



Research Report

A neurophysiological analysis of working memory in amyotrophic lateral sclerosis

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ABSTRACT

Frontal lobe functions, in particular working memory (WM) and verbal fluency, have been found to be deficient in amyotrophic lateral sclerosis (ALS). To study the neural correlates of WM-impairment, ALS patients and healthy age-matched controls were subjected to two working memory tasks following the 2-back paradigm, one requiring the storage of figural information, the other storage of spatial information. A significant proportion of ALS patients were unable to perform the WM-tasks. Those who could showed worse performance in the spatial task than the controls. Event-related brain potentials recorded during the task revealed a topographical change of the working memory effect in the ALS patients. Thus, behavioral and electrophysiological data suggest an alteration of working memory, in particular for spatial information, in ALS. Additionally, the patients also took part in two Go/Nogo tasks (spatial, figural) using the same stimulus material but defining targets prior to the experiment instead of a working memory manipulation. Here, an anteriorization of the nogo-P3 was found which has been established as an index of impaired inhibitory functions.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of the nervous system of still unknown cause with muscular atrophy, spasticity and bulbar signs as its clinical hallmarks. Besides the obvious involvement of the upper and lower motor neurons, pathological (Brownell et al., 1970; Iwanaga et al., 1997), neuropsychological (Abrahams et al., 1997; Frank et al., 1997; Hanagasi et al., 2002; Lakerveld et al., 2008; Massman et al., 1996; Murphy et al., 2007; Phukan et al., 2007; Schreiber et al., 2005) as well as neuroimaging results (Abrahams et al.,

1995; Abrahams et al., 1996; Hatazawa et al., 1988; Kew et al., 1993; Ludolph et al., 1992; Mohammadi et al., 2009a,b; Schreiber et al., 2005) suggest, however, that the disease process involves other parts of the nervous system. A number of studies have suggested a dysfunction of frontal cortical areas resulting in impairments of metacognitive, executive functions. For example, Abrahams et al. (Abrahams et al., 2000) have found impairments on a range of fluency tests, namely the written verbal fluency, category fluency (generation of animal names) and design fluency, a deficit that has also been found by other studies (Frank et al., 1997). Abrahams et al.

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(Abrahams et al., 2000) also found significantly reduced working memory capacity and concluded that working memory and fluency impairments in ALS might result from a higher order dysfunction involving the supervisory attentional system or central executive component of working memory.

In the present study, we therefore set out to investigate a potential deficit in working memory in ALS in more detail. A general consensus has been reached that WM can be conceptualized as a multi-component system with different subsystems for different kinds of information. For example, Baddeley (Baddeley, 1986) proposed a system of working memory with separate storage and retention systems for verbal and visual-spatial information that are under the control of one central executive mechanism. Behavioral studies as well as animal work have further suggested that an additional functional and neuroanatomical dissociation might exist between object and spatial information within visual WM (Logie and Marchetti, 1991; Tresch et al., 1993; Ungerleider and Haxby, 1994; Wilson et al., 1993).

Many neurocognitive models assume that the prefrontal cortex (PFC) plays a pivotal role in the executive control of the WM content. Whereas some (e.g., Friedman and Goldman-Rakic, 1994; Wilson et al., 1993) have argued for an information specific architecture of the PFC with specific areas dedicated to particular kinds of information, others (e.g., Petrides, 1994) have proposed a process-specific (maintenance vs. manipulation) subdivision of the PFC.

Working memory processes can also be studied and dissociated by using the spatio-temporal properties of event-related brain potentials (ERPs). In contrast to functional imaging techniques such as PET or fMRI, ERPs have a relative poor spatial resolution. However, the temporal resolution is in the range of milliseconds and thus can provide information on the relative timing of cognitive processes underlying working memory performance such as onset, offset, and duration that otherwise is not available. Indeed, several ERP studies have found slow late components to be specifically related to the kind and amount of information to be stored in WM (Bosch et al., 2001; Mecklinger and Meinshausen, 1998; Mecklinger and Pfeifer, 1996; Ruchkin et al., 1992; Ruchkin et al., 1994; Ruchkin et al., 1995; Ruchkin et al., 1997). Bosch et al. (2001) compared ERPs during WM retention of object, spatial, and verbal information using a delayed matching task and reported frontal and parieto-occipital slow waves with different scalp topographies for object and spatial information.

Of particular importance for the present study is previous work on the so-called N-back task (McEvoy et al., 1998). In such a task stimuli are presented serially and participants have to decide whether the current stimulus is identical to the one that was presented N times before.

