Narrative discourse deficits in amyotrophic lateral sclerosis

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ABSTRACT

Objective: We examined narrative discourse in amyotrophic lateral sclerosis (ALS) to assess the role of executive functioning in support of language and the neuroanatomical basis for such support.

Methods: We analyzed a semistructured speech sample in 26 patients with ALS and 19 healthy seniors for narrative discourse features of coherence. Regression analyses related a measure of discourse coherence ("local connectedness") to gray matter atrophy and reduced white matter fractional anisotropy.

Results: Patients with ALS were impaired relative to controls on measures of discourse adequacy, including local connectedness and maintenance of the theme. These discourse measures were related to measures of executive functioning but not to motor functioning. Regressions related local connectedness to gray matter atrophy in ventral and dorsal prefrontal regions and to reduced fractional anisotropy in white matter tracts mediating projections between prefrontal regions.

Conclusion: Patients with ALS exhibit deficits in their ability to organize narrative discourse. These deficits appear to be related in part to executive limitations. Consistent with the hypothesis that ALS is a multisystem disorder, this deficit is related to disease in prefrontal regions.
Neurology® 2014;83:520–528

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSFRS-R** = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; **bvFTD** = behavioral variant frontotemporal dementia; **FA** = fractional anisotropy; **GM** = gray matter; **VC** = vital capacity; **WM** = white matter.

Amyotrophic lateral sclerosis (ALS) is typically viewed as a motor system disorder, but cognitive impairments in ALS are increasingly recognized.[1,2] Language impairments in ALS may result in part from deficits in executive functioning,[3–5] but they have also been shown to be at least in part independent of executive dysfunction.[6–8] Most reports of language performance in ALS have focused on the comprehension or production of single words.[1,7,9,10] There are few studies of spontaneous, continuous speech—referred to as "connected speech"—in these patients, despite the importance of connected speech in everyday life. In this study, we elicited a semistructured speech sample in the form of a narrative of sufficient length to allow subjects to demonstrate the full range of their linguistic capabilities. We examined the discourse structure of the narratives to determine whether executive impairments were associated with difficulty in telling the story, and we assessed the contribution of motor weakness to narrative production.

MRI studies of ALS have demonstrated gray matter (GM) atrophy and white matter (WM) reduced fractional anisotropy (FA) in prefrontal regions,[11,12] consistent with the claim that ALS is a multisystem disorder.[13,14] To elucidate the neuroanatomical basis of narrative discourse deficits in ALS, we related performance to high-resolution GM and WM structural imaging in a subset of patients. Based on previous fMRI work in healthy adults and nonaphasic patients with

Supplemental data at Neurology.org

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behavioral variant frontotemporal dementia (bvFTD),[15–17] we expected the narrative disorder in ALS to be related in part to their prefrontal disease.

METHODS **Subjects.** We studied 26 nonaphasic patients with ALS and 19 healthy seniors recruited as control subjects. Patients were diagnosed by experienced neurologists (L.M., L.E., D.J.I., M.G.) in the ALS Clinic and the Penn FTD Center of the Department of Neurology at the University of Pennsylvania according to revised El Escorial criteria.[18] A consensus evaluation was used to assess overall cognitive functioning, including a semistructured neurologic history, a complete neurologic examination, and a detailed mental status assessment. Exclusionary criteria included vascular disease, structural brain abnormalities, medical diseases interfering with cognition, and primary psychiatric disorders. We also excluded patients with visual-perceptual difficulty that could limit their ability to perceive the pictures of the story used to elicit the speech sample (see below). Overall motor disease severity was assessed with the ALS Functional Rating Scale–Revised (ALSFRS-R),[19] and we also collected supine vital capacity (VC). For this, patients form a seal around the mouthpiece and inhale deeply. The nose is then occluded with a clip, and the patient exhales fully through the tube. A mask is used for patients with significant facial weakness who are unable to form a seal around the mouthpiece. Demographic and clinical characteristics are summarized in table 1. One-way analyses of variance indicated that ALS and control groups were matched for age and education. With scoring adjusted proportionately for the tasks that could not be performed because of a motor limitation, the mean score on the Mini-Mental State Examination[20] of patients with ALS did not differ from that of controls.

