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Deficits in sentence expression in amyotrophic lateral sclerosis

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Abstract

Quantitative examinations of speech production in amyotrophic lateral sclerosis (ALS) are rare. To identify language features minimally confounded by a motor disorder, we investigated linguistic and motor sources of impaired sentence expression in ALS, and we related deficits to gray matter (GM) and white matter (WM) MRI abnormalities. We analyzed a semi-structured speech sample in 26 ALS patients and 19 healthy seniors for motor- and language-related deficits. Regression analyses related grammaticality to GM atrophy and reduced WM fractional anisotropy (FA). Results demonstrated that ALS patients were impaired relative to controls on quantity of speech, speech rate, speech articulation errors, and grammaticality. Speech rate and articulation errors were related to the patients' motor impairment, while grammatical difficulty was independent of motor difficulty. This was confirmed in subgroups without dysarthria and without executive deficits. Regressions related grammatical expression to GM atrophy in left inferior frontal and anterior temporal regions and to reduced FA in superior longitudinal and inferior frontal-occipital fasciculi. In conclusion, patients with ALS exhibit multifactorial deficits in sentence expression. They demonstrate a deficit in grammatical expression that is independent of their motor disorder. Impaired grammatical expression is related to disease in a network of brain regions associated with syntactic processing.

Keywords

Dementia; aphasia; cognitive neuropsychology; language; speech

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Supplementary material available online

Supplementary Appendices 1 – 4.

Introduction

Amyotrophic lateral sclerosis (ALS) is traditionally viewed as a motor system disorder, but recent studies suggest that cognitive impairments occur in up to half of ALS patients (1–3). Investigations of cognition in ALS have often focused on executive difficulty (1,4–6). However, a major confound for cognitive deficits is the motor disorder of ALS, and recent work has emphasized the identification of deficits that are independent of motor limitations (7,8). Deficits in language appear to occur at least as frequently as executive difficulty (5). Most assessments of language in ALS have focused on comprehension and naming of single words (5,9–11), and one case report describes effortful speech in two ALS patients (12). Few studies have attempted to identify speech measures that are minimally confounded by the motor deficit in ALS.

In this study we elicited a semi-structured sample of connected speech in ALS and examined the contributions of motor and cognitive deficits to impaired sentence production. We also related language impairments to gray matter (GM) and white matter (WM) MRI abnormalities to assess the neuroanatomic basis for sentence production deficits. We hypothesized that patients with ALS have sentence expression impairments, that aspects of language production are minimally confounded by a motor disorder and thus can serve as a marker of impaired cognition in ALS, and that these deficits are related to a peri-Sylvian neuroanatomic distribution that does not involve the motor system.

Methods

Subjects

We studied 26 patients with ALS and 19 healthy seniors recruited as control subjects. Patients were diagnosed by experienced neurologists (LM, LE, DJI, MG) in the ALS Center and the Penn FTD Center of the Department of Neurology at the University of Pennsylvania according to El Escorial revised criteria (13). Three patients had ALS-FTD (2). Since ALS-FTD comprises a portion of the ALS population (14,15), these patients were included in our study to represent the spectrum of disease. None had dysarthria or a pronounced motor impairment, and they were similar to the other ALS patients on the grammatical variables in this study. Diagnosis employed a consensus evaluation including a semi-structured neurologic history, a complete neurologic exam, and a detailed mental status assessment. Exclusion criteria included vascular disease, structural brain abnormalities, medical diseases interfering with cognition, visual-perceptual difficulty, and primary psychiatric disorders. Overall disease severity was assessed with the ALS Functional Rating Scale-Revised (ALSFRS-R) (16). The degree of upper motor neuron (UMN) impairment across right and left upper limbs, right and left lower limbs, and bulbar regions was assessed on a scale ranging from 0 to 7 for each of the five body parts. We collected seated percent forced vital capacity (VC) to measure patients' capacity for phonation. Demographic characteristics are summarized in Table I. One-way ANOVAs indicated that ALS and control groups were matched for age and education. With scoring adjusted proportionately for the tasks that could be performed despite a motor limitation, there was no significant difference between the ALS and control groups on the Mini Mental State Exam (MMSE) (17).

