Frontal lobe abnormalities on MRS correlate with poor letter fluency in ALS

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ABSTRACT

Objective: To examine whether frontal lobe abnormalities on magnetic resonance spectroscopy (MRS) in amyotrophic lateral sclerosis (ALS) correlate with poor letter fluency (LF).

Methods: Twenty-five patients with ALS (20 with definite, probable, or possible ALS and 5 with progressive muscular atrophy) performed an LF task, involving F word generation in 1 minute, and underwent MRS. Comparisons were made between patients with ALS with impaired LF and unimpaired LF based on an empirically derived cutoff score. A Spearman correlation was performed between the patient's *N*-acetyl acetate/creatinine-phosphocreatinine ratio (NAA/Cr) and the number of F words generated.

Results: LF was impaired in 50% of patients with ALS. Patients with impaired LF had reduced NAA/Cr in the DLPFC compared with those with unimpaired LF ($p = 0.007$). There was a significant correlation between LF and NAA/Cr in the DLPFC ($r = 0.51$, $p = 0.0009$). The ALS Functional Rating Scale score, clinical region of motor onset, and disease category had no effect on LF or NAA/Cr in the DLPFC.

Conclusions: A reduced NAA/Cr in the DLPFC of patients with ALS is a marker of neuronal dysfunction and correlates with impaired performance on a clinical measure of executive function. *Neurology*® 2012;79:583-588

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALS-FRS** = ALS Functional Rating Scale; **ANOVA** = analysis of variance; **AVG** = average; **Cr** = creatine-phosphocreatinine; **DLPFC** = dorsolateral prefrontal cortex; **LF** = letter fluency; **LFi** = letter fluency index; **MRS** = magnetic resonance spectroscopy; **NAA** = *N*-acetyl aspartate; **NAA/Cr** = *N*-acetyl aspartate/creatinine-phosphocreatinine ratio; **PMA** = progressive muscular atrophy; **TE** = echo time; **TR** = repetition time.

Cognitive abnormalities have been described in amyotrophic lateral sclerosis (ALS) for more than a century.¹ Observational studies suggest that up to one-half of patients with ALS have neuropsychological abnormalities, most commonly manifesting as executive dysfunction.²⁻⁴

Functional neuroimaging of patients with ALS has related impaired performance on executive measures such as letter-guided naming fluency to abnormal activation in prefrontal and temporal regions, particularly in the dorsolateral prefrontal cortex (DLPFC).⁵⁻⁹ These imaging findings reflect detailed clinical-pathologic studies demonstrating histopathologic abnormalities in ALS that extend beyond the motor cortex to include the DLPFC.¹⁰

Magnetic resonance spectroscopy (MRS) is a neuroimaging tool that measures brain metabolites using the resonance frequencies of protons in chemical compounds. *N*-Acetyl aspartate (NAA) is thought to reflect neuronal health because of its abundance in neurons.¹¹ Therefore, wherever there is neuronal loss, there is often a corresponding decrease in NAA. NAA is often measured as a ratio to creatine-phosphocreatinine (Cr), because Cr is typically unaffected in nonacute pathologic conditions. MRS has been used to investigate motor changes in ALS.¹²⁻¹⁴ One study demonstrated that MRS changes in the frontal lobes of patients with ALS correlate with clinical performance on the Wisconsin Card Sorting Test.¹⁵ Letter fluency (LF), however,

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Table 1 Clinical and demographic features of patients with ALS with comparisons of LF-unimpaired and LF-impaired groups

