J Neurol (2005) 252 : 772–781
DOI 10.1007/s00415-005-0739-6

ORIGINAL COMMUNICATION

**Herbert Schreiber**
**Tanja Gaigalat**
**Ursula Wiedemuth-Catrinescu**
**Michael Graf**
**Ingo Uttner**
**Rainer Muche**
**Albert Christian Ludolph**

# Cognitive function in bulbar- and spinal-onset amyotrophic lateral sclerosis

## A longitudinal study in 52 patients

**Abstract** We performed a longitudinal study of frontal and temporal lobe functions in patients with amyotrophic lateral sclerosis (ALS) and compared the evolution of cognitive performance with that of motor deficits in patients with spinal and bulbar-onset of the disease. Fifty two patients suffering from sporadic ALS according to the El Escorial criteria were examined; 37 patients had a spinal, 15 a bulbar onset of the disease. The data profile included examinations at entry (E1), every four months at follow-up (E2, E3, E4) and after 18 months (E5), if possible. Neuropsychological testing covered the domains of executive functions, memory and attentional control. ALS patients showed executive dysfunctions that were most prominently represented by deficits of non-verbal and verbal fluency and concept formation. Memory-related deficits were also present but less expressed. The same held true for phasic and tonic alertness and divided attention. In contrast to motor functions declining concomitantly with disease progression, cognitive deficits appeared in early disease, were essentially present at initial testing and did not substantially decline on follow-up. A subgroup analysis revealed that bulbar-onset ALS patients performed consistently poorer in many cognitive tests than spinal-onset ones with special reference to verbal and non-verbal fluency and interference control. This subgroup difference persisted or even increased throughout follow-up. We conclude that there is a fronto-temporal pattern of cognitive dysfunction in ALS expressing itself early in the course of the disease and mainly with bulbar forms. The cognitive deficits do not progress in synchrony with motor decline, but distinctly more slowly. We suggest that cognitive dysfunctions reflect functional and possibly morphological deficits outside the primary motor system that is specific for the nature and evolution of the disease and might also give clues to etiopathogenesis.

**Key words** amyotrophic lateral sclerosis · motor neuron disease · neuropsychology · cognition · executive function · memory · frontal lobe · temporal lobe

Received: 28 January 2004
Received in revised form: 3 September 2004
Accepted: 8 September 2004
Published online: 8 March 2005

H. Schreiber, MD · T. Gaigalat, MD · U. Wiedemuth-Catrinescu, PhD · I. Uttner, PhD · Prof. Dr. A. C. Ludolph
Department of Neurology
University of Ulm – RKU
Oberer Eselsberg 45
89081 Ulm, Germany
Tel.: +49-731/177-1200
Fax: +49-731/177-1202
E-Mail: albert.ludolph@rku.de

M. Graf, MD
CHU Pitié-Salpêtrière
Department of Clinical Pharmacology
47–83, Boulevard de l'Hôpital
75013 Paris, France

R. Muche, PhD
Department of Biometry
and Medical Documentation
University of Ulm
Schwabstraße 13
89075 Ulm, Germany

## Introduction

Amyotrophic lateral sclerosis (ALS) is caused by the progressive degeneration of bulbar and spinal motoneurons and of the corticospinal tracts resulting in motor deficits, bulbar palsy and finally respiratory insufficiency. Although selective vulnerability of motor neurons is the pathogenic hallmark of the disease, it becomes increasingly evident that extramotor neuronal degeneration may occur and contribute to the clinical syndrome.

Evidence for extramotor neuronal degeneration comes from several perspectives. (1) Clinical observa-

JON 1739

tions indicate that ALS may be accompanied by a fronto-temporal dementia [23, 35] and that mental dysfunction may be coincident with motor decline or even precede it [49]. (2) Neuropathological evidence suggests that in demented and non-demented ALS patients degeneration may occur outside the motor cortex – mainly in cortical and subcortical regions of the prefrontal lobes and in the temporal and limbic areas [26, 39, 51, 52]. (3) MRI studies have shown that a subgroup of ALS patients exhibits frontal atrophy, shrinkage of the frontal white matter and widespread subcortical frontotemporal gliosis [6, 25, 29]. (4) Functional imaging has provided evidence of hypometabolism in demented and non-demented ALS patients that is predominantly expressed in frontal areas and along the limbic-thalamo-cortical pathways [2, 3, 28, 32]. Also neuropsychological findings support the concept of extramotor pathology in ALS. A series of cross-sectional studies have shown cognitive impairment in non-demented ALS patients and delineated deficits that are compatible with frontal-executive and temporal lobe dysfunctions. Among executive functions, fluency seems to be predominantly affected [1, 4, 5, 16, 32], but this is also true for interference control [15, 33], response inhibition [33], set shifting [15], concept formation and problem solving [16]. Likewise, verbal and non-verbal memory deficits were found in non-demented ALS patients [16, 37]. Since cross-sectional studies predominate to date, little is known about the onset and the evolution of cognitive functions in individual ALS patients.

In this paper, we present a longitudinal investigation of cognitive functions in 52 patients suffering from sporadic ALS. The aim of the study was three-fold: (1) to assess a fronto-temporal profile of cognitive functions in ALS patients, (2) to evaluate this in bulbar and spinal-onset subgroups, (3) to monitor the beginning and evolution of cognitive functions during disease progression in relation to motor decline.

## Methods

### Study design

We performed a prospective follow-up investigation. The data profile included examinations at entry (E1), every 4 months during follow-up (E2, after 4 months; E3, after 8 months; E4, after 12 months) and, if possible, a further examination after 18 months (E5).

### Subjects

In total, 52 patients (37 males, 15 females) with a mean age (± SD) of 56.8 (± 12.3) years entered the study. All of them were suffering from sporadic ALS according to the El Escorial criteria [10]. 15 patients (9 males, 6 females) showed a bulbar-onset, 37 patients (28 males, 9 females) a spinal-onset of the disease. To check premorbid intelligence, a multiple-choice vocabulary test (MWT-B) was assessed at study entry [31]. To screen for emotional well-being and influences of depression on neuropsychological testing, Beck's depression inventory (BDI [8]) was assessed in an adapted version [20] at study entry and regularly during follow-up. Behavioral and clinical data at study entry (E1) are summarized for the complete patient sample and of the spinal-onset and bulbar-onset subgroups in Table 1. All groups were very comparable with respect to age and premorbid intelligence.