Neuropsychological performance is summarized in Table I. Six of the ALS patients, including the three with ALS-FTD, exhibited a significant impairment ($p < .05$ on a one-tailed test) of executive functioning on letter-guided (FAS) (18) or semantically-guided naming fluency (18). To minimize the possibility that apparent language deficits were due to executive dysfunction, we assessed ALS performance excluding these six patients. To control for a bulbar motor disorder that could interfere with speech production or sentence expression, we identified six patients with dysarthria, five with a flaccid dysarthria and one with spastic dysarthria. We analyzed language characteristics separately in dysarthric and non-dysarthric patients.

All subjects completed a written informed consent procedure in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Pennsylvania.

Materials and procedure

The subjects' task was to tell the story of the word-less children's picture book, *Frog, Where Are You?* (19). The book's sequence of 24 drawings elicited an extended speech sample with a known target that was comparable in content across subjects. We used this method to avoid the interruptions of turn-taking that occur in conversation, and we used a relatively unknown story to avoid the confounds associated with narrating an over-learned story such as a fairy tale.

Each participant looked through the book to become familiar with the story; then the participant was asked to start at the beginning and narrate the story while paging through the book, as if telling it to a child. Narratives were recorded digitally and transcribed in detail by trained transcribers using the signal processing software Praat (20). The transcription conventions used to capture the irregularities in patients' speech are defined elsewhere (21). The narratives were scored from transcripts by trained judges. All coding was checked by a linguist (SA) with expertise in phonetic and grammatical analysis. We assessed features of speech fluency, grammaticality, and lexical access. These included the overall duration of the speech sample, number of words produced, number of utterances, words per minute, phonological and phonetic articulation errors, percentage of utterances that were grammatically well-formed sentences, and occurrences of nouns and tense-marked verbs. We related language functioning to motor performance using the bulbar measure from the UMN score, the speech subscale from the ALSFRS-R, and VC. To avoid the confound of impaired motor performance (4), we used the untimed task of reverse digit span as an index of executive functioning to be related to language production.

Statistical considerations

Statistical analysis was conducted using SPSS. Levene's tests indicated that most language measures did not meet the requirement of homogeneity of variance for parametric statistical tests, so we used nonparametric tests (Mann-Whitney *U* and Wilcoxon signed ranks) to assess between-group differences. Correlations were calculated using Spearman's rho.

Imaging data acquisition and analysis

A structural T1-weighted three-dimensional spoiled gradient-echo sequence and diffusion-weighted imaging (DWI) was available for 10 ALS participants, including the three with co-occurring FTD. Exclusion criteria included health and safety (e.g. difficulty breathing while supine, metallic implants, shrapnel, claustrophobia) and reluctance to participate. Details of the image acquisition and analysis are provided in Appendix 1 which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/doi/abs/10.3109/21678421.2014.974617. Imaging was acquired on average within 105 (± 90) days of recording the narrative. The subset of patients for whom imaging data were available did not differ ($p > 0.15$) on any demographic, neuropsychological, or language performance measures from the total group of patients (Appendix 2 – which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/doi/abs/10.3109/21678421.2014.974617). Imaging was also collected on 34 healthy controls who were comparable to the patient groups in age, education, and gender.

We used the Randomise tool in FSL (http://fsl.fmrib.ox.ac.uk/fsl/randomise/) to perform a non-parametric, permutation-based statistical analysis (permutations = 10,000) to assess GM density, FA in WM, and to perform regression analyses. Comparisons of GM density were restricted to voxels containing GM using an explicit mask generated from the average GM probability map of all subjects. We considered only clusters that exceeded an extent threshold of 50 voxels and a height threshold of $p < 0.05$ (ALS < Seniors, uncorrected for multiple comparisons), and we considered subpeaks as well as peaks, depending on the extent of a cluster. Regression analyses related GM atrophy to the percentage of utterances that were grammatically well-formed sentences and were restricted to areas of GM disease as determined by the GM atrophy analyses in order to relate performance to areas of known disease. Clusters with a height threshold of $p < 0.05$ (uncorrected for multiple comparisons) and an extent threshold of 30 voxels were considered significant.

