with nouns than with verbs, but this difference was not disproportionate relative to the difference in the normal population. The noun-verb asymmetry likely reflects the effect of a number of semantic and/or grammatical-class features (not entirely specified) that differ between the two word categories; and, in the light of our findings, it cannot be attributed exclusively to the relatedness of the words' semantics to action, typically greater for verbs than for nouns. In fact, when this aspect was balanced (like in the current design), the performance difference with verbs and nouns remained, in ALS-patients as well as in the normal population.

Moreover, we found that ALS-patients failed in tasks requiring the retrieval of the logical/temporal sequence of motor events that recur in a purposeful action. This function is ascribed to the domain of frontal-executive functions; this ALS-patients' impairment is therefore regarded as an expression of the executive dysfunction associated with this neurological condition. The current work sets in a new light the contribution that the study of ALS can make to cognitive neuroscience: ALS patients can provide a valuable model to study the relationship between the motor centers and the executive-control machinery housed in the frontal brain, and the specific role that executive functions may play in action processing.

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Figure caption

Figure 1. Performance (expressed as percentage of correct responses) of ALS-patients and controls across the praxis tests: pantomiming on verbal command (povc), pantomime imitation and tool use. Error bars denote standard error of the mean.

Figure 2. Performance (expressed as percentage of correct responses) of ALS-patients and controls in verb and noun production (naming) and in verb and noun comprehension. Error bars denote standard error of the mean.

Figure 3. Performance (expressed as percentage of correct responses) of ALS-patients and controls in the verbal (sentences) and pictorial (photographs) version of action sequencing.

Table 1. Studies that reported intra-individual differences between verbs and nouns (i.e., advantage for nouns over verbs), in single-cases or groups of patients with Amyotrophic Lateral Sclerosis. The number of cases with verb-noun and action-object difference supported by quantitative information are indicated.

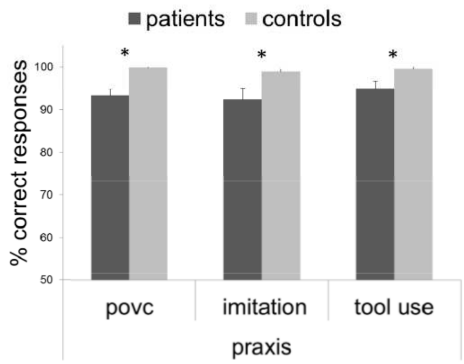
	APPROACH	N CASES	N CASES WITH SIGNS/ DIAGNOSIS OF		NOUNS (N) > VERBS (V)			OBJECTS > ACTIONS
			Dementia	Executive dysfunction	Naming	Word-picture matching	Other tests**	PPT vs. KDT***
BAK & HODGES 1997	Single-case	3	3	3	3	1*	-	-
BAK ET AL. 2001	Single-case	6	2	5	3*	6	-	-
BAK & HODGES 2004	Single-case	3	0	3	0*	0*	-	3
HILLIS ET AL. 2006	Group	13	13	0	Significant in written (not oral)	-	Non-significant	Non-significant
GROSSMAN ET AL. 2008	Group	34	Unknown	14	-	-	Significant	-
CONSONNI ET AL. 2013	Group	23	3	8	N: ALS = controls◊ V: ALS < controls◊	-	-	-

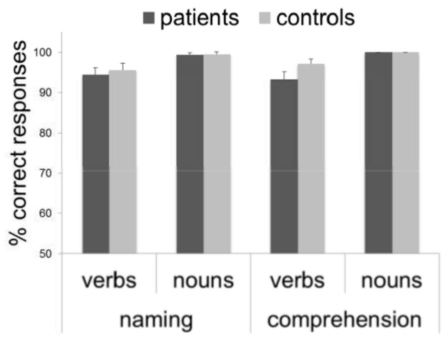
Note. * The remaining patients did not exhibit a verb-noun difference or did not complete the test. ** Other tests for assessing verb-noun differences were: in Grossman et al. (2008), word-word matching and word-description matching; in Hillis et al. (2006), word-word matching. ***PPT = Pyramids and Palmtrees Test (Howard and Patterson, 1992) for testing action knowledge; KDT = Kissing and Dancing Test (Bak and Hodges, 2003) for testing object knowledge. ◊This difference only concerns the 8 ALS patients with cognitive impairment (i.e. executive dysfunction; *N*=8). ALS patients with no executive dysfunction or other cognitive impairments did not differ from controls.