To further investigate to what extent working memory processes are impaired in ALS and whether a differential impairment could be found for spatial vs. object information, we conducted an ERP study using an N-back design. Based on findings of Awh et al. (1998) who found spatial selective attention to be important for spatial WM but not object WM (see also, Awh et al., 1999) and earlier work from our group revealing impairments of visuospatial functions in ALS (Müntz et al., 1998, 1999), we expected to find greater impairments in the ALS group for the spatial n-back task.

The experiment was designed such that the same stimulus sequences could be employed in a spatial and in an object working memory task. Moreover, we also included control conditions in which pre-specified spatial positions or objects were designated targets throughout a run, thus allowing to differentiate target detection from working memory processes.

2. Results

It turned out that three of the ALS patients had too many artefacts in their EEG to yield meaningful ERPs. Moreover, of the remaining 17 patients only 11 were able to do the working memory n-back task. The 6 patients discontinued the ERP measurements because they did not understand the n-back task despite elaborate and repeated instructions. The patients' problems appeared especially pronounced in the object-task. The patients who did not complete the n-back tasks did not have lower ALSFRS-R scores (6 patients, n-back not accomplished: mean=34.00, sd=9.14, min=22, max=44 ; 11 patients, n-back accomplished: mean=36.73, sd=5.90 min=23, max=43). We thus based our between group comparisons of the go/nogo tasks on the data of 17 patients and the comparisons involving the working memory tasks on 11 patients. We will call the latter group WM-subgroup. We included only the matched controls in these comparisons to achieve equal group sizes.

2.1. Neuropsychological Findings

The neuropsychological results of ALS patients and the control groups are summarized in Table 2. Subtest of the WAIS revealed a highly significant performance reduction of Vocabulary in the ALS group whereas Similarities, Picture Completion and Block Design did not show differences. A significant impairment was found for short term verbal memory performance (test: VLMT) which assesses free recall of a word list. A tendency for impairment was also found for the recurring words test which assesses verbal recognition memory. In contrast, no differences were found for non-verbal memory tests. Also, no differences between patients and controls were found for working memory measures (digit span, and reading span test). In the domain of executive functions a tendency towards worse performance was seen in the patients with regard to the number of perseverative errors in the Wisconsin Card sorting test, the application of strategies in the Ruff Figural Fluency test and the Controlled oral word association test. No differences between groups were found for attention tests (alertness and Go/NoGo of the TAP).

ALSFRS-R scores were not significantly correlated (Pearson product-moment correlation coefficient) with the neuropsychological findings (all $p > .1$). In both groups, the Wechsler Vocabulary subtest significantly correlated with Similarities (ALS: $r(20) = .65$, $p < .01$, Controls: $r(20) = .58$, $p < .01$), digit span (ALS: $r(20) = .47$, $p < .05$, Controls: $r(20) = .65$, $p < .01$), and Wisconsin Card Sorting scores (Categories ALS: $r(20) = .58$, $p < .01$, Controls: $r(20) = .49$, $p < .05$; errors ALS: $r(20) = -.50$, $p < .01$, Controls: $r(20) = -.47$, $p < .05$). Differential correlation patterns for the Vocabulary subtest were found for Recurring Words (ALS: $r(20) = .27$, $p > .05$, Controls: $r(19) = .52$, $p < .05$), Recurring Figures (ALS: $r(20) = .30$, $p > .05$, Controls: $r(19) = .52$, $p < .05$), Reading Span Test (ALS: r

Table 1 – Group details.

Pat No.	completed tasks	SEX		AGE		SCHOOL		(Years)		ALSFRS-R
		ALS	control	ALS	control	ALS	control	control	ALS	
1	G	m	m	50	47	12	12	12	24	
2	G	w	w	65	50	10	12	12	22	
3	G	w	w	56	60	12	8	8	44	
4	G	m	m	60	60	10	10	10	42	
5	G	m	w	51	53	12	10	10	35	
6	G	m	w	74	67	10	12	12	37	
7	G / WM	m	m	66	64	10	12	12	37	
8	G / WM	w	m	64	69	10	12	12	39	
9	G / WM	m	w	65	63	8	8	8	36	
10	G / WM	m	m	42	42	10	12	12	23	
11	G / WM	m	m	59	57	12	12	12	40	
12	G / WM	m	m	55	44	8	8	8	40	
13	G / WM	w	m	31	40	12	12	12	39	
14	G / WM	m	m	61	55	10	10	10	43	
15	G / WM	m	m	61	64	12	12	12	36	
16	G / WM	w	w	60	56	12	12	12	42	
17	G / WM	m	w	43	45	10	12	12	29	
18	no eeg	w	w	50	60	10	12	12	29	
19	no eeg	w	m	70	62	8	10	10	40	
20	no eeg	m	m	48	49	8	8	8	35	

M: Man, W: woman; G: Go/Nogo, WM: Working Memory.