We compared FA in WM between ALS and controls, restricting analysis to areas of WM by averaging all patients and controls and generating a mask consisting of voxels with FA greater than 0.25. Significant clusters survived an extent threshold of 200 voxels and an uncorrected height threshold of $p < 0.01$. Regression analyses related reduced FA to the percentage of utterances that were grammatically well-formed sentences and were restricted to diseased tracts as determined by extending the reduced FA regions found above. To define tracts, we used a deterministic tractography method, implemented in Camino, that generated WM fibers in a group of healthy seniors. We used all WM fibers passing through voxels of reduced FA as the mask for regression analysis. We used a height threshold of $p < 0.001$ (uncorrected for multiple comparisons) and an extent threshold of 100 voxels to establish cluster significance.

Results

Language production

Measures of language production in ALS and controls are summarized in Table II. ALS patients produced fewer words and fewer utterances than controls, and their speech rate was reduced. Patients also made more speech articulation errors than controls, including both phonetic and phonemic errors. Many of the speech errors consisted of the weakening of stop consonants, as in do[γ] for *dog*, [β]oy for *boy*, and [χ]ept for *kept*. These segments result from incomplete closure of the vocal tract due to failure of the articulators to reach their targets, a consequence of motor weakness. There were also many deletions of segments, as in *cli* for *cliff* and *suck* for *stuck*.

ALS patients produced fewer grammatically well-formed sentences than controls. All but one of the 26 ALS patients (96%) produced at least one utterance that was not a well-formed sentence. In contrast, just 14 of the 19 controls (74%) produced one or more utterances that was not a well-formed sentence. Eleven (42%) ALS patients produced a percentage of grammatically well-formed sentences at least 2 standard deviations below the control mean. Analysis of the grammatical errors revealed that the most frequent type of error was an incomplete sentence (34% of errors). Other frequent errors were a missing determiner (17%) and verb phrase errors (16%). Examples of all the types of errors are given in Appendix 3 – which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/doi/abs/10.3109/21678421.2014.974617. A table of patient and control error types is given in Appendix 4 – which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/doi/abs/10.3109/21678421.2014.974617.

We examined subsets of ALS patients to investigate the basis for deficits in sentence production. Measures of language production in ALS patients with and without dysarthria are displayed in Table II. Patients without dysarthria exhibited the same impairments as the entire cohort of ALS patients and the subset of ALS patients without executive impairment in letter-guided or semantic fluency, except on speech rate and speech articulation errors. On these measures, non-dysarthric ALS patients were not impaired relative to controls, and dysarthric ALS patients were impaired relative to both controls and to non-dysarthric ALS patients. This suggests that both impaired speech rate and articulation errors are related to a disorder of the motor speech apparatus. Dysarthric ALS patients were also impaired relative to non-dysarthric ALS patients on the total UMN score ($U = 10.5$, $p < 0.01$), the bulbar motor score ($U = 19$, $p < 0.05$), and the speech subscale of the ALSFRS-R ($U = 8$, $p < 0.001$), but not on the total ALSFRS-R score or on VC.

Table II also displays measures of language production in ALS patients without an executive impairment in letter-guided or semantic fluency. All the features of language production that differed between the entire cohort of ALS patients and controls were also impaired in this ALS subgroup.

To examine the contribution of a motor or cognitive impairment to the language deficits in ALS from another perspective, we correlated the language production variables for which ALS patients showed impairment with the bulbar motor score from the UMN assessment, the ALSFRS-R speech subscale, and VC. Significant correlations are displayed in Table III. Speech rate, number of words produced, and articulation errors were correlated with the bulbar motor score, and speech rate was correlated with the speech subscale of the ALSFRS-R. In contrast, there was no correlation of the percentage of grammatically well-formed sentences with any of the measures of motor functioning, nor was there a correlation of well-formed sentences with reverse digit span ($s = .34$, $p > 0.05$).