Neuropsychological performance is summarized in table 1. Four patients with ALS, including 2 of 3 with co-occurring bvFTD, exhibited impaired executive functioning compared with norms established by a set of 25 controls. (The third patient with bvFTD had only a social disorder.) For these 4 patients with an executive impairment, there was difficulty on letter-guided fluency,[21] semantically guided category naming fluency,[21] or both. To minimize the possibility that impaired language performance was biased only by executive dysfunction, we separately assessed performance in the subset of 22 patients with ALS who did not have executive impairment. To evaluate the contribution of a bulbar motor disorder, we identified dysarthria in 6 patients, 5 with flaccid dysarthria and one with spastic dysarthria (appendix e-1 on the *Neurology*® Web site at Neurology.org). We analyzed language characteristics separately in patients with and without dysarthria.

Table 1 Mean (SD) demographic and clinical characteristics of the patients with ALS and controls

	ALS	Controls
No., M/F	19/7	6/13
Age, y	61.0 (9.2) [26]	66.3 (8.4) [19]
Education, y	14.7 (2.8) [26]	15.3 (2.5) [19]
Disease duration, y	3.8 (2.4) [26]	—
ALSFRS-R (max = 48)	31.7 (8.9) [25]	—
Vital capacity, supine	67.1 (16.3) [16]	—
MMSE (max = 30)[a]	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]
Letter fluency (FAS)	34.7[b] (13.6) [26]	44.6 (10.9) [13]
Reverse digit span	5.1 (1.1) [22]	5.4 (1.5) [11]
Forward digit span	6.9[b] (1.1) [23]	7.7 (1.2) [12]

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; max = maximum; MMSE = Mini-Mental State Examination.
Number of subjects with available data is given in square brackets.
[a] Score adjusted proportionately for tasks that could be performed despite a motor limitation.
Differs from controls, [b] $p < 0.05$.

Standard protocol approvals, registrations, and patient consents. 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 wordless children's picture book, *Frog, Where Are You?*,[22] described elsewhere.[17] The book's sequence of 24 detailed drawings elicited an extended speech sample with a known target, while avoiding the formulaic character of an overlearned story such as a fairy tale.

Subjects first reviewed the story and then paged through it, narrating the story as if telling it to a child. The narratives were recorded digitally and transcribed in detail by trained transcribers using the signal processing software Praat.[23] The narratives were scored from transcripts by trained judges, referring to the original speech files as needed. All coding was checked by a linguist (S.A.) with expertise in phonetic, grammatical, and discourse analysis. The narrations were scored for accurately reported content and 3 discourse variables: local connectedness, global connectedness, and maintenance of the search theme. Local connectedness is the linking of each event with the preceding event, which is accomplished by rhetorical markers such as sequencing adverbials, pronominal reference to preceding nouns, reference by definite as opposed to indefinite determiners, and statements of cause and effect. Global connectedness is a categorical variable that registers whether the speaker acknowledges the point of the story, namely, that the frog found at the end is the frog that was present in the boy's room at the beginning. Maintenance of the theme of searching for the frog is scored from 0 to 4 by counting points accrued for mentions of the search.[24]

Summary features of speech production were also recorded (table 2). These include duration of the narrative, number of complete words spoken, number of utterances, and pauses within and between utterances with a duration of ≥2 seconds. An utterance is defined as an independent clause and all clauses dependent on it.[25] Words per minute was calculated, and adjusted words per minute was computed to exclude lengthy pauses on the grounds that they may be attributable to a motor impairment, rather than to executive or other cognitive deficits. Accuracy of content requires the full reporting of each event, with no contradictory content.

Statistical considerations. Statistical analysis was conducted using SPSS version 21 (IBM Corp., Armonk, NY). Levene 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*) to assess differences between groups. Correlations were calculated using Spearman ρ.