(14) = $-.13$, $p > .05$, Controls: $r(19) = .51$, $p < .05$), Go/Nogo (ALS: $r(18) = -.17$, $p > .05$, Controls: $r(20) = .68$, $p < .01$), and the Total Learning Score of the VLMT (ALS: $r(20) = .52$, $p > .05$, Controls: $r(20) = -.21$, $p > .05$). All the other neuropsychological subtests did not correlate with the Vocabulary subtest (all $p > .1$).

2.2. ERP study

2.2.1. Behavioral results

Table 3 summarizes the behavioral results. For the working memory tasks patients as well as control participants showed a better performance for the spatial instruction which was reflected in a significant effect of the factor material for hits ($F(1,20) = 36.50$, $p < 0.001$) and correct rejections ($F(1,20) = 17.34$, $p < 0.001$). There was no effect of group, however (hits: $F(1,20) = 0.86$, n.s.; correct rejections: $F(1,20) = 2.92$, n.s.), and no interaction of material and group (hits $F(1,20) = 1.10$, n.s.; correct rejections $F(1,20) = 2.91$, n.s.). With regard to reaction times, faster reactions were seen for the spatial instruction, which was reflected by a main effect of material ($F(1,20) = 52.34$, $p < 0.001$). There was neither an effect of group ($F(1,20) = 1.20$, n.s.) nor a group \times material interaction ($F(1,20) = 0.06$, n.s.). The d' as an index of discriminability showed better performance in the spatial task ($F(1,20) = 5.71$, $p < .03$). A group \times material interaction ($F(1,20) = 4.93$, $p < .05$) reflected the fact that ALS patients showed impaired performance in particular in the spatial task.

For the Go/Nogo tasks a nearly perfect performance was seen in the patients and control participants. With regard to hit-rate neither an effect of group ($F(1,32) = 0.18$, n.s.) nor an effect of material ($F(1,32) = 0.01$, n.s.) nor an interaction ($F(1,32) = 1.26$, n.s.) was seen. For the percentage of correct rejection an effect of material ($F(1,32) = 6.81$, $p < 0.05$) was seen in the absence of a group-effect ($F(1,32) = 0.33$, n.s.) and a group \times material interaction ($F(1,32) = 0.95$, n.s.). Both groups showed a

faster reaction time under spatial instructions ($F(1,32) = 283.8$, $p < 0.001$). The slower reaction time of ALS patients under spatial instructions gave rise to a material \times group interaction ($F(1,32) = 6.26$, $p < .05$) but a main effect of group was not observed ($F(1,32) = 1.14$, n.s.). Neither group differences ($F(1,20) = 2.71$, n.s.) nor a group \times material interaction ($F(1,20) = 0.93$, n.s.) was found for d' .

2.3. ERPs: Working memory tasks

Fig. 2 illustrates the group averages from the working memory tasks for patients and control participants, which were characterized by a pronounced late positivity for the targets from about 400 ms onwards. This positivity was widely distributed over frontal, central and parietal areas. For ALS patients much more than for control participants a clear differentiation of spatial and object instructions was seen. The difference between target and non-target stimuli was more pronounced for the spatial task in ALS patients and showed a clear fronto-parietal gradient (Fig. 3). The ERPs were quantified by mean amplitude measures in successive time-windows. The corresponding ANOVA statistics are summarized in Table 4. In accord with the visual inspection, a stimulus \times material interaction was found in the time-windows 200–400 and 400–600 ms. Also, a main effect of the factor material was evident between 400–600 ms and 600–800 ms. The differential distribution of the target / non-target difference in ALS and control participants gave rise to a group \times stimulus \times material \times electrode site interaction.

2.4. Go/Nogo task

Fig. 4 shows the group averages for spatial and figural Go / Nogo tasks ($n = 17$). Both conditions were associated with a prominent

Table 2 – Neuropsychological Results.