Imaging analyses

As summarized in Table IV and illustrated in Figure 1 Panel A, significant GM atrophy was found in frontal and temporal lobes bilaterally, extending into parietal lobes. Table IV and Figure 1 Panel B display regressions relating GM atrophy to percent grammatically well-formed sentences. Areas of GM atrophy implicated in ALS patients' grammatical difficulty include inferior frontal, anterior temporal, and striatal regions of the left hemisphere.

Table V and Figure 1 Panel B summarize areas of significantly reduced FA in WM. These include the corpus callosum, cingulum, and WM of the frontal and temporal lobes bilaterally, and superior longitudinal fasciculus, inferior frontal-occipital fasciculus, and inferior longitudinal fasciculus. The regressions summarized in Table V and illustrated in Figure 1 Panel B relate percent grammatically well-formed sentences to reduced FA in the corpus callosum, superior longitudinal fasciculus, and inferior frontal-occipital fasciculus.

Discussion

Language impairments are reported with increasing frequency in ALS (1,5,22). It is important to identify measures of impaired language that are minimally confounded by a motor disorder. In this study we examined sentence production deficits in the spontaneous speech of non-demented ALS patients. We found reduced speech rate and frequent articulatory errors, which were related to the patients' motor deficits. We also observed impaired production of grammatically well-formed sentences, which was not related to a motor deficit. This grammatical deficit was associated with disease in inferior frontal, anterior temporal, and striatal regions of the left hemisphere and to WM projections in frontal-temporal regions that are associated with a sentence-processing neural network (23–26).

The reduced speech output parallels in part the slowed speech seen in naPPA (27). Some patients with ALS have co-occurring naPPA (12,28), although none of the participants in this study exhibited the speech and language pattern seen in this condition (27,29). Slowed speech rate in ALS appears to be largely due to their motor deficit. This was established in several ways. First, measures of speech output in ALS were related to clinical measures of motor function: words per minute, number of words produced, and speech articulation errors were correlated with bulbar motor impairment. Secondly, the qualitative analysis of speech errors suggested that they were largely due to motor deficits, and they were more frequent in patients with dysarthria than in controls and non-dysarthric ALS patients. Finally, speech

rate correlated with measures of motor difficulty, and there was no difference between the speech rates of non-dysarthric ALS patients and controls.

In contrast, grammaticality in sentence expression, as measured by the percentage of utterances that were grammatically well-formed sentences, was minimally confounded by motor functioning, but ALS patients were significantly impaired relative to controls. Errors in sentence expression were present in all but one ALS patient, and a significant deficit was seen in 42% of ALS patients. The speech elicitation task was untimed, and grammatical difficulty was evident in non-dysarthric as well as dysarthric patients, so it is likely that grammaticality was minimally confounded by motor demands. Consistent with this interpretation, grammaticality did not correlate with measures of motor functioning. Since grammatical impairment was present in patients who did not exhibit an executive impairment, it was independent of executive difficulties. Also, the production of grammatically well-formed sentences did not correlate with reverse digit span, an untimed measure of working memory that has minimal motor demands. Other studies have reported a link between working memory and grammaticality in sentence processing (10,30,31). The present investigation suggests that sentence production in ALS, in contrast to sentence comprehension, may rely more heavily on purely linguistic resources than on executive resources. This may be due in part to the speaker's control over the content of speech, which allows patients to avoid expressing content that requires working memory. Sentence production is complex, and additional work is needed to investigate whether other cognitive factors may contribute to sentence expression deficits in ALS.

