

Cognitive function in patients with late stage amyotrophic lateral sclerosis

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ABSTRACT

Background: Subtle cognitive deficits have been found in a substantial percentage of patients with early stage amyotrophic lateral sclerosis (ALS). Cognitive function in later stages of the disease remain to be investigated because the neuropsychological tests that are usually employed, such as written or verbal fluency tests, cannot be performed by those patients because of motor or speech impairment, or both.

Methods: In the present study, 11 patients with late stage ALS who were severely physically impaired and matched controls underwent a neuropsychological test battery to explore their cognitive function with respect to disease related functional status. Testing was restricted to tasks that used a binary (yes/no) signal and did not require verbalisation or measures of reaction time to index performance.

Results: Although some patients displayed deficits in aspects of executive function, learning and memory, overall test results indicated normal cognitive function. A statistically highly significant negative correlation was found between the performance on two learning and memory tasks and the functional status of the patients.

Conclusion: The results of this study indicate a superior performance on learning and memory tasks of patients whose disease had further progressed. This may have important implications for our view on cognitive function in relation to the course of the disease.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by a progressive degeneration of the first and second motor neurons which results in paralysed limbs or bulbar musculature, or both. The worldwide incidence of ALS is approximately 1.2–1.8 per 100 000.¹ The impairment due to ALS is commonly known to be physical only; however, many studies have demonstrated cognitive impairment in a substantial proportion of patients with ALS. Impairment of executive functions such as logic, strategy, problem solving and planning are often observed.^{2–4} Most consistent are reports of a decreased performance on fluency tests,^{5–7} such as the Controlled Oral Word Association Test, in which patients have 3 min to name or write as many words as they can think of starting with the letter “F”, “A” and “S”. Using this test, Schreiber *et al* found a significant decrease in performance over time, when a group of 52 patients with ALS were tested longitudinally in the early stages of the illness.⁸

Reports on memory and learning impairment are less consistent.⁹ Language deficits are occasionally found in the early stages of the disease.¹⁰ Furthermore, it has been suggested that cognitive deficits might occur in a continuum, ranging from

subtle cognitive dysfunction to frontotemporal dementia (FTD).^{11–12} These findings of FTD in patients with ALS were confirmed in post-mortem examinations showing focal degeneration of the frontal and temporal neocortex.^{11–13} Prospective longitudinal studies suggest that cognitive deficits may slightly increase as the disease progresses.^{2–14–16} However, these longitudinal studies did not evaluate patients in later stages of ALS. A recent study indicates a slightly better performance in some neuropsychological tests by patients with a longer disease duration.¹⁷ To our knowledge, assessment of cognitive function in patients with later stage ALS has never been undertaken, most probably because of the physical and verbal requirements of typical cognitive test batteries. The severe disabilities that ALS causes may therefore interfere with neuropsychological testing,¹⁸ because even moderate motor or speech impairment poses problems for the assessment of cognitive function.¹⁹

In a completely “locked in” state, seen in patients with later stage ALS, state-of-the-art neuropsychological examination is not feasible. Communication becomes very difficult because of complete loss of voluntary muscular movement, including eye muscles. However, this state is rarely observed because patients die as a result of respiration failure. An attempt has been made to assess cognitive function in a small number of these locked in patients with the use of EEG and event related potentials.^{20–22} Most patients with late stage are, however, even when artificially ventilated, still able to blink or move their eyes because ocular motility is usually preserved up to the final stage of the disease.²⁰ In 2004, Neumann and Kotchoubey compiled a neuropsychological test battery which can be performed as long as a single “switch” response remains available; either an eye blink, lip movement or a twitch with the eyebrow.²³ As described in the methods section, the tests do not have a time limit, do not require fast reactions, talking, writing or drawing. This makes assessment of cognitive function possible at almost any stage of the disease.

The aim of the current study was to investigate whether this test battery would confirm findings of significant cognitive impairment in patients with ALS, as suggested in the literature.^{14–15–24} It was hypothesised that if cognitive decline progresses with motor degeneration, we would find, firstly, that the poorer performance in patients with later stage ALS would be below the mean of the control group results, as well as normative data, and secondly, that the difference between patients and controls in this study would be larger

than the differences reported in previous studies in which only patients in earlier stages of the disease were examined.

