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Screening of Visuospatial Abilities in Amyotrophic Lateral Sclerosis (ALS): A Pilot Study Using the Battery for Visuospatial Abilities (BVA)

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Abstract: (Background) Cognitive deficits related to frontotemporal dysfunction are common in Amyotrophic Lateral Sclerosis (ALS). Visuospatial deficits, related to posterior cerebral regions, are often underestimated in ALS, though they play a crucial role in attending daily living activities. Our pilot study aims at assessing visuospatial abilities using a domain-specific tool in ALS patients compared to healthy controls (HC). (Methods) Twenty-three patients with early ALS and 23 age- and education-matched HC underwent the Battery for Visuospatial Abilities (BVA), including visuo-perceptual and visuo-representational subtests. (Results) When compared to HC, ALS scored worse in 2 out of 4 visuo-perceptual subtests (i.e., Line Length Judgment and Line Orientation Judgment) and 1 out of 4 visuo-representational tasks (i.e., Hidden Figure Identification, HFI) ($p < 0.01$). No correlations arose between ALS clinical features and BVA performance. More than 80% of the ALS cohort obtained abnormal scores in HFI subtest. (Conclusions) Our findings revealed that ALS scored worse (compared to HC) on selective tests tapping "perceptual" and "representational" visuospatial abilities, since early stages of disease. In clinical practice, our findings highlight the need of multi-domain neuropsychological assessment, for monitoring disease course and properly organizing care management of patients with ALS.

Keywords: Amyotrophic lateral sclerosis; visuospatial abilities; BVA; ECAS

1. Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset motor neuron and multisystem disease [1] that is mainly characterized by progressive motor symptoms, such as muscle weakness, muscle atrophy, and spasticity. Over the past twenty years, several clinical studies have highlighted that clinical presentation in ALS can be quite heterogeneous [2, 3]. Up to 50% of ALS cases are first identified with cognitive dysfunctions [4], which may worsen and show different profiles across stages of the disease [5-9]. Executive and behavioral dysfunctions may have prognostic implications [10, 11]. Moreover, in ALS, motor and cognitive components appear to worsen in parallel, especially when the bulbar function is involved [8, 12]. Notably, advanced neuroimaging studies revealed widespread damage to extra-motor networks underlying cognitive and behavioral functions during disease progression [13-15]. Consequently, ALS-specific cognitive and behavioral impairments are more frequent in more advanced disease stages [7, 9]. However, cognitive and motor involvement

may present with distinct trajectories across the disease course, suggesting a differential vulnerability of motor and non-motor cortical networks in different disease phenotypes [5, 13]. Increasing evidence suggests that cognitive and behavioral impairment in ALS overlaps with pathological and genetic features, as TDP-43 pathologic burden has been associated with cognitive impairment [16, 17] and *C9orf72* repeat expansion has been revealed in ALS patients with rapid cognitive decline and poor survival [18, 19].

The cognitive profile generally described in ALS includes deficits in verbal fluency, language, social cognition, and executive functions [4]. Conversely, visuospatial abilities in their visuo-perceptual and representational components are not assessed systematically; for instance, the most used assessment tool, the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS) [20], does not tap these cognitive aspects.

Evidence in ALS suggested that the visuo-representational and the visuo-perceptual abilities play a crucial role in managing activities of daily living and in preserving patients' well-being [21], such as in spatial orientation mediated by environmental cues [22]. Moreover, visuo-representational and visuo-perceptual abilities participate in generating, retaining, and transforming visual images [23], processing overall configuration of perceptual stimuli, appreciating their position, and performing mental operations on their spatial representation [24]. In terms of neural correlates, visuo-representational and visuo-perceptual functions are mediated by wide, distributed neural network including the parietal lobes, the lateral prefrontal cortex, the medial temporal lobes, the inferior temporal cortex, the occipital cortex, and the basal ganglia, particularly in the right hemisphere [24].

A useful battery to explore both the perceptual component and the representational component of the visuospatial abilities, independent from motor impairment, is the Battery for Visuospatial Abilities (BVA, known in Italy as TeRaDiC; [25-27]), available in English and Italian. Yet, to date, no study applied the BVA in the ALS.

The present pilot study aims at filling the literature gap on the impairment of visuospatial abilities in ALS by means of the 8 subtests included in the BVA. We expected to observe an impairment in visuospatial abilities in ALS, with some subtests possibly showing impairment of selected visuospatial skills. To identify an early impairment of these functions in the ALS course will help improve clinical management.