Inferior frontal, anterior temporal, and striatal regions of the left hemisphere appear to be implicated in the grammatical deficit of ALS patients. Portions of these regions are adjacent to the primary motor cortex and are often affected in ALS (10,12). Effortful speech and grammatical difficulty has been associated with disease in inferior prefrontal regions in ALS with naPPA (12). The present study extends these findings to ALS patients with grammatical deficits who do not have naPPA. Regression studies of speech expression in naPPA (23,25,32,33) and imaging studies of healthy adults (34,35) have associated the left inferior frontal region with grammatical expression. Grammatical deficits in naPPA have also implicated anterior temporal regions (23,25); the present study has associated anterior temporal atrophy with grammatical deficits in ALS as well. Some work has shown that there is disease in the striatum in ALS, particularly as the disease progresses (36). This is consistent with evidence that the striatum is implicated in language disorders, including grammatical processing deficits, in patients with Parkinson's disease (37,38). Additional work is needed to compare the types of grammatical errors seen in ALS and other disorders.

WM disease in ALS appears to contribute to the patients' grammatical difficulty, affecting fiber tracts such as superior longitudinal fasciculus and inferior frontal-occipital fasciculus of the dorsal and ventral streams that are thought to play a role in sentence processing (39). Previous work has implicated these projections in the grammatical processing deficits of patients with naPPA (24,25). WM disease has been implicated in motor (40,41) and executive (42) deficits in ALS, but we are not aware of previous work relating language difficulty to WM disease in ALS.

Several caveats should be kept in mind when considering our results. While our imaging cohort was representative of the entire group of patients, imaging studies were available in only a subset of patients. A non-verbal executive measure was not available to identify individuals with potential executive limitations, although we did not find a correlation between grammatical expression and an untimed verbal measure of working memory. Further work is needed to examine the role of cognitive resources in grammatical expression in ALS. A more direct connection between a motor deficit and articulatory errors could be obtained through cinematographic or electrical methods of monitoring motor functioning during speech. With these caveats in mind, we conclude that sentence production difficulties in ALS are multifactorial in nature. While motor system difficulty contributes to slowed speech and articulation errors, patients with ALS also appear to have a deficit in grammatical expression. This is independent of their motor speech deficit, and it is related to a network of GM and WM structures which is compromised in ALS. Measures of grammaticality in speech thus may be valuable in monitoring cognitive deficits in ALS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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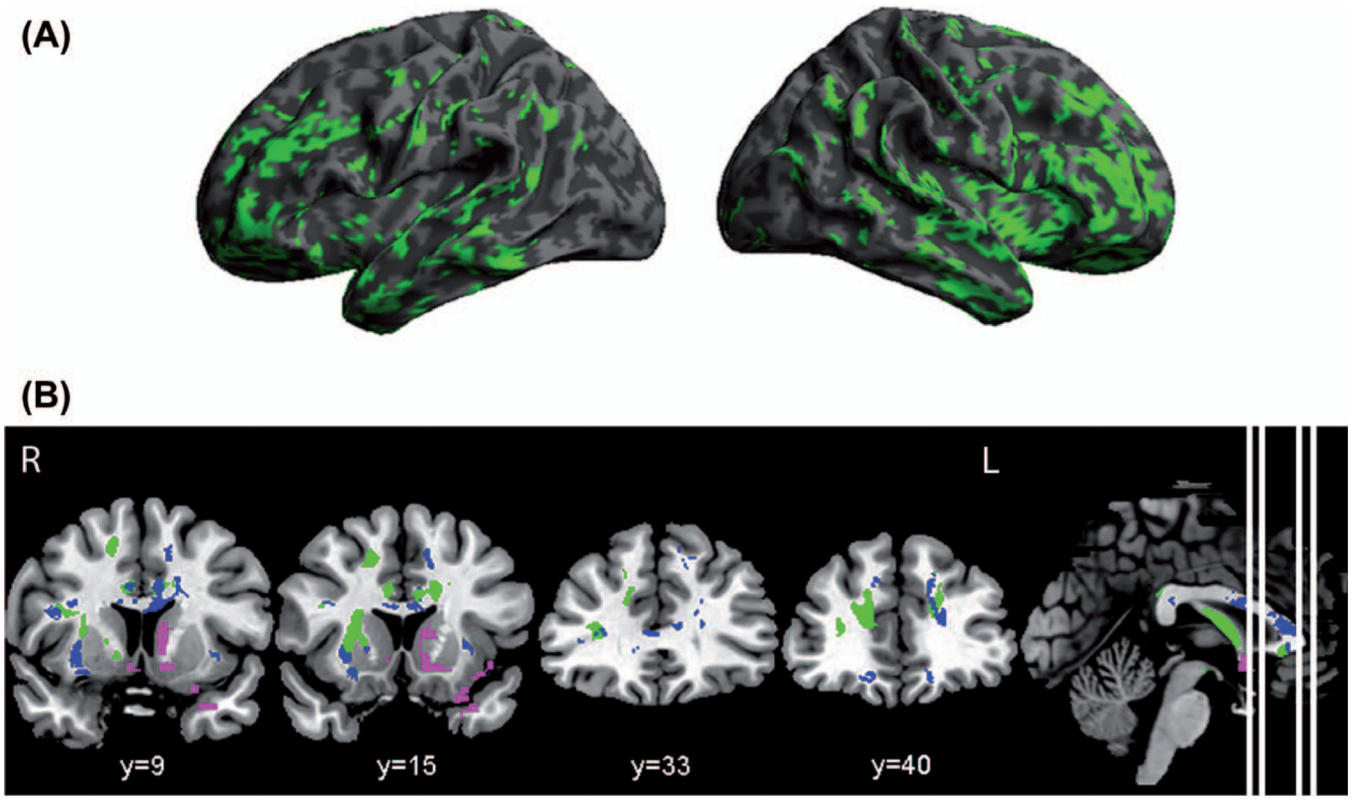