METHODS

Participants

Eleven severely physically impaired patients with ALS (six males; mean age 52.3 (10.4) years) and 11 controls (six males; mean age 53.2 (12.6) years) were recruited by the Institute of Medical Psychology and Behavioural Neurobiology in Tübingen, Germany. Patients were recruited from the institute's current patient pool and none of the patients declined participation. Control participants were either recruited by means of an announcement or were directly asked by one of the experimenters. None of the directly asked control persons refused participation. The mean years of education of the patient group was 15.0 (3.8) and 16.0 (3.7) years for the controls. All participants, or their authorised representatives, gave informed consent, which had been reviewed and approved by the ethics committee of the medical faculty of the University of Tübingen. Clinical characteristics are presented in table 1.

Eight patients were tetraplegic. Before assessment, a non-vocal response mode of "yes-no" was used by six patients. In all six, muscles of the face were used for a "yes-no" signal. One patient who was artificially ventilated with an endotracheal tube was still able to give vocal responses. According to the El-Escorial criteria, two patients (patient Nos 3 and 8) had been diagnosed with familial ALS and the remainder with sporadic ALS.²⁵ One of the patients with sporadic ALS (patient No 6) reported that a direct family member suffered from FTD. Disease duration since diagnosis varied from 15 months to 14 years (mean 56.8 (43.8) months).

The degree of physical disability was defined using the ALS functional rating scale (ALS-FRS),²⁶ ranging from complete functionality (40) to total dependency (0). The mean score on the ALS-FRS was 11.9 (8.2) (range 0–25), indicating severe disability. Two patients were permanently artificially ventilated and three patients received intermittent artificial respiration. Current mood of the patients was measured with the ALS Depression Inventory (ADI-12)^{27,28} to control for symptoms of depression because an abnormal cognitive profile might be related to the emotional state.²⁹ Values above 28 indicate clinically relevant depression and values between 22 and 28

indicate mild to moderate depressive symptoms. None of the patients had clinically relevant depression, but six patients displayed mild to moderate symptoms of depression. In the control group, no one had symptoms of (clinical) depression, as measured with the German *Allgemeine Depressionsskala* (ADS-L).³⁰

None of the patients had a history of other neurological or psychiatric disorders. All patients were tested between March and August 2005 except for one patient who was tested earlier (2001) and whose results were published by Neumann and Kotchoubey.^{1,23} Because of their inability to travel, 10 patients were tested at home.

To be defined as "severely physically impaired", a patient had to fulfil the following criteria: (a) at least 15 months since diagnosis OR (b) at least 30 months since first symptoms of the disease AND (c) severe tetraparesis approaching tetraplegia OR (d) moderate tetraparesis or paraparesis in combination with the inability to speak. The least impaired patient in our group fulfilled criteria (a) and (d). This patient was still able to walk, with the aid of walking sticks, and volunteered to visit our institute to take part in the study. Control persons were matched for sex, age and total years of education. The controls were not matched for response mode (eg, using eyes, finger, etc, as for the patients with ALS). The control subjects responded vocally with yes or no.

Neuropsychological assessment

The neuropsychological test battery devised by Neumann and Kotchoubey²³ to assess cognitive function in severely physically impaired individuals was used in the present study. The test battery does not require fast motor responses or verbalisation from patients, only the ability to indicate yes and no. Therefore, a distinct motor signal to indicate the yes and no responses was defined and agreed upon in advance of each test session. Although all tests could be administered as indicated in the test manuals, some modifications were made in accordance with the protocol described by Neumann and Kotchoubey²³ to account for severe paralysis. Stimulus material such as test cards were presented but not looked at by the assessor to ensure that the experimenter did not influence answers. Thus without looking at the stimulus material, the answers of each test were retrieved and repeated aloud and written down only if the patient did not object. This thorough procedure was carried out in all tests, with all patients and controls, to maintain test objectivity.

Testing was divided into two sessions, depending on the fatigue of the patient, with the interval between sessions being two weeks or less.

Neuropsychological tests

The test battery addresses general intelligence, executive function, learning and memory, and speech comprehension, and will be explained in detail below. Test assessment and administering was performed in the same way and in the same order as noted below for the patient and control groups.