Test	Parameter	ALS mean (sd)	Controls mean (sd)	% within deficient range (P/C) ²	Number (P/ C)	Significance
1. Learning and Memory						
VLMT						
supra span D1	# words	5.1 (1.5)	6.7 (1.8)	20/5	20/20	p<0.01
learning D5	# words	11.5 (2.9)	12.8 (2.0)	15/10	20/20	n.s.
total learning Σ D1-D5	# words	42.8 (10.8)	51.8 (9.3)	20/5	20/20	p<0.05
interference	# words	6.2 (1.7)	5.9 (2.1)	5/5	20/20	n.s.
immediate verbal recall (D6)	# words	8.4 (4.2)	10.6 (3.3)	35/10	20/20	p<0.08
Recurring Words	t-value	40.9 (9.7)	50.2 (13.6)	30/10.5	20/19	p<0.06
Recurring Figures	t-value	48.3 (7.6)	49.7 (9.4)	10/10.5	20/19	n.s.
2. Working Memory						
Digit Span ³	Points	10.1 (2.9)	10.7 (2.0)	10/0	20/20	n.s.
Forwards	Raw-values	6.3 (2.1)	7.4 (1.7)	25/0	20/20	n.s.
Backwards	Raw-values	6.2 (2.2)	7.0 (1.9)	5/0	20/20	n.s.
Reading Span Test ^{1, 3}	# words	9.2 (4.1)	10.3 (3.6)	28.6/5.3	14/19	n.s.
last run	# words	3.1 (1.6)	3.6 (1.0)	7.1/0	14/19	n.s.
3. Executive Functions						
Controlled Oral Word Assoc. (total)	# words	33.1 (10.6)	41.1 (12.2)	35/10	20/20	p<0.08
Words beginning with F	# words	10.7 (4.7)	13.2 (4.1)	55/20	20/20	p<0.05
Words beginning with A	# words	9.7 (3.7)	13.9 (4.5)	60/15	20/20	p<0.005
Words beginning with S	# words	12.3 (4.0)	14.1 (4.9)	15/5	20/20	n.s.
Ruff Figural Fluency ¹						
Designs	t-value	44.5 (10.3)	47.2 (11.6)	18.8/10	16/20	n.s.
Strategies	#	1.5 (1.2)	2.8 (0.4)		16/20	p<0.005
Wisconsin Card Sorting						
Categories completed	#	6.3 (0.9)	6.6 (0.9)	0/0	20/20	n.s.
perseverative errors	#	2.2 (2.1)	1.5 (2.5)	0/0	20/20	p<0.8
4. Attention						
Alertness (TAP) ¹						
w/o warning tone	t-value	49.8 (15.0)	52.5 (14.3)	22.2/10	18/20	n.s.
w/ warning tone	t-value	52.6 (17.5)	55.6 (12.3)	11.1/5	18/20	n.s.
Phasic alertness	t-value	53.4 (9.3)	55.1 (10.1)	5.6/5	18/20	n.s.
Go/NoGo (TAP) ¹	t-value	50.9 (11.7)	51.5 (10.7)	5.6/15	18/20	n.s.
5. subtests WAIS						
Vocabulary	Points	9.6 (3.6)	13.0 (2.9)	21.1/0	19/20	p<0.005
Similarities	Points	11.5 (3.5)	13.5 (2.1)	10.0/0	20/20	p<0.08
Picture Completion	Points	11.1 (3.9)	9.9 (3.3)	5/15	20/20	n.s.
Block Design ¹	Points	11.3 (2.1)	12.1 (3.0)	0/5	16/20	n.s.

¹ Because of marked motor symptoms 4 patients were not tested on block-design and the Ruff figural fluency test. Because of technical problems 2 patients did not receive testing with the TAP.

² At or below the 10th percentile if not specified differently. ³Limits to impairment: digit forward=4, backward=3, FAS total <30, and <10 for single letters, Reading Span Test: words >6, last run =0.

Table 3 – Overview of the behavioral results of the ERP tasks.

n=17	Go/Nogo Spatial				Go/Nogo Figural				
	Performance	Hit (%)	CR (%)	d'	beta	Hit (%)	CR (%)	d'	beta
ALS- Patients	96.2 (9.6)	97.8 (3.2)	3.78	1.57	97.8 (2.9)	95.9 (3.6)	3.75	.59	
Controls	98.5 (3.0)	98.1 (1.7)	4.24	.82	96.8 (6.2)	94.1 (8.4)	3.41	.61	
Reaction Times	Hit (ms)				Hit (ms)				
ALS- Patients	487 (73)				603 (47)				
Controls	449 (54)				605 (44)				
n=11	WM Spatial				WM Figural				
	Performance	Hit (%)	CR (%)	d'	beta	Hit (%)	CR (%)	d'	beta
ALS- Patients	76.8 (13.0)	94.5 (10.3)	2.33	2.74	65.4 (12.7)	92.4 (9.0)	1.82	2.57	
Controls	83.7 (9.9)	97.5 (1.6)	2.94	4.21	67.5 (14.4)	92.5 (4.8)	1.89	2.54	
Reaction Times	Hit (ms)				Hit (ms)				
ALS- Patients	461 (67)				522 (66)				
Controls	493 (65)				550 (73)				