	ALS			p Value
	All ALS	LF-unimpaired	LF-impaired	
No. (male/female)	25 (15/10)	13 (9/4)	12 (6/6)	0.32
Age, y, mean (SD)	58.7 (11.1)	59.6 (12.7)	57.8 (9.4)	0.68
MMSE score, mean (SD)	28.4 (2.4)	28.7 (2.0)	28.0 (2.8)	0.44
ALS-FRS score, mean (SD)	36.7 (6.7)	37.4 (6.5)	35.9 (7.1)	0.59
Education, y, mean (SD)	15.4 (3.2)	16.4 (3.7)	14.3 (2.4)	0.12
Disease duration, mo, mean (SD)	32.0 (28)	33.2 (23.9)	30.6 (33.8)	0.99
El Escorial				0.38
Definite	12	4	8	
Probable	5	3	2	
Possible	3	2	1	
PMA	5	4	1	
Region of onset				0.75
Bulbar	5	4	1	
Cervical	11	6	5	
Lumbar	9	5	4	

Abbreviations: ALS = amyotrophic lateral sclerosis; ALS-FRS = ALS Functional Rating Scale; LF = letter fluency; MMSE = Mini-Mental State Examination; PMA = progressive muscular atrophy.

is the most clear and consistent measure of executive dysfunction in ALS reported in the literature.^{2,3,7-9,16-18} In this report, we examined whether LF, a clinical measure of executive function, is correlated with frontal lobes changes seen on MRS in patients with ALS.

METHODS Subjects. Twenty-five unselected, patients without dementia were recruited from the ALS Association Center at the University of Pennsylvania between 2009 and 2011. Twenty patients had clinically definite (n = 12), probable (n = 5), or possible (n = 3) ALS, and 5 patients had progressive muscular atrophy (PMA), a variant of ALS with only lower motor neuron clinical features. Revised El Escorial Criteria¹⁹ were used by 2 experienced clinicians (L.M. and L.E.) to select patients. Exclusion criteria were age younger than 18 years, non-native English speaker, evidence of another neurologic disease, or contraindication to MRI. An analysis estimating a difference in NAA/Cr of 1 to 1.5 and a SD of 1.5 between the impaired and unimpaired LF groups indicated that we would need between 16 and 36 patients to have sufficient power for the study. Demographic and clinical characteristics of participants are summarized in table 1.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki, and the study was approved by the institutional review board at the University of Pennsylvania.

Materials. LF testing was performed as part of a cognitive screening process. LF was quantified using the number of unique F words produced in 1 minute. LF is often measured with a

series of word-generation tasks (e.g., FAS words). A single measure was used in our clinic to allow time for other clinical and research measures. A letter fluency index (LFI), a measure established to control for motor speech deficits in performance of an oral fluency task, was obtained in 18 patients (we did not have an LFI in the remaining patients because of time limitations during the clinic visit; these patients did not differ clinically or demographically from the remaining patients). The LFI was generated by first asking patients to read the words generated during the LF task. This word reading time was subtracted from the time for word generation (1 minute) and was divided by the total number of words generated²⁰. A high LFI indicates poor LF. LF and LFI measures were separated from the time of acquisition of MRS data by an average of 9 weeks.

Imaging. MRS was performed with a 3.0-T whole-body imager (Trio; Siemens, Erlangen, Germany) equipped with a 12-channel phased array head coil. Magnetic resonance pulse sequences included T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient-echo (repetition time [TR]/echo time 1,620/3.9 msec, flip angle of 15°, voxel size 0.98 × 0.98 × 1 mm³), fast fluid-attenuated inversion recovery (TR/TE/inversion time 9,190/97/2,500 msec) and fast T2-weighted (TR/TE 4,000/85 msec) sequences. Spin echo 3-dimensional echo-planar spectroscopic imaging data were acquired with chemical shift-selective water suppression pulses and lipid inversion nulling with an inversion time of 198 msec.^{21,22} Parameters included were TR/TE = 1,710/70 msec, 50 × 50 × 18 phase-encoding steps, excitation angle = 73°, voxel size = 5.6 × 5.6 × 10 mm³, field of view = 280 × 280 × 180 mm³, and number of excitations = 1. The sequence also included an interleaved water reference scan as an internal standard using a gradient-echo acquisition with excitation angle = 20° and TE = 6.3 msec.