### Clinical assessment

The severity and progression of ALS were assessed by the Norris Scale [21] and vital capacity (VC) measurements at study entry (E1) and regularly during follow-up (E2–E5). As summarized in Table 1 for study entry (E1), the complete patient sample and the bulbar- and spinal-onset subgroups were well comparable concerning disease duration, clinical severity (Norris), vital capacity (VC) and mood (BDI). Statistical analysis did not show any significant differences.

### Neuropsychological assessment

Neuropsychological assessment focused on cognitive domains considered to represent prefrontal (executive) functions and temporal lobe (memory) functions as well as attentional control. The test profile included the following individual tests.

#### Executive functions

Perceptual interference was assessed by the Colour Word Interference Test (CWIT [46]) in a version adapted by Bäumler [7]. As in the original version, this applies verbal (color words) and non-verbal material (color dots) including a mismatch condition (word-color) to test for interference processing. Assessment parameters were: reading time (of color words, in seconds), naming time (of color dots, in sec-

**Table 1** Demographic, behavioral and clinical data at study entry (E1)

| male/female ratio (patients) | complete patient sample (N = 52) 37/15 | spinal-onset (N = 37) 28/9 | bulbar-onset (N = 15) 9/6 |
|---|---|---|---|
| age, in years (mean, ± SD) | 57.92 ± 11.51 | 56.72 ± 11.43 | 60.80 ± 11.56 |
| MWT-B (IQ) (mean, ± SD) | 109.15 ± 16.51 | 110.00 ± 16.94 | 108.89 ± 16.03 |
| ALS, duration in months (mean, ± SD) | 27.17 ± 17.68 | 28.46 ± 18.69 | 24.00 ± 15.00 |
| Clinical stage (Norris, %) (mean, ± SD) | 66.84 ± 18.45 | 64.29 ± 19.84 | 74.73 ± 10.43 |
| Vital capacity in % (mean, ± SD) | 78.40 ± 20.99 | 81.53 ± 21.83 | 71.75 ± 18.61 |
| Beck Depression Inventory (mean, ± SD) | 11.81 ± 7.84 | 11.57 ± 7.63 | 12.40 ± 8.60 |

onds), interference time (in seconds) and error rate. Verbal fluency was assessed by a modified Controlled Word Association Test (COWAT) derived from Thurstone's written version [48]. Naming and/or writing of words beginning with the letter "S" measuring formal-lexical fluency was required. Assessment parameters were: the number of words (generated within a defined time-period of 3 minutes), error score and ratio errors/number of words generated. Response time included a span of 3 minutes in order to reduce bias by mechanical slowing of speech or writing. The test modality (oral or written) was chosen with respect to the clinical deficits of the patients. The equivalence of written and spoken modalities of the COWAT concerning formal-lexical fluency had been ascertained prior to study initiation by reviewing normative data [9, 22, 47]. Figural (design) fluency was assessed by the non-verbal 5-Point Fluency Test (5-PFT [42]). This requires the generation of as many unique geometrical designs as possible by interconnecting five dots within a time period of 3 min. Assessment parameters were: number of designs generated, error rate (repetitions, incomplete designs), and ratio errors/number of designs. Concept formation, abstract reasoning and the ability to shift cognitive strategies were assessed by the Wisconsin Card Sorting Test (WCST [19]). A PC-version with 64 cards close to the design of Milner [34] was used. Assessment parameters were: categories achieved, error score, perseverative error score.

#### Memory functions

The span of apprehension of verbal material was tested by the Digit Span (DS, forward), a subtest of the Wechsler Adult Intelligence Scale (WAIS [50]). Non-verbal recognition memory was assessed by the Recurring Figures Test (RFT [30]). The assessment parameter was error score. The Auditory Verbal Learning Test (AVLT [43]) was used to assess immediate and delayed free recall, learning achievement and delayed recognition memory of verbal material (words). Assessment parameters were: number of words recalled after the first (words at I) and the 5$^{th}$ presentation (words at V), difference in performance between words at I and V (learning achievement), loss of items due to an interference list after V (loss by interference), delayed free recall (recall after 30 min), and recognition of previously presented words interspersed in a list of fifty items given at the end of the testing session (delayed recognition).

#### Attention control

Vigilance was assessed by the subtest "Alertness" of the TAP test battery [53]. Reaction times (RTs) were measured to test for the patients' ability to improve RT performance after presentation of a warning tone (phasic alertness) relative to RTs without a warning tone (tonic alertness). Assessment parameters were RTs (in seconds) after imperative stimuli with and without warning tones. Divided attention as an index of parallel processing capacity was assessed in a dual-task paradigm taken from the TAP [53]. The task required the patients' reaction to sequences of simultaneously presented visual and auditory cues. Assessment parameters were: reaction times (RTs) and number of omissions (no reaction).

### Data analysis

Data are given as mean and standard deviation (mean, SD) for the continuous variables, respectively as relative and absolute frequencies for discrete variables. The longitudinal analysis of test results represents comparisons across follow-up examinations E1-E4. It was done for the complete patient sample and separately for the bulbar- and spinal-onset patients by using the non-parametric exact Friedman-test, a non-parametric two-way ANOVA with repeated measurements [14, 44]. Because of disease-related drop-out over time, the longitudinal analysis included only those individuals in whom data on all four time points of assessment were available. This subgroup was compared with the complete sample for checking representativity and avoiding bias. No bias was found. Findings of the exact Friedman test in the bulbar-onset subgroup were not considered representative owing to the small number of subjects entering analysis and are therefore not presented. Inter-group differences of bulbar- vs. spinal-onset patients were evaluated using the non-parametric Mann-Whitney U-test. Where appropriate, Pearson product moment and Spearman rank order correlation coefficients were calculated. The significance level was set to 5%. Because of the exploratory manner of the analysis, no adjustment for multiple testing was done. Findings at E5 were not evaluated statistically due to the small number of subjects available. All analyses were done using SPSS (Version 10) except for the Friedman-test (StatXact 3.0)

## Results

### Comparison of test results to normative data

To integrate our patients' test performance into the normal spectrum of cognitive behavior we compared their test results with normative data. The lower limit of normality was defined for each parameter as respective mean minus one standard deviation (SD). The most important deficits were evident in executive functions as represented by word and design fluency and some aspects of concept formation (total and perseverative error scores in WCST). In these domains, all patients groups, and most prominently the bulbar ones, performed below the normal range. Concerning interference control (CWIT), it was only the bulbar-onset subgroup that performed at the limit or below normality. Deficits in memory functions were less expressed. Nevertheless, impaired memory performance was shown in three subtests of the AVLT in all groups. The same was true for phasic and tonic alertness (reaction times with and without warning tones) and reaction times under divided attention.