Table 2. Characteristics of patients in the ALS-group.

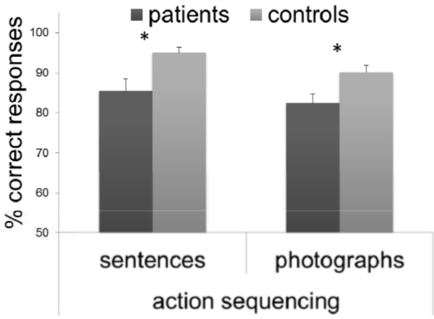
CASE	SEX	HOSPITAL	AGE (YEARS)	EDUCATION (YEARS)	ONSET SITE	TESTING POST-ONSET (MONTHS)	SCREENING POST ONSET (MONTHS)	ALSFRS-R	PICTURE NAMING*		
									%N	%V	P
1	F	UD	56	12	Spinal	14.4	14.4	44	98	86	0.02
2	F	UD	79	5	Bulbar	7.8	7.8	42	96	63	<0.01
3	F	TS	73	7	Spinal	18	18	37	84	62	0.0001
4	F	TS	80	7	Spinal	26.4	26.4	29	88	88	-
5	F	UD	57	11	Spinal	15	-	25	100	92	0.04
6	F	UD	70	5	Spinal	20	29	41	100	96	n.s.
7	M	UD	73	6	-	24	-	33	88	74	n.s.
8	F	UD	61	5	Spinal	15	28	30	84	58	<0.01
9	M	UD	64	10	Bulbar	6	6	38	98	92	n.s.
10	M	UD	45	11	Bulbar	12	-	39	100	100	-
11	M	TS	49	11	Spinal	60	60	28	100	94	n.s.
12	M	UD	62	8	Bulbar	19.2	19.2	30	96	73	0.02
13	M	UD	63	25	Spinal	15.6	-	42	100	98	n.s.
14	F	TS	67	5	Spinal	60	60	20	94	76	0.01
15	M	UD	65	13	Bulbar	15	15	-	98	84	n.s.
16	M	TS	23	15	Spinal	21.6	21.6	26	98	100	n.s.
17	M	UD	65	7	Spinal	36	50	43	100	92	0.04
18	F	UD	41	22	Spinal	48	-	-	100	96	n.s.
19	M	TS	78	5	Spinal	6	6	20	94	84	n.s.
20	M	UD	74	11	Spinal	36	-	19	98	78	0.002
21	M	UD	84	5	Spinal	15	-	31	68	52	n.s.

Note: Patients are sorted alphabetically by their initials. F = female. M = male. UD = neurological unit of the "Azienda Ospedaliero-Universitaria- Santa Maria della Misericordia" in Udine. TS = neurological unit of the "Ospedali Riuniti" in Trieste. ALSFRS-R = ALS Functional Rating Scale: Individual item scores are added to produce a reported score between 0=worst and 48=best (Cedarbaum, Stambler, Malta et al., 1999). Picture naming = object and action picture naming (Crepaldi et al., 2006); *% of accurate responses in object naming (N), in action naming (V) and *p* values (alpha-level = 0.05) of the chi square tests assessing the difference between the two conditions (α=0 .05).


patients
controls
% correct responses
100
90
80
70
60
50
*
*
*
povc
imitation
tool use
praxis



patients
controls
% correct responses
100
90
80
70
60
50
verbs
nouns
verbs
nouns
naming
comprehension



patients
controls
% correct responses
100
90
80
70
60
50
*
*
sentences
photographs
action sequencing