Data were processed offline using the Metabolite Imaging and Data Analysis System.²³ Spectroscopic parametric maps of NAA and Cr were interpolated to 64 × 64 × 32 points. Areas under the curve for NAA and Cr were measured from 10 voxels, selected by experienced researchers (S.C. and S.W.) from the left and right DLPFC and control regions in the left and right occipital lobes, illustrated in figure 1. NAA/Cr was then computed. Analysts were blinded to the clinical performance of patients, although they were aware of the diagnosis of ALS.

Statistical analysis. Two independent approaches were used to examine the relationship between LF and NAA/Cr. First, based on LF performance, patients with ALS were dichotomized into 2 groups, impaired and unimpaired, using a 2 SD cut point of 11, reflecting abnormal F word performance, derived from 25 age- and education-matched healthy adults. Demographic characteristics were compared between groups according to Fisher exact or two-tailed *t* tests as appropriate. Unpaired two-tailed *t* tests were used to compare NAA/Cr in the left and right DLPFC and an average (AVG) of both left and right DLPFC as well as left, right, and AVG control occipital regions. Second, we used Spearman rank correlation to examine the relationship between LF and NAA/Cr in the DLPFC and occipital lobe of the entire ALS group. Right, left, and AVG NAA/Cr values were used. Spearman rank correlation was also used to compare the LFI and NAA/Cr in the DLPFC in the subset of 18 patients with ALS.

Further analysis was performed by grouping patients by region of disease onset (bulbar/cervical/lumbar) and disease category (PMA, possible/probable/definite ALS). Analysis of variance (ANOVA) was performed to evaluate the impact of these groupings on LF and NAA/Cr in the DLPFC. Unpaired two-tailed *t* tests were used to perform a comparison of LF and

Figure 1 MRI images demonstrating the region of interest and representative spectrogram

(A) Axial T1 image (left) used as reference for selection of region of interest in echo-planar spectroscopic imaging (EPSI) (right). Ten voxels were selected from the right and left dorso-lateral prefrontal cortex (shown here) and from the right and left occipital cortex. (B) A representative spectrograph demonstrating the separate peaks of *N*-acetyl aspartate (NAA) and creatinine-phosphocreatine (Cr).

NAA/Cr in the DLPFC of patients with PMA with those in other disease categories. Finally, Spearman rank correlation was used to examine the relationship between the ALS Functional Rating Scale (ALS-FRS) on verbal fluency and NAA/Cr in the DLPFC.

All analyses were performed using STATA 10.0 software (StataCorp, College Station, TX) with significance at $p < 0.05$.

RESULTS LF performance. Patient characteristics are summarized in table 1. No significant differences were noted in the impaired and unimpaired LF groups in terms of age, sex, Mini-Mental State Examination score, ALS-FRS, education, or disease duration.

LF testing revealed a group mean of 11.8 (SD ± 4.9). Twelve (48%) of 25 individual patients were impaired on LF testing. The average LF in the LF-impaired group was 7.6 (± 2.2) compared with 15.7 (± 3.2) in the LF-unimpaired group. The mean LFi for the entire ALS group was 4.4 (± 1.7). The average LFi was 3.6 (± 1.3) and 5.4 (± 1.5) in the impaired and unimpaired groups, respectively. LF and LFi were strongly negatively correlated ($r = -0.69$, $p = 0.0001$).

Imaging results. NAA/Cr values in the DLPFC and occipital regions are summarized in table 2. Comparisons of NAA/Cr between the LF-impaired and LF-unimpaired group revealed a lower NAA/Cr in the left DLPFC ($p = 0.01$) and AVG DLPFC ($p = 0.007$) in LF-impaired subjects. There was lower NAA/Cr in the right DLPFC that approached statistical significance ($p = 0.08$). When the 5 patients with PMA were excluded, the significant difference between impaired and unimpaired groups in NAA/Cr of AVG DLPFC ($p = 0.05$) was maintained. There was no difference between the LF-impaired and LF-unimpaired groups in the occipital control regions (AVG $p = 0.48$, left $p = 0.17$, right $p = 0.76$).