### Longitudinal analysis of test results

Means of longitudinal test profiles at examinations E1, E2, E3 and E4 are summarized for the complete patient sample in Table 2a. The number of patients consecutively dropped from 52 (E1) to 19 (E4). Drop-out was disease-related and caused by death or major physical handicap. Results of the longitudinal statistical analysis (exact Friedman test) are shown for the complete sample in Table 2b.

#### Clinical and behavioral parameters

In the complete patient sample, Norris and VC scores decreased significantly between E1 and E4 ($p < 0.01$ and $p < 0.002$, respectively) indicating disease progression (Table 2b). The same was true for VC scores in the spinal-onset subgroup ($p < 0.02$). Norris scores also declined in the spinal subgroup, but without statistical sig-

**Table 2** **a:** Means of longitudinal test profiles at study entry and follow-up examinations in the complete patient sample. **b:** Longitudinal statistical analysis (Friedman exact)

| | **2a:** means at baseline and at follow-up | | | | | | | | **2b:** Friedman-test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E1 (n = 52) | | E2 (n = 32) | | E3 (n = 24) | | E4 (n = 19) | | Number (n) | E1-E4 (p) |
| Test | mean | SD | mean | SD | mean | SD | mean | SD | | |
| *Clinical parameters and behavioral data* | | | | | | | | | | |
| VC | **94.5** | 9.2 | **87.5** | 3.5 | **79.5** | 9.2 | **80.0** | 2.8 | 10 | **0.01** |
| Norris | **74.9** | 11.6 | **72.1** | 6.0 | **64.0** | 9.7 | **61.6** | 9.8 | 10 | **0.002** |
| BDI | **10.8** | 7.0 | **9.0** | 7.1 | **11.2** | 7.1 | **10.3** | 6.9 | 12 | n. s. |
| *Executive functions* | | | | | | | | | | |
| CWIT1 | **33.0** | 8.6 | **33.6** | 8.0 | **37.1** | 8.2 | **35.8** | 6.8 | 9 | n. s. |
| CWIT2 | **43.9** | 6.7 | **44.1** | 6.6 | **48.1** | 6.5 | **47.5** | 9.1 | 9 | **0.004** |
| CWIT3 | **87.1** | 16.7 | **84.7** | 13.3 | **80.5** | 14.6 | **82.2** | 14.3 | 9 | n. s. |
| CWIT4 | **3.0** | 2.6 | **4.1** | 5.4 | **1.9** | 2.3 | **2.5** | 3.3 | 9 | n. s. |
| COWAT 1 | **21.2** | 9.7 | **24.1** | 9.8 | **26.7** | 12.6 | **29.4** | 12.2 | 13 | n. s. |
| COWAT2 | **2.7** | 3.1 | **1.5** | 1.6 | **2.2** | 2.3 | **2.8** | 2.9 | 13 | n. s. |
| COWAT3 | **0.13** | 0.15 | **0.06** | 0.06 | **0.08** | 0.06 | **0.09** | 0.08 | 13 | **0.009** |
| 5-PFT1 | **24.6** | 8.4 | **24.9** | 7.2 | **25.9** | 12.3 | **26.6** | 11.1 | 8 | n. s. |
| 5-PFT2 | **3.0** | 3.1 | **2.1** | 2.0 | **1.9** | 2.6 | **2.5** | 3.6 | 8 | **0.01** |
| 5-PFT3 | **0.11** | 0.09 | **0.09** | 0.11 | **0.07** | 0.09 | **0.08** | 0.11 | 8 | **0.03** |
| WCST1 | **2.0** | 1.5 | **2.0** | 1.1 | **2.7** | 1.0 | **2.7** | 1.4 | 6 | n. s. |
| WCST2 | **22.3** | 9.2 | **23.7** | 7.0 | **16.8** | 9.11 | **19.5** | 9.1 | 6 | n. s. |
| WCST3 | **21.0** | 12.8 | **17.0** | 1.6 | **15.4** | 13.4 | **9.6** | 9.1 | 6 | n. s. |
| *Memory functions* | | | | | | | | | | |
| DS | **5.5** | 0.7 | **5.6** | 1.0 | **5.8** | 1.0 | **5.8** | 1.1 | 13 | **0.009** |
| RFT | **27.0** | 8.2 | **25.1** | 9.9 | **27.7** | 14.0 | **25.9** | 8.7 | 12 | n. s. |
| AVLT1 | **5.1** | 0.9 | **5.4** | 1.8 | **7.0** | 2.4 | **5.8** | 1.3 | 13 | n. s. |
| AVLT2 | **11.9** | 1.6 | **10.9** | 1.9 | **12.5** | 2.4 | **11.3** | 1.9 | 13 | n. s. |
| AVLT3 | **7.0** | 2.0 | **5.5** | 2.5 | **5.5** | 2.3 | **5.5** | 1.5 | 13 | **0.05** |
| AVLT4 | **3.4** | 2.4 | **2.3** | 1.7 | **2.8** | 1.9 | **3.1** | 1.4 | 13 | **0.03** |
| AVLT5 | **8.7** | 2.4 | **7.8** | 2.0 | **10.0** | 2.5 | **8.3** | 2.8 | 13 | n. s. |
| AVLT6 | **45.9** | 1.9 | **45.0** | 3.8 | **46.8** | 4.3 | **45.0** | 4.3 | 13 | n. s. |
| *Attentional control* | | | | | | | | | | |
| Alert.1 | **283** | 100 | **334** | 119 | **351** | 121 | **395** | 156 | 6 | n. s. |
| Alert.2 | **294** | 115 | **311** | 110 | **325** | 114 | **385** | 153 | 6 | **0.03** |
| DivAtt1 | **705** | 145 | **735** | 108 | **717** | 113 | **708** | 125 | 5 | n. s. |
| DivAtt2 | **2.0** | 2.6 | **2.7** | 2.9 | **3.0** | 1.7 | **1.0** | 0 | 5 | n. s. |

Exact Friedman test; level of significance $p < 0.05$. *VC* Vital capacity; *BDI* Beck Depression Inventory; *CWIT* Colour Word Interference Test: 1 reading-time (sec), 2 naming-time (sec), 3 interference-time (sec), 4 error score; *COWAT* Controlled Word Association Test: 1 number of words, 2 number of errors, 3 ratio number/errors; 5-PFT, 5-Point Fluency Test: 1 number of designs (figures), 2 number of errors, 3 ratio number/errors; *WCST* Wisconsin Card Sorting Test: 1 number of categories, 2 number of errors, 3 number of perseverating errors; *DS* Digit span: number; *RFT* Recurring Figures Test of Kimura: number of errors; *AVLT* Auditory Verbal Learning Test: 1 words at I. presentation, 2 words at V. presentation, 3 learning achievement, 4 loss by interference, 5 recall after 30 min, 6 recognition; *Alertness1* reaction time without warning tone (in ms), *Alertness2* reaction time with warning tone (in ms); *Divided Attention, 1* reaction time (ms), *2* missing outs

nificance. In the bulbar-onset subgroup, longitudinal test profiles (means) confirmed that both Norris and VC scores declined distinctly between E1 and E4. For the reasons indicated in Methods, effects in the bulbar subgroup were not evaluated statistically. Emotional well-being (mood) as indicated by the BDI score remained remarkably stable during the whole observation period in the complete patient sample and in both subgroups. No statistically significant effect was detected.