Table 2 Mean (SD) measures of language production in all patients with ALS, patients with ALS without executive impairment, nondysarthric patients with ALS, and controls

	Controls (n = 19)	All ALS (n = 26)	ALS without executive impairment (n = 22)	ALS without dysarthria (n = 20)
Speech output				
Duration, s	258 (103)	235 (112)	236 (119)	219 (86)
No. of words	594 (219)	417[a] (190)	428[a] (184)	429[b] (181)
No. of utterances	58.5 (18.3)	39.4[a] (17.3)	38.9[a] (17.0)	40.2[a] (17.5)
Words per min	142 (22)	113[b] (43)	116[b] (40)	122 (43)
Adjusted words per min[c]	150 (19)	141 (40)	138 (39)	154 (34)
% Pause time (for pauses ≥2 s)	5.5 (5.9)	20.4[a] (18.0)	16.7[a] (13.4)	22.3[a] (19.2)
Accurate report (max = 30)	23.5 (4.6)	17.2[a] (7.4)	18.3[a] (6.9)	17.0[a] (73)
Discourse				
Local connectedness (max = 30)	27.5 (2.7)	23.0[a] (6.7)	23.7[a] (5.0)	22.6[a] (7.1)
Search theme (max = 4)	3.9 (0.2)	3.4[b] (1.1)	3.7[b] (0.5)	3.4 (1.2)
% Subjects with global connectedness	95 (23)	77 (43)	86 (35)	70 (47)

Abbreviations: ALS = amyotrophic lateral sclerosis; max = maximum.
ALS differs from controls, [a] $p < 0.01$; [b] $p < 0.05$.
[c] Speech rate calculated with exclusion of the duration of pauses ≥2.0 seconds.

Imaging data acquisition and analysis. A structural T1-weighted, 3-dimensional, spoiled gradient-echo sequence and a diffusion-weighted imaging from the same scan session were available for 10 participants with ALS. Reasons for exclusion included health and safety (e.g., difficulty breathing while supine, metallic implants, shrapnel, claustrophobia), intercurrent illness, scheduling and transportation difficulty, and lack of interest in an imaging study. Details of the image acquisition and analysis are provided in appendix e-2. 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, clinical, neuropsychological, or language measures from the total set of patients (appendix e-3). Imaging was also collected on 34 healthy controls who were comparable to the patients with ALS in age ($t_{42} = 0.02$; $p = 0.99$), education ($t_{41} = 1.45$; $p = 0.15$), and sex ($\chi^2_1 = 1.90$; $p = 0.17$).

We used the Randomise tool in FSL (FMRIB's Software Library) (http://fsl.fmrib.ox.ac.uk/fsl/randomise/) to perform a nonparametric, permutation-based statistical analysis (permutations = 10,000) to compare GM density between patients with ALS and controls. Analyses 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, family-wise error–corrected for multiple comparisons after threshold-free cluster enhancement).[26] We also used the Randomise tool to perform regression analyses to relate GM atrophy to the local connectedness score (permutations = 10,000). Regression analyses were restricted to areas of GM disease as determined by the GM atrophy analysis. Clusters with a height threshold of $p < 0.05$ (uncorrected for multiple comparisons) and an extent threshold of 10 voxels were considered significant.

We also compared WM FA between patients with ALS and controls using Randomise (permutations = 10,000). We restricted analysis to areas of WM by averaging all patients and controls and generating a mask consisting of voxels with $F > 0.25$. Significant clusters survived an extent threshold of 200 voxels and height threshold of $p < 0.05$ (ALS < seniors, family-wise error–corrected for multiple comparisons after threshold-free cluster enhancement).[26] We used Randomise to perform regression analyses, relating reduced FA to the local connectedness score (permutations = 10,000). Regression analyses 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 a map of 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 $p < 0.05$ (uncorrected for multiple comparisons) and an extent threshold of 100 voxels to establish cluster significance.

RESULTS

Discourse measures. Measures of discourse performance in ALS and controls are summarized in table 2. Patients with ALS were impaired in local connectedness and maintenance of the search theme relative to controls. These results were observed in the entire group of patients with ALS (n = 26), the subset of patients who were not impaired on executive measures (n = 22), and the nondysarthric patients (n = 20). These results were also found for the subgroup of 23 patients with ALS who did not have co-occurring bvFTD (data not shown). Patients with ALS did not differ from controls on global connectedness.