There was a correlation between LF and NAA/Cr in AVG DLPFC ($r = 0.51$, $p = 0.009$) (figure 2) and right DLPFC ($r = 0.50$, $p = 0.011$). The association of NAA/Cr with left DLPFC NAA/Cr approached significance ($r = 0.34$, $p = 0.096$). There was no correlation between LF and NAA/Cr in the occipital control regions (AVG $r = 0.11$, $p = 0.61$; left $r = -0.16$, $p = 0.45$; right $r = 0.09$, $p = 0.39$).

Using the 18 patients for whom LFi was available, we found a correlation between LFi and NAA/Cr in AVG DLPFC ($r = -0.49$, $p = 0.04$). There was an association between LFi and NAA/Cr in the right DLPFC ($r = -0.44$, $p = 0.07$) that approached statistical significance. There was no correlation between LFi and NAA/Cr in the left DLPFC ($r = 0.36$, $p = 0.14$). There was no correlation between LFi and NAA/Cr in the occipital control regions (AVG $r = -0.03$, $p = 0.90$, left $r = -0.11$, $p = 0.66$; right $r = -0.23$, $p = 0.37$).

ANOVAs revealed that region of onset (bulbar/cervical/lumbar) did not affect either LF ($p = 0.99$) or NAA/Cr in the DLPFC (right $p = 0.27$, left $p = 0.99$, AVG $p = 0.70$). Likewise, ANOVAs showed no impact of disease category on LF ($p = 0.19$) or NAA/Cr in the DLPFC (right $p = 0.83$, left $p = 0.12$, AVG $p = 0.20$). However, in separate analysis of PMA compared with the other disease categories, patients with PMA had higher NAA/Cr in the left DLPFC and AVG DLPFC ($p = 0.019$, $p = 0.03$). There was no difference in LF ($p = 0.13$) or NAA/Cr in the right DLPFC ($p = 0.96$). The ALS-FRS score was not correlated with either LF ($r = 0.017$, $p = 0.93$) or NAA/Cr in the DLPFC (AVG $r = 0.08$, $p = 0.68$; left $r = 0.08$, $p = 0.68$; right $r = 0.048$, $p = 0.82$).

DISCUSSION In this study, we showed that patients with ALS with abnormal LF test results had decreased NAA/Cr in the DLPFC. We believe these

Table 2 LF and NAA/Cr in dorsolateral prefrontal cortex (DLPFC) and occipital regions in LF-unimpaired and LF-impaired patients with ALS

	LF-unimpaired (≥11 F words)	LF-impaired (<11 F words)	p Value
DLPFC NAA/Cr, mean (SD)			
Right	1.53 (0.11)	1.44 (0.15)	0.075
Left	1.59 (0.19)	1.41 (0.13)	0.012
AVG	1.56 (0.10)	1.43 (0.13)	0.007
Occipital NAA/Cr, mean (SD)			
Right	1.51 (0.24)	1.48 (0.17)	0.76
Left	1.42 (0.24)	1.57 (0.29)	0.169
AVG	1.46 (0.24)	1.53 (0.22)	0.484

Abbreviations: ALS = amyotrophic lateral sclerosis; AVG = average; DLPFC = dorsolateral prefrontal cortex; LF = letter fluency; N-acetyl acetate/creatinine-phosphocreatinine ratio.

radiologic findings reflect executive difficulties due to neuronal dysfunction of the DLPFC in ALS.