## Executive functions

In the complete patient sample, interference processing as represented by CWIT2 (naming time) was significantly prolonged ($p < 0.004$) between E 1 and E4. The same was true for CWIT1 (reading time), but without reaching statistical significance. All parameters assessing word fluency (COWAT), design fluency (5-PFT) and concept formation (WCST), and two parameters of the CWIT (interference time, error score) did not significantly change during the observation period (Table 2b).

Means showed that their values did not decline along with disease progression, but remained stable or even improved (Table 2a). COWAT3 (ratio of errors/number of generated words; $p < 0.009$), 5-PFT2 (error score; $p < 0.01$) and 5-PFT3 (ratio of errors/generated designs; $p < 0.03$) even improved significantly. For details of Friedman test results refer to Table 2b. In the spinal-onset patient group, similar test results were obtained. Only parameter CWIT2 deteriorated significantly ($p < 0.006$). The other executive test parameters remained stable or improved during follow-up. Significant improvements were obtained with COWAT3 ($p < 0.05$), 5-PFT2 (p 0.05) and 5-PFT3 ($p < 0.05$). Longitudinal effects in the bulbar subgroup were not evaluated statistically. Mean values, however, indicated that executive functions in bulbar patients did not improve but deteriorate or at best keep their level.

### Memory functions

In the complete patients sample, one AVLT subtest (AVLT3, learning achievement) showed a statistically significant ($p < 0.05$) decline during follow-up. The other memory-related parameters remained roughly stable. This was true for the digit span (DS), non-verbal recognition memory (RFT) and most parameters of the AVLT (words recalled at I, words recalled at V, delayed recall, recognition). Parameter AVLT4 (loss by interference) was the only one to improve significantly ($p < 0.03$). For details of statistical analysis and means in the complete patient sample refer to Table 2. In the spinal-onset subgroup, very similar test results were obtained. All memory-related parameters remained stable or slightly improved during follow-up, and no statistical significance was noted. Only AVLT4 (loss of interference) significantly improved over time. In the bulbar-onset subgroup, however, mean values of memory functions clearly decreased over time. Longitudinal effects were again not evaluated statistically.

### Attention control

In the complete patient sample, tonic and phasic alertness as expressed by reaction times without (Alertness 1) and with warning tone (Alertness 2) deteriorated over time (E1: 283ms and 294ms, E4: 395ms and 385ms, respectively). However, significance for this effect was only achieved with Alertness 2 ($p < 0.03$). No significant difference was obtained also for divided attention (Table 2b). Also in the spinal-onset subgroup, attention parameters deteriorated but without yielding a statistically significant effect. Visual inspection of means in the limited number of bulbar-onset patients showed that their values were markedly prolonged both for tonic and phasic alertness at E4 compared with E1. On the other hand, their performance in divided attention remained stable.

## Subgroup analysis of test results in bulbar-onset vs. spinal-onset patients

Statistical findings evaluating differences between bulbar- and spinal-onset patients are illustrated for each assessment point E1 to E4 in Table 3.

### Clinical and behavioral parameters

Norris score was comparable between bulbar- and spinal-onset patients throughout the study, and no significant inter-group differences were detected between E1 and E4 (Table 3). Concerning VC, bulbar-onset patients had consistently lower values than the spinal-onset ones throughout the observation period. A significant difference between subgroups emerged at E3 when bulbar patients scored a significantly lower VC than the spinal ones (Table 3). Mood (BDI) did not show any significant inter-group differences during follow-up.

### Executive functions

Word and design fluency performance in subgroups is shown in Figs. 1 and 2. Word generation (COWAT, number) proved to be significantly reduced in the bulbar compared with the spinal-onset patients already at study entry (E1: $p < 0.01$; Fig. 1 and Table 3). Fig. 1 shows that this inter-group difference increased during follow-up leaving the bulbar group behind with significantly poorer performance (E1: $p < 0.01$, E2: $p < 0.005$; E3: $p < 0.01$, E4: $p < 0.06$, trend). A summary of statistical data is given in Table 3. Design fluency performance in subgroups is shown in Fig. 2. Again, bulbar-onset patients achieved worse at study entry (E1: $p < 0.08$, Table 3), and the subgroup difference increased during follow-up leaving the bulbar patients significantly behind (E2: $p < 0.01$; E3: $p < 0.03$; E4: $p < 0.08$, trend).

Concerning CWIT3 (interference time), a significant inter-group difference was provided in terms of a slower performance of bulbar-onset patients at E1 ($p < 0.01$), E2 ($p < 0.05$) and E4 ($p < 0.05$). CWIT4 (error score) and the parameters assessing concept formation and abstract reasoning did not statistically discriminate between subgroups.

### Memory functions

Immediate recall as assessed by the Digit Span was highly comparable between bulbar and spinal patients and provided no statistically significant subgroup difference. A subgroup difference, however, was evident in non-verbal recognition memory (RFT). At study entry (E1), the RFT error score was significantly higher in bulbar-onset compared to spinal-onset patients ($p < 0.03$). During follow-up, statistical analysis confirmed a significant group effect at E2 ($p < 0.04$) and a trend at E4