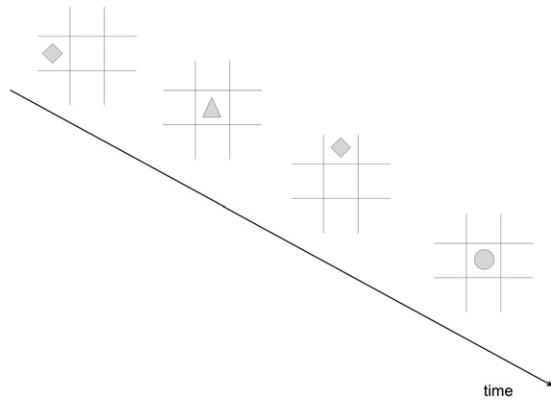


Fig. 1 – Illustration of stimulus setup. Each stimulus comprised the presentation of one of nine geometrical shapes at one of nine positions within a 3 x 3 matrix. Depending on the instructions, participants had to press a button either when the shape of the current trial was the same as the shape of trial n-2 (regardless of position) or when the position of the current trial was the same as the position of trial n-2 (regardless of shape). Thus, either figural or spatial information were crucial. In two further conditions, a set of positions or shapes was designated targets for the given run. The third stimulus would be a target under figural instructions, whereas the fourth stimulus would be a target under spatial instructions.

centro-parietal positivity with a peak latency of approximately 400 ms which was more pronounced in the control group.

The ALS group showed a marked positivity for the non-targets which was widely distributed and present for frontal, central and parietal sites. By contrast, the controls showed only a more circumscribed central differentiation between non-targets and targets.

The statistical findings are summarized in Table 4. A main effect of material was observed for all three time-windows. The more prominent positivity for the non-targets in the ALS patients was reflected by a group x task x stimulus interaction.

3. Discussion

The starting point of this investigation involved previous findings suggesting that executive functions, in particular working memory and fluency, are impaired in ALS (Abrahams et al., 2000; Frank et al., 1997). To further elucidate such deficits, we investigated behavioural and electrophysiological effects in an n-back design and also manipulated the information (spatial vs. figural) relevant for the task. In addition, neuropsychological measures were obtained.

Whereas the neuropsychological examination did not reveal working memory deficits in ALS (Digit Span, Reading Span Test), verbal fluency was found to be impaired. Further indications of problems in executive functions were an increased number of perseverative errors in the Wisconsin Card Sorting test and a reduced use of strategies in the Ruff-Figural Fluency Test.

For the ERP-study two 2-back paradigms were used which differed only in the instructions (spatial vs. figural). Remarkably, a significant proportion (6 of 17) of ALS patients were

unable to perform the working memory tasks, in particular when spatial information was relevant (see result section for further information). Thus, only 11 patients could be included in the analysis. For this set of patients again an impaired performance was seen for the spatial task, whereas for the figural task performance was comparable to the control participants. This is best seen when hit and false alarm rates are used to compute d' , a measure from signal detection theory (Green and Swets, 1966) reflecting the detectability of a stimulus independent of the participant's response criterion which is captured by the parameter beta. Thus, the high proportion of ALS-patients unable to perform the n-back working memory tasks and the difference in d' corroborate earlier findings of working memory deficits in ALS (Abrahams et al., 2000; Frank et al., 1997). Obviously, the question arises why n-back tasks appear to be more sensitive in ALS than the span tasks that are often used in clinical neuropsychological examinations to assess working memory. Conway et al. (2005) in a review of working memory tasks conclude that n-back tasks are more dynamic, because they "require subjects to monitor a continuous stream of stimuli ... and to respond according to only a subset of the stimuli presented. The subjects in these tasks must, therefore, continuously update their mental representation of the target items while also dropping now irrelevant items from consideration." Miyake et al. (2000) in a factor-analytic approach towards executive functions pointed out that the updating function (as required by n-back tasks) "goes beyond the simple maintenance of task-relevant information in its requirement to dynamically manipulate the contents of working memory." Unlike simple span tasks, n-back tasks require to actively manipulate relevant information in working memory, rather than passively store information. We believe that this updating feature has made the n-back task a sensitive tool for the assessment of executive dysfunction in ALS (Abrahams et al., 2000) but also in other neuropsychiatric disorders such as schizophrenia. With regard to the latter condition, Glahn et al. (2005) reviewed the available neuroimaging data and found evidence for bilateral reductions in activity of the dorsolateral prefrontal cortex (DLPFC) and increases in anterior cingulate and frontal pole activity in patients relative to controls in n-back tasks. The demand on DLPFC-supported functions, which appear impaired in both, ALS and schizophrenia, apparently makes the n-back task particularly sensitive to deficits in these conditions.