Whereas ALS clearly affects the motor system, it is now widely acknowledged that cognitive difficulties are common in patients with ALS. This finding may reflect the observation of histopathologic abnormalities throughout the cerebrum. Quantitative assessments of the density of histopathologic disease reveal the greatest disease burden in motor regions of the frontal lobe, with dense disease extending anteriorly into prefrontal brain regions, posteriorly into the parietal lobe, and inferiorly into anterior portions of the temporal lobe.¹⁰ The current study demonstrates the measurable consequence of this disease for cognitive functioning. Thus, we associated LF difficulty in ALS with DLPFC neuronal dysfunction. Importantly, our findings selectively implicated the

DLPFC, and we did not observe changes in occipital NAA/Cr that were related to LF. This observation probably corresponds with the reduced burden of disease in the occipital lobe.

Nearly 50% of the patients with ALS recruited in this study had impaired LF, resembling data published previously.^{2,24} Nevertheless, one weakness of our study was the use of a single measure of verbal fluency. The use of multiple measures would increase the reliability of our result. LFi was obtained in most patients to minimize the potentially confounding effects of impaired motor speech that may slow performance on a timed task, and LFi performance strongly paralleled that of LF, indicating that a motor speech disorder contributed minimally to impaired LF.

Our findings implicated the DLPFC bilaterally. Even though LF involves word production, this task measures executive control that depends in part on mental planning and search. Because of the verbal modality, some clinical and functional imaging studies have emphasized the fact that the left DLPFC is particularly involved in LF.^{25,26} However, right hemisphere DLPFC involvement is seen as often.^{9,27,28} In ALS and frontotemporal lobe degeneration, prior studies associated impaired LF with bilateral prefrontal abnormalities.^{8,29} A PET activation study found reduced bilateral DLPFC activation in ALS compared with that in control subjects during performance of an LF task,⁷ for example, and our study demonstrates a similar finding with another measure that directly implicates neuronal dysfunction. Given that this measure may be distributed variably across

Figure 2 Correlation of letter fluency with an average of the left and right N-acetyl aspartate/creatinine-phosphocreatinine ratio (NA/Cr) ratio in the dorsolateral prefrontal cortex (PF) and occipital cortex

(A) The average (AVG) of right and left NA/Cr in the dorsolateral prefrontal cortex correlated with letter fluency, i.e., the number of F words generated in 1 minute (* = statistical significance). (B) The average of right and left NA/Cr in the occipital cortex did not correlate with letter fluency.

both hemispheres, it may be that averaging the left and right DLPFC reduced the variance in our relatively small sample population and increased the power of our study.

Prior studies revealed conflicting data regarding the potential role of the clinical region of motor onset and the presence of cognitive dysfunction. Some work found greater cognitive difficulties in patients with bulbar disease ALS,^{30,31} whereas other studies did not find this association.^{3,32–34} In our study, the clinical region of disease onset did not appear to affect LF.

There was no difference in LF between patient groups according to disease category, either in a comparison of all categories or when patients with PMA were isolated. When looking across all disease categories, we also found no difference in NAA/Cr in the DLPFC. However, when patients with PMA were compared with patients in all other disease categories, patients with PMA appeared to have greater NAA/Cr in the DLPFC. Given our very small sample size, it is not clear whether this finding is truly representative of neuronal sparing in the frontal lobes of patients with PMA. Although some studies examining cognition in patients with PMA have found no cognitive abnormalities,³⁵ more recent work has reported deficits in these patients as well,³⁶ and autopsy examination of the brains of patients with PMA reveal histopathologic evidence for the same abnormalities as seen in patients with ALS.¹⁰ Why a difference was seen between patients with PMA and other patients with ALS only with MRS but not with LF is not entirely clear. It may be indicative of the sensitivity/specificity of each measure or could suggest that a certain level of neuronal loss may be required before clinically significant changes become apparent. Our findings must be also interpreted very cautiously because of our small sample size, which limits our power to find differences between subgroups in our population.