Other speech measures. Patients with ALS were impaired relative to controls on gross measures of output in that they produced fewer words and

correspondingly fewer utterances than healthy seniors. Nondysarthric patients did not differ from controls in speech rate, and the reduction in speech rate was not significant for any group when adjusted for lengthy pauses in their speech. Accurate report of content was also impaired in ALS.

Table 3 summarizes the significant correlations of discourse measures with the most frequently used measure of executive functioning in ALS, letter fluency, and with 2 measures of motor functioning that do not involve executive functioning, ALSFRS-R and VC. The group of all patients with ALS and the 2 subgroups exhibited a correlation of letter fluency with search theme score, and the total group and the subset of patients without a cognitive impairment exhibited a correlation of letter fluency with local connectedness. The absence of a correlation of letter fluency with local connectedness prompted examination of the individual subjects' performance. Two nondysarthric patients had low scores on letter fluency but high scores on local connectedness. Excluding these 2 outliers, letter fluency correlated with local connectedness ($r = 0.61$; $p < 0.01$) and search theme ($r = 0.47$; $p < 0.05$) for the remaining 18 nondysarthric patients. It is noteworthy that one of these individuals had pronominal reference difficulty, a discourse impairment not captured by the coding procedure for the present study. The measures of narrative discourse were not correlated with measures of motor functioning. Furthermore, correlations of narrative discourse measures with number of words and number of utterances were similar for patients with ALS and healthy seniors. Also, there was no correlation of discourse measures with forward or reverse digit span.

Imaging analyses. Table 4 and the figure, A, summarize the distribution of GM atrophy in ALS. Atrophy is found in frontal and temporal lobes bilaterally, including a large cluster in the left inferior frontal region extending dorsally to middle frontal regions. Table 4 and the figure, A and B, also display regressions relating local connectedness to GM atrophy. Areas of GM atrophy implicated in local connectedness deficits in patients with ALS include right dorsolateral prefrontal and bilateral inferior frontal regions.

Table 4 and the figure, B, display areas of reduced FA in WM. These include the corpus callosum, right inferior frontal-occipital fasciculus, and other WM regions. Table 4 and the figure, B, also display regressions relating local connectedness to reduced FA in WM regions of the frontal lobe bilaterally as well as the corpus callosum, right uncinate, and right inferior frontal-occipital fasciculus.

DISCUSSION ALS is a multisystem disorder, and cognitive impairment is common in ALS. In this study, we found that nonaphasic patients with ALS exhibited deficits on a task used to elicit narrative discourse. A critical aspect of their difficulty was achieving cohesiveness of the narrative, both in connecting one event to the next and in sustaining the theme of the story. This is critical because narrative discourse is an essential part of everyday communication. In exchanges with family and friends, poor discourse cohesion constitutes a significant disruption of communication that can reduce safety and quality of life. These deficits could not easily be explained by a motor disorder but were related to interruptions of a prefrontal GM and WM network that supports narrative discourse.

The pattern of impaired narrative discourse in ALS was associated with executive difficulties. This correlation was found for the entire cohort of patients with ALS, for the subset of patients who did not exhibit an overt cognitive impairment, and for the subset of patients who did not have dysarthria. Many studies have demonstrated an executive deficit in ALS.[5,27,28] While other linguistic and cognitive resources also contribute to discourse, the correlations of local connectedness and search theme with a measure of executive functioning reflect in part the planning and organization needed to maintain the coherence of the story. Indeed, these measures of narrative speech may be a more ecologically valid way to assess planning and organization than traditional

Table 3 Correlations of narrative discourse measures with executive and motor functioning in ALS

	Letter fluency (FAS)			Motor disorder (ALSFRS-R)			Motor disorder (vital capacity, supine)		
	All ALS (n = 26)	ALS, no cognitive deficit (n = 22)	ALS, no dysarthria (n = 20)	All ALS (n = 25)	ALS, no cognitive deficit (n = 20)	ALS, no dysarthria (n = 20)	All ALS (n = 16)	ALS, no cognitive deficit (n = 13)	ALS, no dysarthria (n = 13)
Local connectedness	0.41[a]	0.61[b]	NS	NS	NS	NS	NS	NS	NS
Search theme	0.54[b]	0.49[a]	0.49[a]	NS	NS	NS	NS	NS	NS

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; NS = not significant.
[a] $p < 0.05$; [b] $p < 0.01$; NS $p > 0.1$.