2. Materials and Methods

2.1. Participants

Twenty-three right-handed patients with definite or clinical/laboratory-supported probable ALS, according to the El-Escorial revised criteria [28], showing classic (n=7), bulbar (n=2), flail limbs (n=11) and 3 pyramidal phenotypes [29], were included. These patients were prospectively recruited across the First Division of Neurology of the University of Campania "Luigi Vanvitelli" (Naples, Italy) between December 2021 and April 2022. Exclusion criteria were history of other neurologic or psychological conditions; alcohol or drug addiction. Genetic analysis was performed in all patients, exploring *C9orf72* repeat expansion and mutations of *SOD1*, *TARDBP*, and *FUS/TLS*. No mutations of these genes were reported.

Twenty-three age- and education-matched healthy adults were additionally recruited as healthy controls (HC) group through research volunteer panels held by the First Division of Neurology of "Luigi Vanvitelli" University (Naples, Italy), non–blood caregivers of patients with ALS, and local community noticeboards.

Ethics approval was obtained from the Ethics Committee of the University of Campania "Luigi Vanvitelli" in Naples, Italy (Protocol nr. 591/2018). All participants provided informed consent to participate in the study according to the Declaration of Helsinki.

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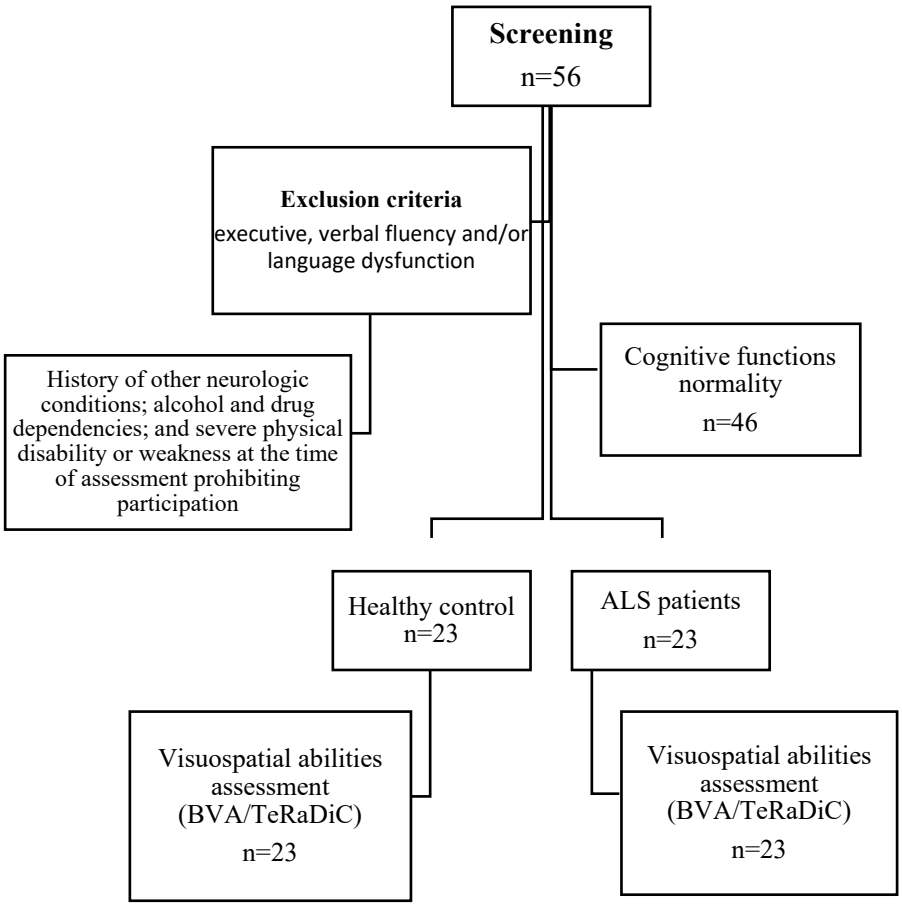

Figure 1. Flowchart showing the enrollment of the participants in the study.

2.2. Materials

ALSFRS-R: the ALSFRS-R is a disease-specific 12-item tool assessing patients' functional abilities to perform independent tasks. The questionnaire is structured on a 5-point scale ranging from 4 to 0, where 4 indicates no loss of function and 0 indicates total loss of function. The ALSFRS-R includes four scales, each measuring one domain affected by the disease [30].