**Table 3** Subgroup analysis of bulbar-onset versus spinal-onset patients at follow-up examinations (E1 – E4)

| | E 1 | | E2 | | E3 | | E4 | |
|---|---|---|---|---|---|---|---|---|
| | N sp/b | p | N sp/b | p | N sp/b | p | N sp/b | p |
| Clinical parameters and behavioral data | | | | | | | | |
| Norris | 34/11 | n. s. | 20/9 | n. s. | 16/6 | n. s. | 12/7 | n. s. |
| Vital capacity in % | 17/8 | n. s. | 15/5 | n. s. | 4/3 | 0.03 | 3/3 | n. s. |
| Beck's Depression-Inventory (BDI) | 37/15 | n. s. | 23/8 | n. s. | 16/8 | n. s. | 12/6 | n. s. |
| Executive functions | | | | | | | | |
| CWIT1 – reading time in sec. | 33/7 | 0.00 | 20/3 | 0.01 | 15/3 | n. s. | 11/4 | 0.06 |
| CWIT2 – naming time in sec. | 33/7 | 0.04 | 20/3 | 0.03 | 15/3 | n. s. | 11/4 | n. s. |
| CWIT3 – interference time in sec. | 33/7 | 0.01 | 20/3 | 0.05 | 15/3 | n. s. | 11/4 | 0.05 |
| CWIT4 – error score | 33/7 | n. s. | 22/9 | n. s. | 15/3 | n. s. | 11/4 | n. s. |
| COWAT1 – number of words | 36/15 | 0.01 | 22/9 | 0.00 | 16/7 | 0.01 | 12/7 | 0.06 |
| COWAT2 – error score | 36/15 | 0.00 | 22/9 | 0.04 | 16/7 | 0.00 | 12/7 | n. s. |
| COWAT3 – number/errors | 36/15 | 0.04 | 22/9 | n. s. | 16/7 | n. s. | 12/7 | n. s. |
| 5-PFT1 – number of designs | 28/13 | 0.08 | 15/7 | 0.01 | 11/6 | 0.03 | 8/6 | 0.08 |
| 5-PFT2 – error score | 28/13 | n. s. | 15/7 | n. s. | 11/6 | n. s. | 8/6 | n. s. |
| 5-PFT3 – number/errors | 28/13 | n. s. | 15/7 | n. s. | 11/6 | n. s. | 8/6 | n. s. |
| WCST1 – number of categories | 30/11 | 0.05 | 14/6 | n. s. | 10/7 | n. s. | 9/4 | n. s. |
| WCST2 – errors | 30/11 | 0.09 | 14/6 | n. s. | 10/7 | n. s. | 9/4 | n. s. |
| WCST3 – perseverating errors | 31/11 | n. s. | 14/6 | n. s. | 10/7 | n. s. | 9/4 | n. s. |
| Memory functions | | | | | | | | |
| Digit span – number | 37/15 | n. s. | 23/9 | 0.05 | 16/6 | n. s. | 12/7 | n. s. |
| Recurring Figures Test – error | 37/15 | 0.03 | 23/9 | 0.04 | 16/7 | n. s. | 12/6 | 0.07 |
| AVLT1 – words at I. pres. | 36/15 | 0.05 | 22/9 | n. s. | 16/6 | n. s. | 12/6 | n. s. |
| AVLT2 – words at V. pres. | 36/15 | 0.01 | 22/9 | 0.02 | 16/6 | n. s. | 12/6 | n. s. |
| AVLT3 – learning achievement | 36/15 | 0.08 | 22/9 | n. s. | 16/6 | n. s. | 12/6 | n. s. |
| AVLT4 – loss by interference | 36/15 | n. s. | 22/9 | n. s. | 16/6 | n. s. | 12/6 | n. s. |
| AVLT5 – recall after 30 min | 36/15 | n. s. | 22/9 | n. s. | 16/6 | n. s. | 12/6 | n. s. |
| AVLT6 – recognition | 36/15 | 0.04 | 22/9 | n. s. | 16/6 | n. s. | 12/6 | n. s. |
| Control Attention | | | | | | | | |
| Alertness without warning tone – RT(ms) | 26/9 | 0.05 | 16/6 | n. s. | 11/6 | n. s. | 9/5 | n. s. |
| Alertness with warning tone – RT (ms) | 26/9 | n. s. | 16/6 | n. s. | 11/6 | n. s. | 9/5 | n. s |
| Divided Attention – reaction time (ms) | 26/7 | n. s. | 14/5 | n. s. | 11/6 | 0.07 | 9/5 | n. s. |
| Divided Attention – missing outs | 26/7 | n. s. | 14/5 | n. s. | 10/2 | 0.09 | 7/5 | n. s. |

N sp/b indicates the number of patients (N) in the spinal-onset (sp) versus bulbar-onset (b) subgroup
*CWIT* Colour Word Interference Test; *WCST* Wisconsin Card Sorting Test; *AVLT* Auditory Verbal Learning Test
Level of significance $p < 0.05$, trend $p < 0.10$

(Table 3). Also concerning recognition memory and free recall of verbal material (AVLT), bulbar-onset patients performed more poorly in most subtests. Statistical analysis, however, did not yield significant group differences. Only for the AVLT parameter "words at V. presentation", which indexes a learning factor, was a significant subgroup difference seen at E1 ($p < 0.01$) and E2 ($p < 0.02$) in favor of the spinal group.

## Attention control

Although reaction times (RT) were consistently slower in bulbar-onset compared to the spinal-onset patients, both RTs without warning tone (Alertness 1) and RTs with warning tone (Alertness 2) did not significantly differentiate between subgroups throughout the observation period. Likewise, divided attention performance was not significantly different with respect to any of the parameters. For details refer to Table 3.

## Findings at examination 5 (E 5)

We were able to test six patients after a time period of 18 months. Because of their limited number, these data were evaluated descriptively. In these six patients, the clinical progression of the disease continued as indicated by a further decline of the mean Norris scale – 48.8 at E5 compared with 58.5 at E4. Likewise, VC declined sharply to 54 % at E5 compared with 66.6 at E4. In contrast, the BDI scored 12.3 and remained in the range

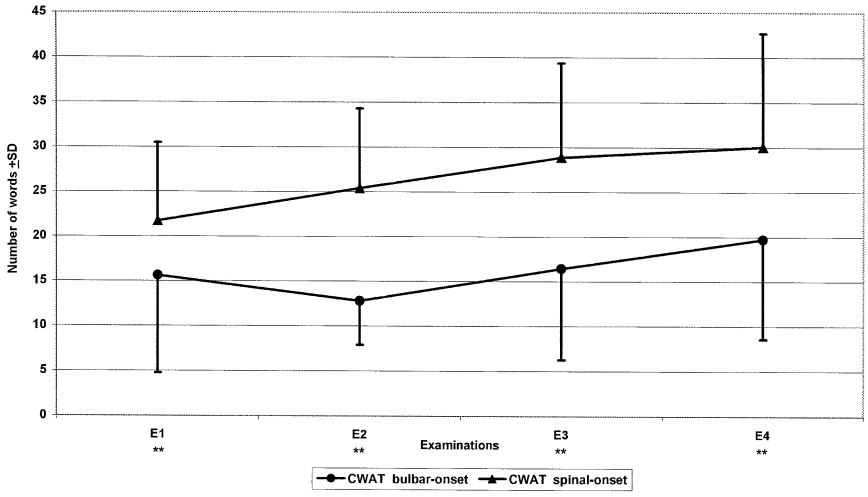


**Fig. 1** Longitudinal word fluency performance (CWAT, number) in bulbar-onset compared with spinal-onset patients. Note significantly better CWAT scores in the spinal-onset subgroup