Table 4 Anatomical locations of GM atrophy and reduced WM FA in ALS and regressions relating atrophy to local connectedness of discourse

Anatomical locus (Brodmann area)	MNI coordinates			Cluster size (voxels)
	x	y	z	
GM atrophy, ALS < Controls				
L orbitofrontal (11)	−28	40	−18	4,792
R middle frontal (10)	32	50	−2	107
R inferior frontal (47)	42	32	2	731
L superior temporal (38)	−30	4	−48	241
R inferior temporal (20)	52	−10	−28	343
Regressions of local connectedness and GM atrophy				
L inferior frontal (10)	−46	48	6	27
L orbitofrontal (11)	−28	38	−22	13
L ventromedial frontal (11)	−4	26	−20	10
L ventromedial frontal (47)	−16	18	−14	16
R cingulate (32)	8	38	18	54
R cingulate (32)	8	18	42	13
R dorsolateral prefrontal (46)	44	40	14	10
R dorsolateral prefrontal (46)	38	30	26	14
R inferior frontal (47)	54	38	−2	18
R inferior frontal (47)	34	20	−12	98
R insula	46	12	4	24
Reduced FA, ALS < Controls				
B corpus callosum (genu)	16	41	15	259
B corpus callosum (genu)	−8	23	1	382
B corpus callosum (body)	7	12	29	474
B corpus callosum (body)	−7	12	27	665
L cingulum	−14	−19	39	299
L postcentral WM	−6	−32	61	2,386
L cerebral peduncle	−17	−13	−14	299
R inferior frontooccipital fasciculus	25	20	12	1,908
R cingulum	13	−42	32	7,723
R cerebral peduncle	19	−17	−14	8,456
Regressions of local connectedness and WM reduced FA				
B corpus callosum (genu)	17	46	14	161
B corpus callosum (genu)	−16	44	24	243
B corpus callosum (genu)	−10	26	45	256
B corpus callosum (body)	7	21	59	120
B corpus callosum (body)	−12	15	23	591
B corpus callosum (body)	−12	−14	33	220
B corpus callosum (splenium)	20	−48	38	273
L superior frontal WM	−16	−11	70	236
R uncinate	27	34	−4	863
R superior frontal (WM)	15	−8	72	276
R precentral WM	32	−3	40	401
R precentral WM	14	−20	73	215
R precentral WM	27	−21	67	562

Continued

Table 4 Continued

Anatomical locus (Brodmann area)	MNI coordinates x	y	z	Cluster size (voxels)
R corticospinal tract	11	−22	−13	1,374
R corona radiata	22	−24	41	448
R inferior frontooccipital fasciculus	33	−61	8	165

Abbreviations: ALS = amyotrophic lateral sclerosis; FA = fractional anisotropy; GM = gray matter; MNI = Montreal Neurological Institute; WM = white matter.

executive measures of speech fluency such as letter fluency (FAS). Previous fMRI studies of healthy adults and correlation studies in nonaphasic patients relate narrative performance to hierarchical organization and planning.[15,16] By comparison, recalling the overall purpose of the story may be relatively preserved in ALS because this depends on memory of a single element rather than on the organizational demands of narrative expression.

Motor functioning is needed for speech. Impaired motor functioning may have contributed to the reduced number of words, utterances, and speech rate; to omissions of content; and to other syntactic and semantic abnormalities in ALS. Investigation of this possibility may be a productive avenue for future research. However, it appears that a motor deficit cannot fully explain the pattern of impairment in the narrative discourse of patients with ALS. We found no correlation between narrative measures and measures of motor functioning such as ALSFRS-R and VC. In addition, we identified patients with bulbar motor impairment causing dysarthria, and patients without dysarthria also had narrative deficits.