Behavioral results of the present study further suggest that spatial information seems difficult for these patients. The brain potentials showed a difference as a function of the material which had to be stored in working memory (figural vs. spatial) in line with earlier studies finding a material-specific modulation of ERPs (Bosch et al., 2001; McEvoy et al., 1998; Mecklinger and Meinshausen, 1998; Mecklinger and Pfeifer, 1996). Interestingly, ALS patients showed a pronounced stimulus effect (target vs. non-target) in the spatial task which was reflected in an interaction of group x task x stimulus x electrode site (Table 4, Fig. 3). This again suggests that processing of spatial information is altered in ALS. Previous imaging and lesion studies have suggested that the right dorsolateral prefrontal cortex is involved in spatial working memory (Bor et al., 2006) which further implies that this region is functionally impaired in ALS.

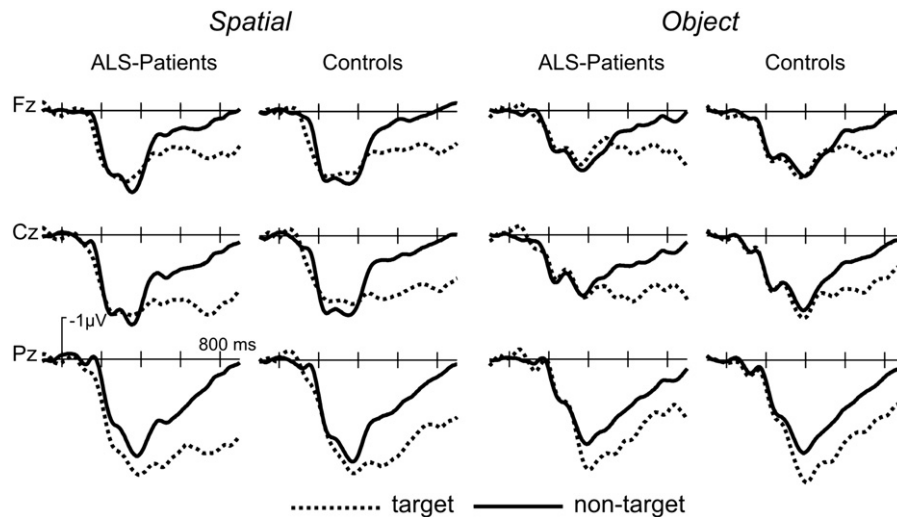


Fig. 2 – Group averages from the midline electrodes for the working memory task. Targets (i.e. stimuli that matched stimulus n-2 with respect to either shape or position) were associated with a positive shift. Whereas the difference between targets and non-targets was similar for ALS patients and controls in the figural task, the former showed a more pronounced effect the parietal electrode in the spatial task.

While the performance of both groups was similar, the ERPs in the Go/Nogo control task revealed a marked difference between patients and controls. Whereas ALS-patients showed a more prominent positivity for non-targets than targets for the three midline electrodes, controls only showed a localized non-target / target difference at the central site. The positivity of non-targets has been termed nogo-P3 (Fallgatter and Strik, 1999; Fallgatter et al., 1998; Strik et al., 1998). An anteriorization of the nogo-P3 has been described in various neuropsychiatric conditions for which an impairment of frontal cortex, in particular of inhibitory functions, has been postulated (Johannes et

al., 2001). In a different cohort of ALS patients using a stop-paradigm (Logan and Cowan, 1984), we found abnormalities of frontal brain potential components indicative of inhibitory dysfunction (Thorns et al., 2010). The more pronounced anteriorization of the nogo-P3 in the current data set may similarly

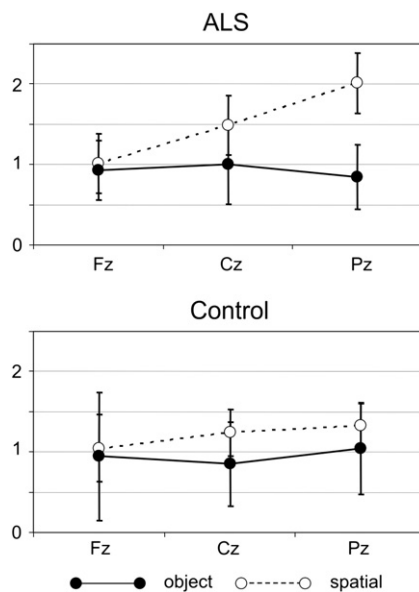


Fig. 3 – Working memory task. Topographical distribution for the target minus non-target difference (mean amplitude 600–800 ms). For the spatial task ALS patients show a pronounced parietal difference that was not seen in the controls.