ECAS: The ECAS is a short screening test (15–20 min) assessing cognitive impairment in ALS [20], providing sub-scores for language, fluency, executive, memory, and visuospatial abilities. Language is evaluated by naming, comprehension, and spelling. Fluency is measured by free production of words beginning with the letter "s" and a restrained production of words beginning with the letter "t" but with only four letters. Executive functions are measured by a reverse digit span, alternation of letters and numbers, inhibitory sentence completion, and social cognition. The memory subscale includes measurements of immediate recall, delayed percentage retention, and delayed recognition. Finally, visuospatial abilities are measured with dot and cube counting, and number location.

BVA - perceptual subtests: this battery consisted of four tasks: each item is composed of a stimulus presented on the left and the four-choice display presented on the right [27]. Items are presented one at a time, and participants are required to point to the only item identical to the stimulus among the distracters without time constraints. Scoring procedures assign one point for each correct response; no penalty is computed for wrong responses. The first subtest is line length judgment (LLJ), in which participants are required to identify the line with the same length as the stimulus in the four-choice display. Item complexity increases during the task as linear differences between stimuli and distracters gradually decrease (score range: 0–20). The second subtest is line orientation judgment (LOJ), in which participants must identify, in the four-choice display, the line with the same orientation as the stimulus presented on the left side. The difference in orientation

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between stimulus and distracters is 30° in half of the items and 15° in the remaining trials. In the first seven items, distracters (of the same length as the stimulus) are arranged as a sunburst, while in the last three items, distracters are randomly spread on the four-choice display (score range: 0–10). The third subtest is angle width judgment (AWJ), in which participants should identify the angle with the same width as the stimulus in the four-choice display. The distracters differ from 15° to 90° from the stimulus (score range: 0–10). The fourth subtest is pointing position identification (PPI): participants are required to identify the square with the same configuration of 1–3 embedded points as the stimulus. Distracters in the four-choice display have the same number of points as the stimulus but in different spatial arrangements (score range: 0–12).

BVA—representational subtests: The four tasks included in this section assess participants' ability to mentally represent spatial relationships; three of them include a four-choice display, as above, and the last task has a different arrangement [27]. Each correct response is assigned one point. The first subtest is mental rotation: participants are required to mentally rotate bidimensional stimuli (the italic capital letter L or S, with small white or black circles at the extremities) on the horizontal plane and to identify the only item in the display matching it. The four-choice displays enclose the stimulus item, rotated by 45°, 90°, 135°, or 180°, together with three mirror forms of the stimulus (distracters), printed at different degrees of rotation. Prior to the task, participants receive two practice trials that can be solved with the aid of solid items (score range: 0–10). The second subtest is complex figure identification (CFI, shape recognition): participants have to identify the only figure matching the nonsense geometrical shape (not easily described verbally and of increasing complexity) presented on the left side in the four-choice display. Two practice trials are given before the task (score range: 0–10). The third subtest is hidden figure identification (HFI): stimuli consist of nonsense, complex geometrical patterns. Participants must disassemble each stimulus in their minds to identify, among the four complex geometrical patterns shown in the four-choice display, the only shape exactly embedded in the stimulus. Two practice trials are given (score range: 0–10). The fourth subtest is mental construction: in this task, participants must mentally assemble bidimensional stimuli. Stimuli consist of squares randomly subdivided into four parts, that are randomly shown on the right side of the display. In every trial, the examiner names two of these components, and participants must identify with which side they are contiguous in the stimulus (printed on the left side). Solid stimuli are used to explain the task in two practice trials. Two questions are foreseen for each trial; each correct response is scored 1 point (score range: 0–20).

2.3. Statistical Analyses

We used the Mann–Whitney test (U-test) or Pearson's chi-squared test ($\chi 2$) to compare the patients with ALS and HC on demographics (i.e., age, education, and sex), BVA-perceptual subtests, and BVA-representational subtests.

We employed Spearman's correlation analyses to explore the associations between the clinical features (i.e., disease duration, ALSFRS-R, and UMN) and the accuracy in BVA subtests. Finally, we reported the percentage of ALS and HC with age- and education-adjusted scores in BVA subtests below normative data [27]. All multiple comparisons were corrected by the Bonferroni procedure, where the corrected p-value lower than 0.05 was considered statistically significant. All analyses were performed using the IBM Statistical Package for Social Science (SPSS) version 25 (Chicago, IL, USA).