We have previously examined narrative discourse in nonaphasic patients with bvFTD using the same measures as in the present study. Consistent with mounting evidence that bvFTD and ALS occur as a spectrum of disease,[29,30] the findings of the present study in ALS parallel the results of the earlier study[17] in many ways. Among the behavioral findings, both ALS and bvFTD patient groups have difficulty maintaining local connectedness and search theme, and these measures correlate with executive performance in both groups. This converging evidence supports the hypothesis that the cognitive component of ALS, rather than the motor component, contributes to the narrative deficit in ALS.

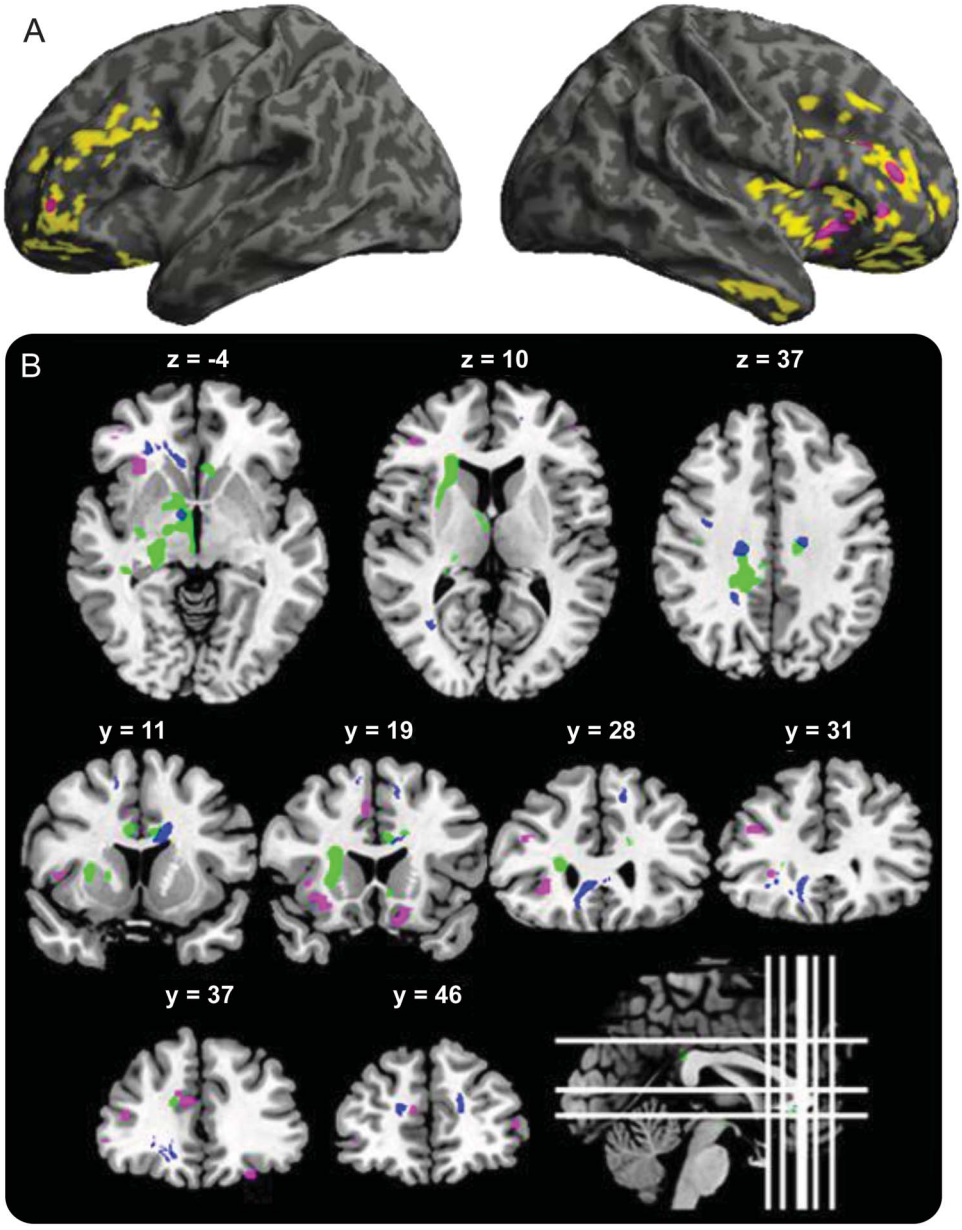
The imaging results are also consistent with the implication of an executive component in the narrative discourse deficit of ALS. As a parallel to our findings in patients with bvFTD,[17] we found GM atrophy in right dorsolateral prefrontal regions associated with local connectedness in ALS. This area has previously been related to letter fluency in ALS.[10] Regions of the right hemisphere have also been implicated in discourse impairments in studies of nonaphasic stroke patients.[31,32] Further evidence that these frontal regions contribute to executive function is provided by fMRI studies of healthy adults showing activation of these areas during planning and working memory tasks.[33,34]