Table 4 – ANOVAs of mean amplitude measures for the two tasks.

	df	200-400		400-600		600-800	
		F	p <	F	p <	F	p <
WM (n=11)							
Group	1,20	2.51		0.01		0.1	
Mat	1,20	0.49		21.51	.0002	54.37	.0001
Group x Mat	1,20	0.04		1.28		1.2	
Stim	1,20	9.9	.006	41.47	.0001	11.34	.004
Group x Stim	1,20	0.29		0.08		0.07	
Mat x Stim	1,20	4.47	.05	14.31	.002	2.53	
Group x Mat x Stim	1,20	0.05		0.01		0.73	
Group x Mat x Stim x El	1,40	4.2	.03	6.8	.003	5.9	.006
Go / Nogo (n=17)							
Group	1,32	0.75		1.9		0.16	
Mat	1,32	15.00	.0005	27.19	.0001	9.33	.005
Group x Mat	1,32	3.45	.08	0.64		0.47	
Stim	1,32	2.43		28.61	.0001	8.31	.008
Group x Stim	1,32	0.48		1.28		0.19	
Mat x Stim	1,32	2.39		4.21	.05	3.75	.07
Group x Mat x Stim	1,32	1.22		5.81	.03	0.38	
Group x Mat x Stim x El	2,64	0.73		1.32		0.88	

Mat: material (spatial vs. figural), Stim: target vs. non-target (Go vs. Nogo), El: electrode site (Fz, Cz, Pz)

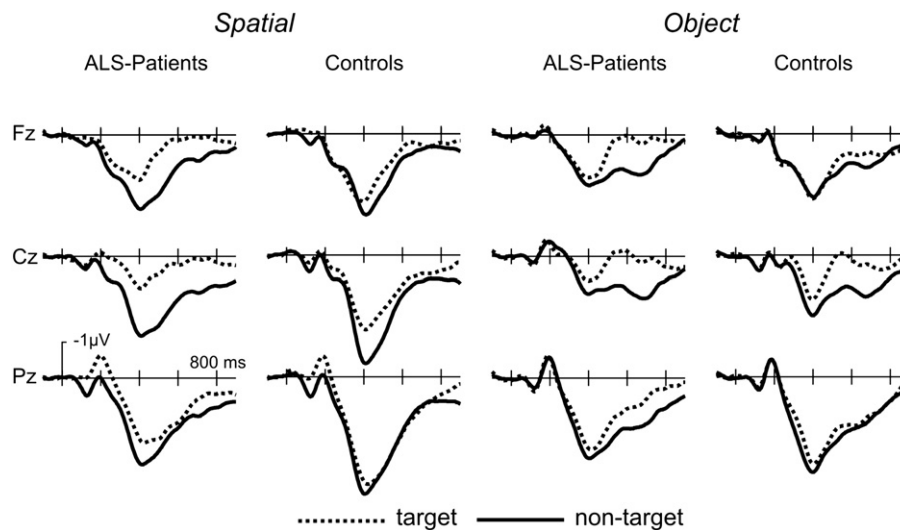


Fig. 4 – Group averages from the midline electrodes for the Go / Nogo task. A typical nogo-P3 component was observed. ALS patients showed a marked difference between non-targets and targets in particular for frontal electrodes.

reflect a disturbed inhibition of prepotent reactions (Fallgatter and Strik, 1999).

It is worth noting that we did not obtain main effects of the group factor in the ERP analyses of the present study. Rather, the effects of ALS emerged in the form of interactions with stimulus, task and topography factors. This implies that the pathology did not change ERP responses “across the board” but in a specific, task dependent manner which is why we felt justified to provide a functional interpretation of our findings.