3. Results

Patients with ALS and HC did not differ in demographics (Table 1).

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Table 1. Descriptive statistics.

Variables	ALS (n= 23)	HC (n= 23)	Mann-Whitney/χ^2	p-value	Adj-p
Demographics:					
Age	64.00 [53.00, 69.00]	61.00 [53.00, 65.00]	231.50	0.468	1.000
Education, years	8.00 [5.00, 13.00]	8.00 [8.00, 13.00]	171.50	0.036	0.108
Sex (male)	17 (73.9%)	9 (39.1%)	5.66	0.017	0.051
Clinical features:					
Disease duration	35 [27.00, 46.00]	-	-	-	-
ALSFRS-R (total score)	29.00 [21.00, 37.00]	-	-	-	-
UMN score	7.00 [3.00, 10.00]	-	-	-	-
Cognitive assessment:					
MoCA	-	24.65 [23.65, 26.98]; 0.0%[a]	-	-	-
ECAS total score	96.48 [81.39, 103.01]; 4.3%[a]	-	-	-	-
ECAS sub-scores:					
Language	22.27 [17.94, 24.73]; 13.0%[a]	-	-	-	-
Verbal Fluency	17.88 [13.77, 22.20]; 8.7%[a]	-	-	-	-
Executive functions	29.15 [24.85, 32.35]; 13.0%[a]	-	-	-	-
Memory	15.84 [12.89, 18.07]; 8.7%[a]	-	-	-	-
Visuospatial abilities	11.54 [11.10, 12.16]; 4.3%[a]	-	-	-	-

Note. Data are reported as median [25th percentile, 75th percentile] or count (percentage); a percentage of patients or healthy controls with age- and education-adjusted score below normal population; Adj-p represents p-value corrected for multiple comparisons using the Bonferroni procedure, and statistically significant differences are shown in bold. **Abbreviations:** ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; UMN, Upper Motor Neuron; ECAS, Edinburgh Cognitive, and Behavioural ALS Screen.

Spearman's correlation analyses did not show significant associations between ALS clinical features and the accuracy in visuo-perceptual and visuo-representational BVA subtests (Table 2).

Table 2. Spearman's correlations (r_s) between clinical features and the accuracy in visuo-perceptual and visuo-representational tasks.

	Disease duration	ALSFRS-R	UMN score
BVA-perceptual tasks:			
Line length judgment (LLJ)			
r_s	-0.04	-0.04	0.20
p-value	0.872	0.847	0.368
Adj-*p*	1.000	1.000	1.000
Line orientation judgment (LOJ)			
r_s	-0.16	0.02	0.25
p-value	0.469	0.921	0.256
Adj-*p*	1.000	1.000	1.000
Angle width judgment (AWJ)			
r_s	-0.03	-0.05	0.01
p-value	0.885	0.831	0.968
Adj-*p*	1.000	1.000	1.000
Point position identification (PPI)			

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r_s	-0.20	-0.04	0.28
p-value	0.351	0.865	0.196
Adj-*p*	1.000	1.000	1.000
BVA-representational tasks:			
Mental rotation (MR)			
r_s	0.13	-0.17	0.16
p-value	0.559	0.426	0.463
Adj-*p*	1.000	1.000	1.000
Complex figure identification (CFI)			
r_s	-0.06	0.01	0.01
p-value	0.771	0.968	0.968
Adj-*p*	1.000	1.000	1.000
Hidden figure identification (HFI)			
r_s	-0.07	0.08	0.33
p-value	0.752	0.726	0.128
Adj-*p*	1.000	1.000	1.000
Mental construction (MC)			
r_s	-0.17	0.32	0.33
p-value	0.443	0.137	0.129
Adj-*p*	1.000	1.000	1.000

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; UMN, Upper Motor Neuron.

Compared with HC, ALS group performed worse on the BVA perceptual LLJ and LOJ subtests and on the BVA-representational HFI subtest (Table 3). Since deficits in language or executive functions could impact these results, we also ran Mann–Whitney analyses considering only the subgroup of ALS free from impairments in executive functions and/or language disturbances (as assessed on ECAS, n=19), which basically confirmed the pattern above (see Supplementary Material 1). Figure 2 reported the percentage of abnormal scores in BVA tasks for ALS and HC.