General intelligence

Current intellectual function was estimated using the Standard Progressive Matrices (SPM).³¹ In this test, the assessor turns the pages of the booklet, which is only visible to the patient.

¹In this article, the results of patient No 10 were published to show the principle applicability of the newly compiled cognitive test battery. However, these results were neither included in any group statistics nor were they compared with control or normative data. This is why we chose to include this patient here.

Table 1 Clinical characteristics of patients with amyotrophic lateral sclerosis

Patient No	ALS-FRS	ADI-12	Time since diagnosis (months)	Time since first signs (months)	Artificially ventilated
1	12	18	94	104	No
2	4	12	36	42	Intermittent†
3	8	18	19	113	Yes
4	17	26	46	51	No
5	10	26	51	56	Intermittent†
6	25	17	15	30	No
7	5	15	76	80	No
8	18	26	48	120	Intermittent†
9	24	24	49	61	No
10*	0	26	168	193	Yes
11	8	23	23	30	No
Mean (SD)	11.9 (8.2)	21.0 (5.1)	56.8 (43.8)	80.0 (49.3)	

*Data already published in Neumann and Kotchoubey (2004).

†Non-invasive positive pressure ventilation.

ADI-12, Amyotrophic Lateral Sclerosis Depression Inventory; ALS-FRS, Amyotrophic Lateral Sclerosis Functional Rating Scale.

Table 2 Neuropsychological assessment of patients and controls

	Patients (n = 11)	Controls (n = 11)	F	p Value
SPM	47.64 (10.1)	48.45 (6.5)	1.113	0.824
WCST				
Categories (max 6)	5.27 (1.6)	5.45 (1.5)	0.367	0.792
Total number of errors	21.36 (16.9)	17.73 (17.8)	0.018	0.629
Trials to first criterion	19.91 (17.1)	11.45 (0.8)	6.012	0.117
Perseverative errors (%)	9.49 (5.4)	9.73 (4.4)	0.000	0.909
VLT	40.45 (8.8)	38.91 (11.6)	0.307	0.729
NVLT	36.09 (9.9)	33.91 (7.4)	0.785	0.565
AAT				
Reading	57.55 (2.1)	55.91 (2.5)	0.192	0.114
Listening	55.91 (4.6)	58.18 (2.4)	1.494	0.160

Values are mean (SD).

AAT, Aachener Aphasia Test; NVLT, Non-verbal Learning Test; SPM, Standard Progressive Matrices; VLT, Verbal Learning Test; WCST, Wisconsin Card Sorting Test.

Following a signal from the participant, the assessor asked if the answer should be 1, 2, 3, etc; if the participant indicated yes, the answer was repeated, written down and checked to ensure no objection.

Executive functions

A full version of the Wisconsin Card Sorting Test (WCST)³² was administered to assess aspects of executive function such as shifting between mental sets or tasks, and maintenance of good strategies.³³ Each of the four key cards had a number (1 to 4). Cards that have to be matched with the four key cards were turned over and showed by the assessor. Again, on a signal from the participant, the answer was retrieved, confirmed and noted.

Learning and memory

The Non-verbal Learning Test (NVLT) and the Verbal Learning Test (VLT) were used.^{34 35} In these tests, participants have to remember figures or meaningless words, respectively, and recognise eight constantly repeating items out of 160 items. When a repetitive card was shown, the patient had to signal “yes”, and “no” when it was not a repetitive card. Responses were confirmed. Correct and incorrect recognition of these items was recorded over the course of the test. This allowed us to investigate learning abilities regarding non-verbal memory material. The VLT addresses verbal learning abilities in terms of storing data in long term memory and recall of learned information after recognition of a visual stimulus. Prior to each of the two tests, a visual discrimination test was carried out to make sure the outcome was not biased by visual infirmity.

Speech comprehension

Speech comprehension disorders, which are typical for central motor area impairment, were assessed with a modified Aachener Aphasia Test (AAT).³⁶ For this test, participants were instructed to match a verbal stimulus to one of four images. These images had a number (1 to 4), and chosen images were marked by the assessor after confirmation. Verbal stimuli were words or sentences that were either read to the participant (listening comprehension) or read by the participant (reading comprehension).