Figure 1.

Gray matter atrophy and reduced white matter fractional anisotropy in ALS relative to controls and regressions relating percent grammatically well-formed sentences to atrophy and reduced fractional anisotropy in ALS. PANEL A: Significant gray matter atrophy in ALS (green). PANEL B: Significantly reduced fractional anisotropy in ALS (green), regressions relating gray matter atrophy in ALS to % grammatically well-formed sentences (magenta), and regressions relating reduced fractional anisotropy in ALS to % grammatically well-formed sentences (blue).

Table I

Mean (SD) demographic and clinical characteristics of ALS patients and controls.[1]

	ALS	Controls
n (male/female)	19/7	6/13
Age (yrs)	61.0 (9.2) [26]	66.3 (8.4) [19]
Education (yrs)	14.7 (2.8) [26]	15.3 (2.5) [19]
Disease duration (yrs)	3.8 (2.4) [26]	–
Bulbar motor score (from Upper Motor Neuron score) (max = 4)	1.08 (1.10) [24]	–
ALSFRS-R	31.7 (8.9) [25]	–
ALSFRS-R speech subscale	3.28 (0.74) [25]	–
Forced vital capacity, seated	68.4 (21.7) [25]	–
MMSE (max = 30)[2]	28.2 (2.3) [26]	29.1 (1.1) [16]
Neuropsychological measures		
Category fluency (animals)	17.5 (6.3) [23]	21.7 (4.8) [15]
FAS	34.7 (13.6) [26]*	44.6 (10.9) [13]
Reverse digit span	4.8 (1.3) [26]	5.4 (1.5) [11]
Forward digit span	6.7 (1.2) [26]*	7.7 (1.2) [12]
Boston naming test (% correct)	86.4 (21.0) [22]	92.1 (10.3) [13]

Differs from controls,

* $p < 0.05$.

[1] Number of subjects with available data is given in square brackets.

[2] Score adjusted proportionately for tasks that could be performed despite a motor limitation.