Table 3. Comparison between amyotrophic lateral sclerosis (ALS) and healthy controls (HC) in age- and education-adjusted perceptive and representational tasks of BVA.

	ALS (*n*= 23)	**HC (*n*= 23)**	**Mann-Whitney**	***p*-value**	**Adj *p***
BVA-perceptual tasks:					
Line length judgment (LLJ)	15.82 [14.80, 17.03]	18.66 [16.77, 19.06]	84.50	<0.001	**<0.001**
Line orientation judgment (LOJ)	6.22 [4.77, 7.48]	8.55 [6.96, 9.27]	137.00	0.005	**0.020**
Angle width judgment (AWJ)	2.07 [0.81, 4.33]	4.90 [1.06, 5.46]	155.00	0.016	0.128
Point position identification (PPI)	8.22 [7.69, 8.93]	8.68 [7.02, 9.70]	263.00	0.974	1.000
BVA-representational tasks:					
Mental rotation (MR)	8.39 [5.34, 8.78]	6.78 [3.30, 9.28]	215.00	0.277	1.000
Complex figure identification (CFI)	8.09 [7.61, 8.43]	7.76 [6.85, 8.22]	208.50	0.219	1.000
Hidden figure identification (HFI)	0.00 [0.00, 1.61]	3.52 [0.30, 5.22]	108.00	<0.001	**<0.001**
Mental construction (MC)	9.52 [4.24, 11.24]	9.11 [5.18, 9.96]	235.00	0.517	1.000

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Note. Data are reported as median [25th percentile, 75th percentile]; Adj-p represents the p-value corrected for multiple comparisons using the Bonferroni procedure, and statistically significant differences are shown in bold.

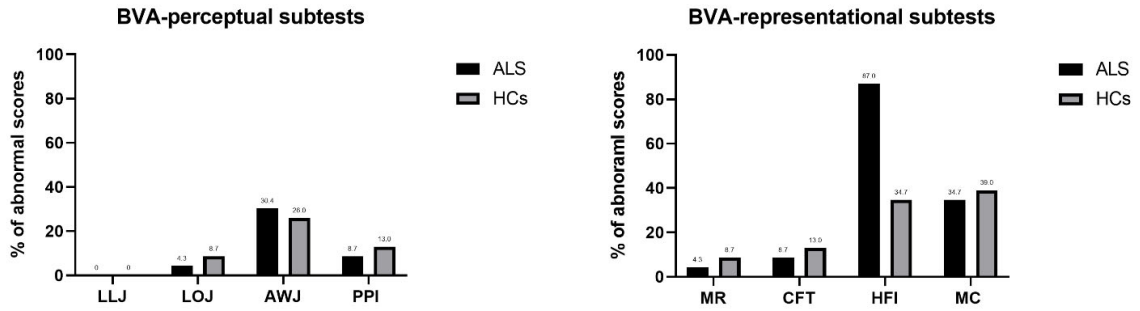

Figure 2. Percentage of ALS and healthy controls with age- and education-adjusted scores in BVA subtests below normative data.

4. Discussion

In the present study, we examined the profile of visuospatial abilities in patients with ALS by BVA, a battery assessing the visuospatial abilities. The battery minimized the role of motor disorders as it requires only simple pointing or verbal responses, as per individual patients' preferences. Overall, our results showed that ALS patients scored worse than the HC in several visuo-perceptual and visual-representational tasks, independently from co-occurrent clinically evident executive and language deficits. Some visuo-perceptual tasks (LLJ and LOJ) and one visual-representational task (HFI) were sensitive to identify visuospatial impairments in patients with ALS, with below cut-off scores in visual-representational abilities (HFI) occurring in more than 80% of our cohort of early ALS. On these bases, the common practice of assessing the visuo-perceptual skills in ALS exclusively by means of screening tests (mainly focusing on visuo-perceptual abilities) might underestimate visuospatial deficits, usually related to posterior cortical atrophy and often associated with the risk of cognitive deterioration in neurological disorders (e.g., Parkinson's disease [31]).