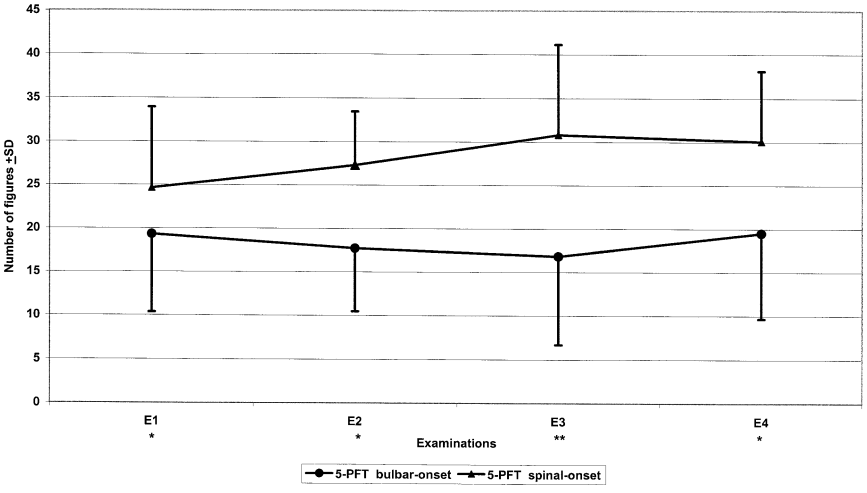


**Fig. 2** Longitudinal design fluency performance (5-PFT, number) in bulbar-onset compared with spinal-onset patients. Performance scores are consistently better in the spinal-onset subgroup

found at E4 (10.2). All parameters assessing executive functions clearly declined at E5 compared with E4. Word fluency (mean number) scored 31.0 at E5 vs 26.0 at E4, design fluency (mean number) 37.5 vs 39.0, CWIT (reading time) 41.8 s vs 38.2 s, CWIT (naming time) 55.8 s vs 49.9 s, CWIT (interference time) 86.8 s vs 85.1, WCST (categories) 3.0 vs 3.5, WCST (error score) 19.0 vs 15.5 and WCST (perseverating error score) 11.3 vs 9.0. Memory functions also showed a decline at E5 vs E4. Mean number of Digit span was 5.8 vs 6.8. Verbal recognition memory (RFT) scored 25.0 vs 23.8. Concerning the AVLT, the parameters "words recalled at I" (6.4) and learning achievement (4.6) particularly deteriorated at E5 compared with E4, while other parameters, i.e. recall after 30 min, remained stable over time. For alertness and divided attention, no data could be collected since the patients were not able to handle the computer any more.

## Discussion

We describe a fronto-temporal pattern of cognitive dysfunction early in the course of ALS which is mainly associated with bulbar forms. Verbal and non-verbal fluency processing as well as concept formation were most affected and the individual deficits spanned a continuum from mild to severe impairment. Thus, we confirm previous findings of predominant deficits of verbal and non-verbal fluency as well as concept formation and problem solving in non-demented ALS patients compared with controls [2, 5, 17, 32, 33, 49]. We also provide evidence that memory functions, although to a milder degree, are affected by the neurodegenerative process of ALS. Memory impairment has already been described in previous ALS studies [11, 17, 24, 33], and it has been confirmed that these deficits are mostly mild in degree and less pronounced than those of executive functions [1]. The question arises whether memory impairment in

ALS reflects neurodegeneration in the temporal lobe itself or may be a consequence of frontal lobe dysfunction. On the morphological level, neuropathological studies [26, 39] and serial MRI [25] have provided some evidence for primary pathology in the temporal lobes and limbic system of non-demented ALS patients. However, the role of temporal pathology in ALS remains controversial, since the reported alterations are non-specific, limited to subgroups and difficult to distinguish from age-related changes. Moreover, it is widely accepted that the frontal lobes themselves play an important role in memory processing [18, 40]. Consequently, memory functions may be affected by primary prefrontal dysfunction, and vice versa, the degeneration of the temporo-limbic areas may exert a secondary influence on frontal lobe functioning.

An innovative aspect of this study is its longitudinal observation of cognitive functions in individual ALS patients. Cross-sectional studies cannot adequately address the longitudinal aspect. From their indirect perspective, no consistent correlation has been reported in ALS patients between duration and severity of the disease and their cognitive functions [16, 28]. Individual follow-up in our patients now provides evidence that their cognitive dysfunction occurs early in the course of the disease. Moreover, no prominent deterioration seems to occur with disease progression. Data for comparison are lacking since there is very limited experience with longitudinal neuropsychological testing in ALS patients. In one study performed by Strong et al., follow-up neuropsychological testing was done in a subgroup of ALS patients after a 6 month observation period [45]. No major changes of cognitive functions were found, and the patients' performance even slightly improved on about half of the test parameters while it moderately declined on the other half. Our results support and extend these data. From our longitudinal perspective, we conclude that cognitive deficits appear early in the course of ALS and that they may even precede important neuronal loss in the motor system. From that we hypothesize that the pathomechanism of ALS may differently affect cognitive and motor functions during its evolution. This is not too speculative since we are clinically focusing on a disease process in the motor system in which deficits can be detected much more easily than in the cognitive domain where careful neuropsychological testing is needed to uncover subtle deficits. Moreover, cognitive functions, after the initial decline, seem to remain relatively stable in contrast to motor decline. However, our interpretation of longitudinal data is limited by the fact that learning effects due to repetitive testing seem to interfere and mask progressive deficits in patients. This may compensate – at least partially – for the effect of disease progression. It is not possible to estimate the size of the learning effect since we have no adequate control data. But also comparison with normal controls would not essentially solve the problem since repetition effects are known to express themselves differentially in healthy subjects and cognitively deficient persons [13]. Thus, normal and cognitively well-trained subjects seem to obtain considerably more benefit from test repetitions than cognitively deficient persons implying a higher learning effect. This aspect remains therefore unresolved. Nevertheless, the putative learning effect is clearly less pronounced in bulbar-onset patients and is most prominent for fluency functions. From this we conclude that a lower learning capacity may characterize the bulbar subgroup and be another facet of their prefrontal dysfunction.