Comparison with normative test data

In addition to control group comparisons, the patients' test results were also compared with normative data. Normative means and SDs were defined according to age and educational status (years of education) of patients. T scores were calculated.

A patient's response was regarded as “normal” when it was within the mean \pm 1 SD (a T score of 40–60).

RESULTS

Group comparisons

Both groups were highly comparable with respect to age ($p = 0.856$), gender ($p = 1.000$) and years of education ($p = 0.831$).

Neuropsychological tests

Test results are presented in table 2. No significant differences were found between patients and controls concerning neuropsychological test results. In some tests or categories of tests, patients scored below or above the mean \pm 1 SD in comparison with normative values but group means of aspects of executive function, learning and memory were within the normal range.

Standard Progressive Matrices

Results indicated identical and normal intellectual functions in both groups. Only patient No 10 scored marginally under the mean \pm 1 SD (T 39/40) in comparison with the normative data.

Wisconsin Card Sorting Test

Raw data comparison showed no statistically significant differences between the groups. Compared with the normative data, five patients scored within the normal range on all subscales. The other six patients (patient Nos 2, 3, 4, 8, 10 and 11) needed more than an average number of trials to complete the first category (five patients were within 2 SDs and one patient was below 2 SDs). Patient No 8 was unable to complete more than one category and repeatedly failed to maintain a good strategy. Patient T scores in two subscales exceeded 40, indicating that their data were above the norm. However, since the exact T score in such cases cannot be obtained, a group mean (SD) was not calculated for these scales.

(Non)-Verbal Learning Test

All patients scored within or slightly above the norm for both tests (NVLT mean 52.0 (11.7); VLT mean 49.9 (11.4)) except for patient No 6 who scored more than 2 SDs below the mean. The same patient, however, scored above average on the SPM, WCST and AAT. The mean scores did not differ between patients and controls.

Aachener Aphasia Test

On average, the performance did not differ between the two groups. Test outcomes (listening comprehension mean 71.2 (8.4); reading comprehension 71.9 (5.0)) suggested no dysfunction in recognition of spoken or read words in any of the tested patients, implying intact language abilities.

Relationship with normative test outcomes and patient characteristics

To investigate the relationship between disease stage and test results, Spearman's rank correlation was applied to the data. A non-parametric correlation was chosen to account for the low sample size and results have to be interpreted with caution.

No significant correlation was found between test results and disease duration. Conversely, a high negative correlation was found between the functional status (ALS-FRS scores) and the VLT ($r = -0.863$, $p < 0.01$). This correlation persisted when controlled for depression and ventilation dependency in a linear regression analysis ($\beta = -0.837$, $p < 0.05$) (see also fig 1). The NVLT also showed a negative correlation with ALS-FRS ($r = -0.692$, $p < 0.05$). Both correlations indicate that the further the disease had progressed, the better were learning and memory functions.

No significant correlations were found between disease duration or functional status and symptoms of depression.

DISCUSSION

The current study investigated cognitive function in patients with late stage ALS. The hypothesis predicting dramatic differences between patients with late stage ALS and healthy controls was not confirmed. Group means of patients did not differ from those of controls and were within the normative range, which indicates normal cognitive function. However, some individual patients displayed deficits in some aspects of executive functioning, learning and memory. Unfortunately, no premorbid test data for patients were available to assist with attributing the cause of the cognitive deficits to ALS.

The fact that not only group means but also standard deviations were similar for patients and controls (table 2) proves that the non-significance of the difference in means cannot be attributed to a large variation among the patients, and that the data do not contain a specific subgroup of patients with particularly poor performance. Even though some scores of

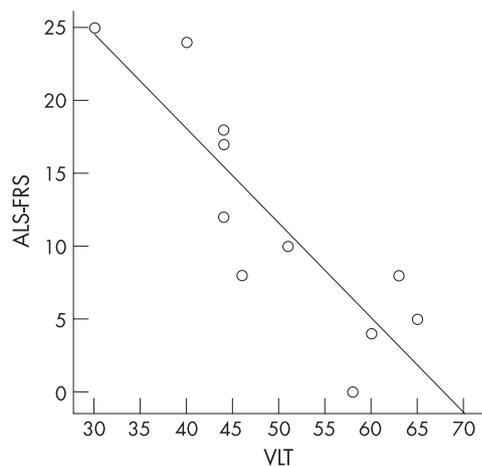


Figure 1 Scores of the Amyotrophic Lateral Sclerosis-Functional Rating Scale (ALS-FRS) plotted against results on the Verbal Learning Test (VLT).