Our study showed that MRS abnormalities in prefrontal regions of patients with ALS correlate with poor LF, a clinical measure of executive function. Prior studies have demonstrated that MRS can detect changes in the precentral gyrus of patients with ALS,^{12–14} indicating that MRS is a potentially useful biomarker for upper motor neuron changes, which can be clinically subtle. Our study suggests a role for extending the use of MRS imaging to look for neuronal loss in the frontal lobes of patients with ALS. The variance in the individual NAA/Cr ratios, however, indicates that further studies of larger samples with additional cognitive measures may be useful in developing markers of disease in individual patients with ALS. Future investigators could also examine the po-

tential interaction between MRS and local volume changes, perhaps using a technique such as voxel-based morphometry, inasmuch as regional atrophy may in fact explain the MRS changes detected in this study. Ideally, future studies would also be designed to detect whether MRS changes could predict clinical changes, because this would be most helpful for early diagnosis and early intervention and detecting response to intervention.

AUTHOR CONTRIBUTIONS

C. Quinn: Conceptualization and design of the study, statistical analysis, and drafting the manuscript. L. Elman: Design of study and revising the manuscript for intellectual content. L. McCluskey: design of study and revising the manuscript for intellectual content. K. Hoskins: analysis of data. C. Karam: revising the manuscript for intellectual content. J.H. Woo: design of the study and revising the manuscript for intellectual content. H. Poptani: conceptualization of the study. S. Wang: analysis of data and revising the manuscript for intellectual content. S. Chawla: analysis of data and revising the manuscript for intellectual content. S. Kasner: analysis and interpretation of the data and statistical analysis. M. Grossman: conceptualization of the study and revising the manuscript for intellectual content.

DISCLOSURE

C. Quinn, L. Elman, L. McCluskey, and K. Hoskins report no disclosures. C. Karam serves on the editorial board of the *Neurology*[®] Resident & Fellow Section. J.H. Woo, H. Poptani, S. Wang, S. Chawla, and S. Kasner report no disclosures., M. Grossman serves on the editorial board of *Neurology*[®]. **Go to Neurology.org for full disclosures.**

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REFERENCES

1. Marie P. Leçons sur les maladies de la moelle. Masson G, ed. Paris: Librairie de L'Académie de Médecine de Paris; 1892:470.
2. Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003;60:1094–1097.
3. Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1996;61:450–455.
4. Hu WT, Seelaar H, Josephs KA, et al. Survival profiles of patients with frontotemporal dementia and motor neuron disease. *Arch Neurol* 2009;66:1359–1364.
5. Kew JJ, Goldstein LH, Leigh PN, et al. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis: a neuropsychological and positron emission tomography study. *Brain* 1993;116:1399–1423.
6. Kew JJ, Leigh PN, Playford ED, et al. Cortical function in amyotrophic lateral sclerosis: a positron emission tomography study. *Brain* 1993;116:655–680.
7. Abrahams S, Leigh PN, Kew JJ, Goldstein LH, Lloyd CM, Brooks DJ. A positron emission tomography study of frontal lobe function (verbal fluency) in amyotrophic lateral sclerosis. *J Neurol Sci* 1995;129(suppl):44–46.
8. Abrahams S, Goldstein LH, Simmons A, et al. Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. *Brain* 2004;127:1507–1517.