It is interesting to note that ALS patients with bulbar-onset of symptoms performed significantly more poorly on a series of tests compared with those with spinal-onset of the disease. This subgroup difference was most pronounced for executive functions, in particular fluency processing, and independent of the presentation of verbal or non-verbal material. It also held true for memory-related tasks, but to a minor degree. Our group data indicate that the subgroup difference was not explained by demographic or behavioral factors or differences in duration and severity of the disease. This holds also true for respiratory failure which might affect cognitive function, above all speed performance, concentration and test accuracy, in predominantly bulbar patients. However, levels and course of VC scores over time argue against a significant influence of respiratory failure on cognitive deficits in the two subgroups of the study. VC dropped from 81.5 (E1) to 69.0 (E4) in spinal patients and from 71.7 (E1) to 64.3 (E4) in bulbar ones representing only a moderate and comparable decline in both groups. Moreover, cognitive deficits were essentially present at study entry and did not decline along with VC scores. Respiratory failure therefore appears to exert no major influence on cognition in our study. Moreover there is no consistent evidence for a differential subgroup influence. Likewise, upper motor neuron involvement was comparable between subgroups. Consistent with our data, other studies found that reduced fluency was most prevalent in patients with dysarthria and those with bulbar predominance [33], and that bulbar-onset patients were more impaired in recognition memory tasks [45]. Moreover, a relationship between the degree of bulbar involvement and cognitive impairment has been reported [12]. Abrahams et al. [4] have shown that neuropsychological deficits are more prominent in ALS patients with pseudobulbar palsy, although not exclusive to this subgroup. And Portet et al. [41] have recently found that up to 48% of their bulbar-onset MND patients were cognitively impaired with their deficit indicating a predominantly frontotemporal involvement. In view of these data, the hypothesis has been put forward that patients with bulbar palsy may be more suscepti-

ble to develop a frontotemporal dementia than those with predominantly corticospinal features [38].

It is not clear at present which underlying factors might explain the cognitive deficits predominantly in bulbar ALS patients. A hypothesis could be that the topography of the motoneuron degeneration in bulbar ALS patients results in more extensive disruption of cognitive pathways due to widespread degeneration. This might occur in the cortex where the fronto-cortical representation area of bulbar structures is large and close to prefrontal structures. Animal models of ALS strongly suggest that the degeneration process is not specifically directed against motor neurons but also against other populations of neurons, especially interneurons [36]. Interneuron pathology might therefore contribute as a mediator to cognitive pathology in ALS. "Hot spots" for adjacent neuronal degeneration may also be the subcortex and brainstem, where extramotor pathology, particularly in the mesencephalon and basal ganglia, can result in functional disruption of ascending meso-limbic and meso-thalamo-cortical pathways and thus secondary prefrontal dysfunction. Extramotor brainstem pathology in ALS is suggested by the clinical observation that the supranuclear meso-pontine oculomotor system becomes impaired in a considerable proportion of patients in late disease [25]. Also neuropathological studies indicate that there is pathology outside the corticospinal tracts in the form of neuronal degeneration of posterior root ganglia [27], extensive gliosis and shrinkage in the frontal and temporal white matter [26, 29] and progressive atrophy spreading from frontal and temporal lobes to the thalamus and brainstem tegmentum [25]. From a functional point of view, subcortical, brainstem and basal ganglia pathology may deprive the frontal cortex of its afferents. Imaging data confirm the functional importance of these subcortical pathways. Thus, abnormal PET activation in the anterior thalamus has been found to correlate significantly with verbal fluency and picture recall performance [28]. This is also consistent with our previous finding of a significant correlation between resting glucose metabolism in the right thalamus and performance on a verbal fluency test in ALS patients [32]. Based on these findings, one may postulate that subcortical neural pathways connecting the mesiotemporal regions with the prefrontal cortex become functionally disrupted in ALS. All these data give further credit to the idea that ALS is a multisystem disorder and that cognitive deficits reflect cortical and subcortical pathology outside the motor system.

## References


1. Abrahams S, Goldstein LH, Lloyd CM, Brooks DJ, Leigh PN (1995a) Cognitive deficits in non-demented amyotrophic lateral sclerosis patients: a neuropsychological investigation. J Neurol Sci 129(Suppl):54–55
2. Abrahams S, Leigh PN, Kew JJ, Goldstein LH, Lloyd CM, Brooks DJ (1995b) A positron emission tomography study of frontal lobe function (verbal fluency) in amyotrophic lateral sclerosis. J Neurol Sci 129(Suppl):44–46
3. Abrahams S, Goldstein LH, Kew JJM, Brooks DJ, Lloyd CM, Frith CD, Leigh PN (1996) Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. Brain 119(6):2105–2120
4. Abrahams S, Goldstein LH, Al-Chalabi A, Pickering A, Morris RG, Passingham RE, Brooks DJ, Leigh PN (1997) Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 62:464–472
5. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH (2000) Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). Neuropsychologia 38: 734–747
6. Andreadou E, Sgouropoulos P, Varelas P, Gouliamos A, Papageorgiou C (1998) Subcortical frontal lesions on MRI in patients with motor neurone disease. Neuroradiology 40:298–302
7. Bäumler G (1984) Farbe-Wort-Interferenztest (FWIT) nach JR Stroop. Verlag für Psychologie – Dr. C. J. Hogrefe, Göttingen, Toronto, Zürich
8. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
9. Benton AL, Hamsher K, de Varney S, Spreen NR (1983) Contributions to neuropsychological assessment. New York, Oxford University Press
10. Brooks BR (1994a) El Escorial World Federation of Neurology. Criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci 124(Suppl): 96–107
11. Dary-Auriol M, Ingrand P, Bonnaud V, Dumas P, Gil R (1997) Cognitive impairment and amyotrophic lateral sclerosis. Rev Neurol (Paris) 153(4): 244–250
12. David AS, Gillham RA (1986) Neuropsychological study of motor neuron disease. Psychosomatics 27:441–445
13. des Rosiers G, Kavanagh D (1987) Cognitive assessment in closed head injury: stability, validity and parallel forms for two neuropsychological measures of recovery. Int J Clin Neuropsychol 9:162–173
14. Dickinson-Gibbons J (1985) Nonparametric statistical Inference. 2nd Edition. Marcel Dekker Inc., New York
15. Evdokimidis I, Constantinidis TS, Gourtzelidis P, Smyrnis N, Zalonis I, Zis PV, Andreadou E, Papageorgiou C (2002) Frontal lobe dysfunction in amyotrophic lateral sclerosis. J Neurol Sci 195:25–33
16. Frank B, Haas J, Heinze H-J, Stark E, Münte TF (1997) Relation of neuropsychological and magnetic resonance findings in amyotrophic lateral sclerosis: evidence for subgroups. Clin Neurol Neurosurg 99:79–86
17. Gallassi R, Montagna P, Morreale A, Lorusso S, Tinuper P, Daidone R, Lugaresi E (1989) Neuropsychological, electroencephalogram and brain computed tomography findings in motor neuron disease. Eur Neurol 29:115–120