some patients substantially differed from the corresponding means, such cases did not affect the general tendencies. The lack of cognitive impairment found in our group of patients with late stage ALS suggests that degenerative processes of the disease spare several aspects of cognitive function.

Most strikingly, learning and memory significantly improved in patients in the later stages of the disease. These high correlations (indicating as high as almost 50% and 75% common variance for non-verbal and verbal memory, respectively) were still present after controlling for depression and ventilation dependency. As no relationship was found between time since diagnosis and learning and memory abilities, the correlations cannot be explained by a slower progression of the disease. One possible explanation for this result might be that patients with end stage ALS with lower learning and memory abilities were less frequently included because of a higher mortality rate in this subgroup. Another possible reason could be that cognitively impaired patients, who may have a faster progression of the disease, are less likely to volunteer for such a study. We might also speculate that in a more advanced stage of the disease, preserved skills such as learning and memory are more utilised and trained ("trained what remained"). A good learning ability might also help patients to adapt quickly to the wishes explicitly or implicitly uttered by the social environment because patients depend largely on a good relationship with those who care for them. It is also difficult for patients to ask for items to be repeated because communication is not easy. Thus it is essential for them to immediately understand any conversation.

Respiratory weakness may affect cognitive abilities because of hypoventilation¹¹ and thus lead to poor performance on memory tests. When controlling for (intermittent) artificial ventilation, the correlations remained, indicating that respiratory weakness was not a confounding factor.

Verbal fluency, the most consistent cognitive dysfunction associated with ALS in the literature, was not assessed because of participants' physical impairment and loss of speech. In the experiment of Abrahams and colleagues,²⁹ verbal fluency impairment was demonstrated even when motor speed was controlled. Patients had to write down as many words as possible beginning with a given letter in a limited time period. Afterwards, the patients' writing speed was measured when they copied the same words. A verbal fluency index was then calculated taking writing speed into account. However, this control procedure is based on the assumption that word generation and word writing are additive processes, which follow each other but do not interact. This procedure, therefore, does not appear to account for the possibility that word generation itself may be affected by the fact that, firstly, writing was difficult and demanded concentration, and secondly, the patients may not have been able to write as much as they were able to generate.

Because all tests for dementia require motor or speech skills, and hence do not account for the physical and verbal impairments of patients with ALS, no specific assessment of dementia was possible in our group of patients.

Although several studies indicated memory deficits in non-demented patients with ALS,^{37, 38} a consistent pattern has not been identified. Chari *et al* found normal memory in their sample of patients with ALS.³⁹ In line with our results, Papps *et al* demonstrated superior performance of patients with ALS compared with controls on memory for neutral words.⁴⁰ In that study, the authors suggest that learning and memory may be specifically "trained" functions in patients with ALS. This

explanation is also hypothesised in the study of Röttig *et al* in which a superior memory performance of patients with ALS in a later stage is also demonstrated.¹⁷ The reason for this discrepancy in the literature is not completely clear. Again, it could be that the physical and verbal impairment of the patient group was the source of inferior performance on memory tests in previous studies.

A caveat of the current study is the small sample size and the restricted number of tests applied; the latter, however, was because most neuropsychological tests require motor functions. Although the standardised test battery has proven useful in the assessment of cognitive function in severely physically impaired patients, the diagnostic accuracy might be reduced because of the different response mode (yes/no answers only). As this was the first study on cognitive function in patients with late stage ALS, data on objectivity, reliability and validity of the test battery were not available. The patients in our sample were recruited from a research institute and also participated in other research projects. These caveats notwithstanding, our results indicate preserved intelligence, executive functioning, learning and memory in patients with late stage ALS. The strong negative correlation between physical impairment and learning and memory abilities awaits replication and further investigation.

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