Table II

Mean (SD) measures of language production in all ALS patients, ALS patients with and without dysarthria, ALS patients without executive impairment, and controls.[1]

	Controls (*n* = 19)	All ALS (*n* = 26)	ALS without dysarthria (*n* = 20)	ALS with dysarthria (*n* = 6)	ALS without executive impairment (*n* = 20)
Speech output					
Words per minute	142 (22)	113 (43)*	122 (43)	82 (24)**#	119 (40)*
Number of words	596 (220)	417 (190)**	429 (181)*	378 (233)*	430 (190)*
Speech articulation errors/100 words	0.07 (0.15)	1.56 (5.11)*	0.19 (0.29)	6.13 (9.88)**##	1.99 (5.79)*
Number of utterances	58.5 (18.3)	38.3 (17.1)**	40.2 (17.5)**	32.0 (15.5)**	37.2 (17.0)**
% Grammatically well-formed sentences	96.5 (2.8)	90.1 (8.2)**	90.3 (8.5)**	89.2 (7.7)**	91.1 (7.0)**
Nouns/100 words	20.0 (2.6)	21.2 (2.2)	20.7 (2.0)	22.4 (2.3)	21.3 (1.9)
Inflected verbs/100 words	14.2 (1.6)	13.6 (1.0)	13.5 (1.1)	14.0 (1.0)	13.5 (1.1)

[1] ALS differs from controls.

* $p < 0.05$,

** $p < 0.01$;

ALS with dysarthria differs from ALS without dysarthria,

# $p < 0.05$;

$p < 0.01$.

Amyotroph Lateral Scler Frontotemporal Degener. Author manuscript; available in PMC 2015 March 24.

Table III

Correlations of speech performance measures with motor functioning in ALS.[1]

	Motor disorder		
	Bulbar motor score (*n* = 24)	**ALSFRS-R speech subscale (*n* = 25)**	**Vital capacity, seated (*n* = 25)**
Words per minute	−.66**	.50*	NS
Number of words	−.41*	NS	NS
Speech articulation errors/100 words	.44*	NS	NS
% Grammatically well-formed sentences	NS	NS	NS

* $p < 0.05$;

** $p < 0.01$.

[1] Number of subjects with available data is given in square brackets.

Table IV

Peak anatomic locations of gray matter atrophy in amyotrophic lateral sclerosis and regressions relating atrophy to percentage of grammatically well-formed sentences.

Neuroanatomic region (Brodmann Area)	MNI coordinates of peak voxel			Cluster size (voxels)
	x	y	z	
ALS gray matter atrophy				
L medial frontal (8)	−8	32	44	65
L middle frontal (8)	− 30	18	46	64
L middle frontal (6)	− 36	12	58	140
L uncus (20) / superior temporal (38)	− 30	4	− 48	22221
*L inferior frontal (47)	− 42	40	− 6	
*L middle frontal (11)	− 28	40	− 18	
*R inferior temporal (20)	66	− 44	− 18	
*R inferior temporal (20)	52	− 10	− 28	
*R inferior temporal (20)	48	− 2	− 32	
*R fusiform (20)	40	− 18	− 26	
*R middle frontal (11)	32	50	− 2	
*R cingulate (24)	4	28	22	
L thalamus	− 2	− 16	8	250
L postcentral (2)	− 38	− 30	36	98
L postcentral (3)	− 46	− 22	42	123
L postcentral (3/4)	− 16	− 36	78	77
L inferior parietal (40)	− 36	− 38	54	54
L posterior cingulate (30)	− 18	− 56	14	65
L precuneus (7)	− 10	− 58	60	86
L inferior parietal (40)	− 52	− 62	36	172
L fusiform (37)	− 42	− 64	− 12	58
L lingual (18)	− 24	− 78	− 2	66
R medial frontal (6)	18	2	68	97
R precentral (6)	22	− 16	70	114
R postcentral (3)	40	− 28	64	150
R inferior parietal (40)	44	− 34	38	53
R fusiform (37)	50	− 48	− 22	834
R precuneus (7)	8	− 52	60	62
R precuneus (7)	12	− 72	48	86
R inferior occipital (18)	36	− 84	− 10	89
R lingual (17)	8	− 90	2	79
Regression relating grammatical sentences to atrophy in ALS				
L caudate	− 8	16	− 8	192
L inferior prefrontal (47)	− 42	14	− 8	31

Neuroanatomic region (Brodmann Area)	MNI coordinates of peak voxel			Cluster size (voxels)
	x	y	z	
L inferior prefrontal (47)	− 26	12	− 24	41
L anterior temporal (38)	− 30	12	− 28	40
R entorhinal (34)	10	0	− 14	43

* Cluster subpeak.