Bilateral inferior frontal atrophy was also associated with poor local connectedness in ALS. In an fMRI study of healthy adults using the same materials as in the present study, bilateral inferior frontal activation was found during story narration relative to the description of unordered pictures.[15] This experimental contrast depends specifically on maintaining local connectedness, consistent with a role for this region in the organization of narrative discourse. Right inferior frontal cortex was also related to local connectedness in bvFTD.[17]

Regression analyses related local connectedness to reduced FA in several prefrontal WM regions. These presumably contribute to the integration of functioning between inferior and dorsal frontal GM regions that appear to be important in narrative discourse. Regressions also implicated the corpus callosum that joins left and right frontal regions. Atrophy of the corpus callosum has been associated with executive impairments, including reduced verbal fluency, in other work.[35,36] Local connectedness also correlated with reduced FA in the right uncinate fasciculus, which links inferior frontal and anterior temporal regions. A correlation of uncinate with executive functioning has been reported in bvFTD.[37] Additional work is needed to determine whether this correlation is also associated with an executive impairment in ALS.

Several caveats apply to the interpretation of our findings. We were able to obtain imaging in only a small number of patients. We used a protocol that optimized the opportunity to demonstrate narrative expressive capabilities in the patients with ALS. However, this procedure is not feasible in a clinical setting, and it would be valuable to examine connectedness with a briefer protocol.[38] It would also be important to demonstrate empirically the impact of narrative

Figure Gray matter atrophy and reduced white matter fractional anisotropy in ALS relative to controls, and regressions relating local connectedness to atrophy and reduced fractional anisotropy in ALS



(A) Gray matter atrophy in amyotrophic lateral sclerosis (ALS) (yellow) and regressions relating gray matter atrophy to local connectedness in ALS (magenta). (B) Reduced fractional anisotropy in ALS (green), regressions relating gray matter atrophy in ALS to local connectedness (magenta), and regressions relating reduced fractional anisotropy in ALS to local connectedness (blue).

discourse impairments on daily functioning in ALS. Future work could evaluate the relationship between narrative impairments and a motor disorder more directly with quantitative EMG of the oral musculature and with a non-ALS control group with mechanical speech deficits. With these qualifications, our observations support the hypothesis that patients with ALS have a disorder of narrative expression that cannot be fully explained by their motor disorder. It appears to be related in part to executive limitations that interfere with the planning and organization needed for narrative expression and to disruption of a large-scale neural network in the frontal lobe that appears to support narrative discourse.

AUTHOR CONTRIBUTIONS

Sharon Ash drafted/revised the manuscript for content, contributed to study concept/design, contributed to acquisition of the data, performed analysis/interpretation of the data, and performed statistical analysis. Anna Menaged contributed to acquisition and analysis/interpretation of the data. Christopher Olm contributed to acquisition and analysis/interpretation of the data. Corey T. McMillan contributed to analysis/interpretation of the data. Ashley Boller, David J. Irwin, Leo McCluskey, and Lauren Elman contributed to acquisition and analysis of the data. Murray Grossman drafted/revised the

manuscript for content, contributed to study concept/design, contributed to acquisition and analysis/interpretation of the data, obtained funding, and provided supervision.

STUDY FUNDING

Supported by NIH (AG032953, AG017586, AG015116, NS044266, NS053488, AG032953, and AG043503), and the Wyncote Foundation.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received January 21, 2014. Accepted in final form April 28, 2014.

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