Visuo-spatial impairments have been reported in several neurological disorders. In dementias, such as dementia with Lewy bodies, vascular dementia, and Alzheimer's disease (AD), visuospatial deficits have been widely reported, although often neglected [32]. In fMRI studies on AD patients compared to HC, hypoactivation in visual task-related regions, such as the V5 area, the superior parietal lobe, the parieto-occipital cortex, and the premotor cortices have been observed in association with some compensatory hyperactivation in the inferior parietal lobule; these abnormalities were interpreted as the pathophysiological basis for visuospatial disorientation in patients with AD [33, 34]. In Parkinson's disease, visual perception deficits are frequent and likely related to the potential pathophysiological role of basal ganglia and limbic structures in visuospatial functions [35].

In ALS, cognitive deficits are often reported in verbal fluency, language, social cognition, executive functions, and verbal memory, while visuospatial abilities appear to be less impaired [4]. Nonetheless, Boeve & Graff-Radford [36] found different degrees of impairment of cognitive abilities, including the visuospatial ones, in patients with *C9orf72* repeat expansions showing ALS and/or the frontotemporal dementia phenotype (c9FTD/ALS). In this subset of patients, in addition to bifrontal and cingulate cortex atrophy, structural MRI revealed parietal and occipital atrophy that could be part of the MRI signature pattern of c9FTD/ALS [37, 38]; this evidence might help explain the evidence of visuospatial dysfunction in this as well as in other phenotypes of ALS. Particularly, frontotemporal lobar degeneration with ubiquitin and TDP-43 positive neuronal inclusions may be associated with ALS, "progressive supranuclear palsy-like" syndrome, in which early behavioral disturbances, and marked visuospatial impairment are observed [39]. In contrast, Crockford and

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colleagues found no significant differences in visuospatial abilities, explored by ECAS, across disease stages [9], while lower cognitive abilities in ALS-specific functions and more behavioral alterations have been observed during disease course. Probably, assessment tools more specific for detecting impairments in both components of visuospatial abilities, independent from motor disability, such as BVA, might reveal these cognitive dysfunctions in the early stages of the disease, suggesting the potential benefits of specific cognitive training protocols in ALS patients as well as in other neurological disorders [40, 41]. Indeed, from a clinical point of view, the integrity of visual and visuospatial abilities could play a pivotal role in using brain-computer interface (BCI) technology for improving communication abilities, assessing cognitive functions, and controlling external devices in patients with motor disabilities (for a review see [42]).

Although we obtained interesting insights on the visuospatial impairment in ALS, the generalization of the present findings is limited by the small sample size and the cross-sectional design. Moreover, an additional limit is the lacking inclusion of a positive-control group of subjects or of a subset of patients carrying *C9orf72* repeat expansions. Further research might also address the anatomical and functional correlates of visuospatial defects in ALS.

5. Conclusions

The present study suggested an early impairment of visuospatial abilities in ALS, involving both perceptual and representational abilities, as assessed by BVA. In clinical practice, our findings provide new insight into multi-domain cognitive assessment in ALS to monitor disease progression effectively and organize care management properly. Further research on functional connectivity correlates of visuospatial functions might be important to better comprehend the impairment of extra-motor brain networks and address the dynamics of the spreading pathology in ALS.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Comparison between the subgroup of ALS free from impairments in executive functions and/or language disturbances (ALS) and healthy controls (HC) in age- and education-adjusted perceptive and representational tasks of BVA.

Author Contributions: Conceptualization: Mattia Siciliano, Luigi Trojano and Francesca Trojsi; Data curation: Minoo Sharbafshaaer, Mattia Siciliano and Carla Passaniti; Formal analysis: Mattia Siciliano, Valeria Sant'Elia and Luigi Trojano; Investigation, Minoo Sharbafshaaer, Carla Passaniti, Valeria Sant'Elia, Marcello Silvestro, Antonio Russo and Sabrina Esposito; Methodology: Sabrina Esposito and Luigi Trojano; Project administration, Francesca Trojsi; Resources, Carla Passaniti, Valeria Sant'Elia, Marcello Silvestro, Antonio Russo and Sabrina Esposito; Software: Mattia Siciliano; Supervision, Antonio Russo, Gioacchino Tedeschi, Luigi Trojano and Francesca Trojsi; Validation: Mattia Siciliano; Visualization: Marcello Silvestro and Gioacchino Tedeschi; Writing – original draft: Minoo Sharbafshaaer and Francesca Trojsi; Writing – review & editing: Mattia Siciliano, Gioacchino Tedeschi, Luigi Trojano and Francesca Trojsi. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data will be available upon request to the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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