Table V

Reduced fractional anisotropy in white matter of ALS compared to controls and regression relating percentage grammatically well-formed sentences to reduced fractional anisotropy in ALS.

	X	Y	Z	Cluster size (voxels)
Reduced fractional anisotropy in ALS relative to controls				
L corpus callosum (frontal)	−16	43	20	676
L corpus callosum (frontal)	−7	14	26	1668
L extreme capsule/external capsule/claustrum	−29	18	10	217
L cerebral peduncle	−18	−14	−17	889
L precentral gyrus WM	−11	−19	70	3051
L superior corona radiata	−14	−20	39	718
L postcentral gyrus WM	−41	−24	45	854
L corpus callosum (splenium)	−17	−36	17	291
L cingulum	−11	−44	31	320
L superior longitudinal fasciculus	−35	−49	22	245
L middle or lateral occipital gyrus WM	−30	−59	28	450
R corpus callosum (frontal)	18	42	13	1150
R corpus callosum (frontal)	20	23	37	1187
R corpus callosum (frontal)	8	11	29	764
R inferior fronto-occipital fasciculus	30	38	9	404
R anterior corona radiata	15	24	−10	1529
R extreme capsule/external capsule/claustrum	24	16	7	2096
R inferior frontal gyrus WM	40	12	24	572
R superior frontal gyrus WM	22	−6	63	383
R inferior temporal gyrus WM	31	2	−35	209
R inferior longitudinal fasciculus	41	−19	−20	8543
R superior longitudinal fasciculus	33	−28	21	589
R superior longitudinal fasciculus	40	−42	23	300
R cingulum	26	−20	−26	756
R cingulum	12	−40	33	2727
R superior parietal lobule WM	32	−32	44	4702
Regression relating grammatical sentences to reduced FA in ALS				
L uncinate	−14	43	−16	147
L corpus callosum (frontal)	−19	37	15	539
L cingulum	−13	22	38	570
L inferior fronto-occipital fasciculus	−34	9	−2	134
L internal capsule (retrolenticular)	−26	−23	13	127
L superior longitudinal fasciculus	−34	−30	30	382
L postcentral gyrus WM	−22	−32	51	1175
L corpus callosum (splenium)	−14	−34	21	3117
L posterior thalamic radiation	−39	−44	7	326
L cingulum	−9	−48	28	115

	X	Y	Z	Cluster size (voxels)
L precuneus WM	−11	−49	44	105
L middle or lateral occipital gyrus WM	−28	−63	27	699
L corpus callosum (parieto-occipital)	−24	−70	20	365
R corpus callosum (frontal)	13	55	15	234
R corpus callosum (frontal)	9	47	30	323
R corpus callosum (frontal)	6	27	8	8337
R uncinate	18	46	−15	319
R inferior fronto-occipital fasciculus	29	37	7	132
R inferior frontal gyrus WM	44	7	17	492
R internal capsule (anterior)	12	3	−1	201
R uncinate fasciculus	30	−3	−20	3030
R precentral gyrus WM	45	−4	41	115
R internal capsule (posterior)	21	−7	6	274
R corticospinal tract	25	−12	42	329
R anterior thalamic radiation	6	−14	10	241
R corticospinal tract	26	−21	55	251
R cerebral peduncle	16	−22	−9	462
R fusiform gyrus WM	37	−26	−17	133
R superior longitudinal fasciculus	35	−34	22	1107
R superior longitudinal fasciculus	44	−40	6	441
R corpus callosum (splenium)	23	−49	18	313
R corpus callosum (parieto-occipital)	17	−53	51	468
R posterior thalamic radiation	28	−75	10	466