9. Abrahams S, Goldstein LH, Kew JJ, et al. Frontal lobe dysfunction in amyotrophic lateral sclerosis: a PET study. *Brain* 1996;119:2105–2120.
10. Geser F, Martinez-Lage M, Robinson J, et al. Clinical and pathological continuum of multisystem TDP-43 proteinopathies. *Arch Neurol* 2009;66:180–189.
11. Block W, Traber F, Flacke S, Jessen F, Pohl C, Schild H. In-vivo proton MR-spectroscopy of the human brain: assessment of N-acetylaspartate (NAA) reduction as a marker for neurodegeneration. *Amino Acids* 2002;23:317–323.
12. Kaufmann P, Pullman SL, Shungu DC, et al. Objective tests for upper motor neuron involvement in amyotrophic lateral sclerosis (ALS). *Neurology* 2004;62:1753–1757.
13. Unrath A, Ludolph AC, Kassubek J. Brain metabolites in definite amyotrophic lateral sclerosis: a longitudinal proton magnetic resonance spectroscopy study. *J Neurol* 2007;254:1099–1106.
14. Wang S, Poptani H, Woo JH, et al. Amyotrophic lateral sclerosis: diffusion-tensor and chemical shift MR imaging at 3.0 T. *Radiology* 2006;239:831–838.
15. Abe K, Takanashi M, Watanabe Y, et al. Decrease in N-acetylaspartate/creatine ratio in the motor area and the frontal lobe in amyotrophic lateral sclerosis. *Neuroradiology* 2001;43:537–541.
16. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia* 2000;38:734–747.
17. Gallassi R, Montagna P, Ciardulli C, Lorusso S, Mussuto V, Stracciari A. Cognitive impairment in motor neuron disease. *Acta Neurol Scand* 1985;71:480–484.
18. Abe K, Fujimura H, Toyooka K, Sakoda S, Yorifuji S, Yanagihara T. Cognitive function in amyotrophic lateral sclerosis. *J Neurol Sci* 1997;148:95–100.
19. Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000;1:293–299.
20. Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS: a prospective study. *Neurology* 2005;64:1222–1226.
21. Ebel A, Soher BJ, Maudsley AA. Assessment of 3D proton MR echo-planar spectroscopic imaging using automated spectral analysis. *Magn Reson Med* 2001;46:1072–1078.
22. Maudsley AA, Domenig C, Govind V, et al. Mapping of brain metabolite distributions by volumetric proton MR spectroscopic imaging (MRSI). *Magn Reson Med* 2009;61:548–559.
23. Maudsley AA, Darkazanli A, Alger JR, et al. Comprehensive processing, display and analysis for in vivo MR spectroscopic imaging. *NMR Biomed* 2006;19:492–503.
24. Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1996;61:450–455.
25. Milner B. Some effects of frontal lobectomy in man. In: Warren JM, Akert K, eds. *The Frontal Granular Cortex and Behavior*. New York: McGraw-Hill; 1964;313–331.
26. Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu Rev Psychol* 2002;53:401–433.
27. Abrahams S, Goldstein LH, Simmons A, et al. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Hum Brain Mapp* 2003;20:29–40.
28. Sanjuan A, Bustamante JC, Forn C, et al. Comparison of two fMRI tasks for the evaluation of the expressive language function. *Neuroradiology* 2010;52:407–415.
29. Libon DJ, McMillan C, Gunawardena D, et al. Neurocognitive contributions to verbal fluency deficits in frontotemporal lobar degeneration. *Neurology* 2009;73:535–542.
30. Strong MJ, Grace GM, Freedman M, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009;10:131–146.
31. Talbot PR, Goulding PJ, Lloyd JJ, Snowden JS, Neary D, Testa HJ. Inter-relation between “classic” motor neuron disease and frontotemporal dementia: neuropsychological and single photon emission computed tomography study. *J Neurol Neurosurg Psychiatry* 1995;58:541–547.
32. Rippon GA, Scarneas N, Gordon PH, et al. An observational study of cognitive impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2006;63:345–352.
33. Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an underrecognised association? *J Neurol Neurosurg Psychiatry* 1998;65:881–889.
34. Gordon PH, Wang Y, Doorish C, et al. A screening assessment of cognitive impairment in patients with ALS. *Amyotroph Lateral Scler* 2007;8:362–365.
35. Wicks P, Abrahams S, Leigh PN, Williams T, Goldstein LH. Absence of cognitive, behavioral, or emotional dysfunction in progressive muscular atrophy. *Neurology* 2006;67:1718–1719.
36. Raaphorst J, de Visser M, van Tol MJ, et al. Cognitive dysfunction in lower motor neuron disease: executive and memory deficits in progressive muscular atrophy. *J Neurol Neurosurg Psychiatry* 2011;82:170–175.