18. Goldman-Rakic PS (1987) The issue of memory in the study of prefrontal function. In: Thierry AM, Glowinsky J, Goldman-Rakic PS, Christen Y (eds) Motor and cognitive functions of the prefrontal cortex. Springer, Berlin, Heidelberg, New York
19. Grant D, Berg EA (1948) A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Exp Psychol 38:404–411
20. Hautzinger M, Bailer M, Worall H, Keller F (1995) Beck-Depressions-Inventar (BDI). Testhandbuch. 2. Auflage. Verlag Hans Huber, Bern, Göttingen, Toronto, Seattle
21. Brooks BR (1994b) The ALS Norris score: insight into the natural history of ALS provided by Forbes Norris. In: Rose FC (ed) The Forbes H Norris Memorial Volume. ALS: from Charcot to the present and into the future. London, Smith-Gordon
22. Heaten RK, Grant I, Matthews CG (1991) Comprehensive norms for an expanded Halstead-Reitan battery: demographic corrections. Research findings, and clinical applications. Odessa, FL: Psychological Assessment Resources
23. Hudson AJ (1981) Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. Brain 104:217–247
24. Iwasaki Y, Kinoshita M, Ikeda K, Takamiya K, Shiojima T (1990) Cognitive impairment in amyotrophic lateral sclerosis and its relation to motor disabilities. Acta Neurol Scand 81: 141–143
25. Kato S, Hayashi H, Yagishita A (1993) Involvement of the frontotemporal lobe and limbic system in amyotrophic lateral sclerosis: as assessed by serial computed tomography and magnetic resonance imaging. J Neurol Sci 116: 52–58
26. Kato S, Masaya O, Hayashi H, Kawata A, Shimizu T (1994) Participation of the limbic system and its associated areas in the dementia of amyotrophic lateral sclerosis. J Neurol Sci 126:62–69
27. Kawamura Y, Dyck PJ, Shimono M, et al. (1981) Morphometric comparison of the vulnerability of peripheral motor and sensory neurons in amyotrophic lateral sclerosis. J Neuropathol Exp Neurol 40:667–675
28. Kew JJM, Goldstein LH, Leigh PN, Abrahams S, Cosgrave N, Passingham RE, Frackowiak RSJ, Brooks DJ (1993) The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis. Brain 116:1399–1423
29. Kiernan JA, Hudson AJ (1994) Frontal lobe atrophy in motor neuron diseases. Brain 117:747–757
30. Kimura SD (1981) A card from of the Reitan-Modified Halstead Category Test. J Consult Clin Psychol 49:145–146
31. Lehrl S (1989) Mehrfachwahl-Wortschatz-Intelligenztest MWT-B. Manual, 2. Neubearb. Auflage. Perimed Fachbuch-Verlagsgesellschaft, Erlangen
32. Ludolph AC, Langen KJ, Regard M, Herzog H, Kemper B, Kuwert T, Böttger IG, Feinendegen L (1992) Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychologic and positron emission tomography study. Acta Neurol Scand 85:81–89
33. Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH (1996) Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 61:450–455
34. Milner B (1963) Effects of different brain lesions on card sorting. The role of the frontal lobes. Arch Neurol 9: 90–100
35. Mitsuyama Y (1984) Presenile dementia with motor neuron disease in Japan: Clinico-pathological review of 26 cases. J Neurol Neurosurg Psychiatry 47:953–959
36. Morrison BM, Janssen WG, Gordon JW, Morrison JH (1998) Time course of neuropathology in the spinal cord of G86R superoxide dismutase transgenic mice. J Comp Neurol 391:64–77
37. Münte TF, Troger M, Nusser I, Wieringa BM, Matzke M, Johannes S, Dengler R (1998) Recognition memory deficits in amyotrophic lateral sclerosis assessed with event-related brain potentials. Acta Neurol Scand 98:110–115
38. Neary D, Snowden JS, Mann DM (2000) Cognitive change in motor neurone disease/amyotrophic lateral sclerosis. J Neurol Sci 180:15–20
39. Okamoto K (1998) Temporal lobe pathology in patients with amyotrophic lateral sclerosis. Neuropathology 18(2):222–227
40. Petrides M (1989) Frontal lobes and memory. In: Boller F, Frafman J (eds) Handbook of Neuropsychology, Vol 3. Elsevier, pp 75–90
41. Portet F, Cadilhac C, Touchon J, Camu W (2001) Cognitive impairment in motor neuron disease with bulbar onset. Amyotroph Lateral Scler Other Motor Neuron Disord 2:23–29
42. Regard M, Strauss E, Knapp P (1982) Children's production on verbal and non-verbal fluency tasks. Perc mot skills 55:839–844
43. Rey A (1964) L'examen clinique en psychologie. Presses universitaires de France, Paris
44. Sachs L (2002) Angewandte Statistik, 10. Auflage, Springer Verlag, Berlin
45. Strong MJ, Grace GM, Orange JB, Leeper HA, Menon RS, Aere C (1999) A prospective study of cognitive impairment in ALS. Neurology 53:1665–1670
46. Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–681
47. Sturm W, Willmes K, Horn W (1993) Leistungsprüfungssystem für 50–90jährige. Handanweisung, 2. Auflage, Hogrefe, Verlag für Psychologie, Göttingen
48. Thurstone LL, Thurstone TG (1962) Primary mental abilities (Rev). Chicago: Science Research Associates
49. Vercelletto M, Ronin M, Huvet M, Magne C, Feve JR (1999) Frontal type dementia preceding amyotrophic lateral sclerosis: a neuropsychological and SPECT study of five clinical cases. Eur J Neurol 6:295–299
50. Wechsler D (1981) Wechsler Adult Intelligence Scale- revised version (WAIS-R). Psychological corporation, New York
51. Wightman G, Anderson VER, Martin J, Swash M, Anderton BH, Neary D, Mann D, Luthert P, Leigh PN (1992) Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. Neuroscience Lett 139: 269–274
52. Wilson CM, Grace GM, Munoz DG, He BP, Strong MJ (2001) Cognitive impairment in sporadic ALS: a pathologic continuum underlying a multisystem disorder. Neurology 57:651–657
53. Zimmermann P, Fimm B (1993) Testbatterie zur Aufmerksamkeitsprüfung (TAP) – Version 1.0. Handbuch Teil 1. Psytest