To summarize, the current study revealed impairments of working memory functions in ALS patients in particular concerning spatial information. Moreover, the Go / Nogo task showed a group difference for nogo trials suggesting a deficit in the inhibition of prepotent reactions. Thus, the electrophysiological results pointed to an impaired function of the dorso-lateral prefrontal cortex in ALS. The rather high proportion of ALS patients performing in the pathological range in the Controlled Oral Word Association test (Table 2) similarly suggests a frontal impairment. Behavioral and cognitive impairment has increasingly been recognized (e.g., Flaherty-Craig et al., 2009; Frank et al., 1997; Lomen-Hoerth et al., 2003; Ludolph et al., 1992; Massman et al., 1996; Murphy et al., 2007; Ringholz et al., 2005). In two large studies, for example, the proportion of mild cognitive impairment has been reported to be 36% (Massman et al., 1996) and 51% (Ringholz et al., 2005), respectively. Recently, Strong et al. (2009) in consensus paper suggested to assess cognitive and behavioural dysfunction in ALS on a separate axis in a multiaxial classification scheme. These authors distinguished 5 types of cognitive / behavioural involvement in ALS: (1) ALS patients cognitively and behaviourally intact; (2) ALS patients with mild cognitive impairments; (3) ALS patients with mild behavioural impairments; (4) ALS with a full-fledged fronto-temporal dementia; (5) ALS with other non FTD-forms of dementia. There is an ongoing discussion in the literature (summarized, for example, in Zago et al., 2011), whether these 5 types should be viewed as a continuum and whether patients may progress from one type to the next. The present investigation used a sample of consecutive ALS

patients seen in our neurological department and did not aim to include only patients with clear neurocognitive deficits. It nevertheless suggested profound changes in prefrontal functioning in ALS and further implies that the inclusion of neurophysiological measures might increase sensitivity for prefrontal dysfunction. Further studies are needed to assess neurophysiological and brain imaging markers of prefrontal dysfunction in relation to the different subtypes of ALS suggested by Strong et al. (2009).

4. Experimental procedures

4.1. Participants

The study was approved by the ethical committees of the University of Magdeburg.

All participants were German native speakers and had normal or corrected-to-normal vision. Twenty adults (seven woman, mean age 56.6 years) with the diagnosis of ALS as defined by the modified El Escorial criteria (Brooks et al., 2000) participated in this study. Twenty neurological healthy matched participants (eight woman, mean age 55.4) were recruited and were closely matched to the patients with respect to age, gender, school education and handedness. Table 1 gives the demographic and clinical characteristics of both groups. All participants were informed about the methods and gave written consent before they participated in the study.

4.2. Neuropsychological testing

The test battery included subtests of the German version of the Wechsler intelligence scale (Vocabulary, Similarities, Block Design and Picture Completion). Verbal memory performance was tested with the VLMT, a German version of the Rey Auditory Verbal Learning Task (RAVLT, Lezak et al., 2004) and the Recurring Words test (Sturm and Willmes, 1999). Non-verbal memory was tested with the Recurring Figures test (Sturm

and Willmes, 1999). To test working memory function, we included the Digit Span and the Reading Span Test (Lezak et al., 2004). To address executive frontal functions, the Wisconsin Card Sorting Test (Lezak et al., 2004), the Ruff Figural Fluency test (Ruff et al., 1987) and the Controlled Oral Word Association Test (Lezak et al., 2004) were included. Attention was tested using subtests Alertness and Go/NoGo from a computerized battery of attention tests (TAP) (Zimmermann and Fimm, 2002). The duration of the neuropsychological testing was between two and three hours.

Based on previous experience of our group (Frank et al., 1997), we attempted to select mostly tests with no or minimal motor requirements. Virtually no demands on motor dexterity are made by the following tests of our battery: Vocabulary, Similarities, Picture Completion, VLMT, Recurring Words, Recurring Figures, Digit Span, Reading Span, Controlled Oral Word Association, Wisconsin Card Sorting. The computerized tests Alertness and Go/NoGo required only minimal motor functions as the index finger of the response hand rested on a sensitive response button and only minimal force had to be exerted to give a response. Please note (see Table 2) that we chose to not test 4 patients with marked motor symptoms on the Ruff Figural Fluency test and the Block Design test, as these require manual dexterity and we did not want to put motor-impaired patients at a disadvantage in these tests.

4.3. Event-related potentials

4.3.1. Experimental procedure

The ERP experiments were performed on a different day than the neuropsychological testing. Both sessions were conducted within 10 days. The ERP session comprised four different blocks with a duration of about 10 minutes. The stimuli were identical for the four blocks and were made up of ten different red geometrical symbols (circle, square, diamond, downward pointing triangle, upward pointing triangle, all forms presented either as outline figures or filled figures). The geometric figures were presented in a randomized order in a three x three matrix on a black background. The visual angle of the matrix was 11° in height and width. The matrix was presented constantly and each figure was presented with duration of 800 ms with a ISI of 1400–2000 ms (Fig. 1). The participants were required to give a response or to withhold a response depending on the type of instruction. The ratio of targets and non-targets was 1:3 in each of the conditions: *Spatial Go/NoGo*: The participants were required to press a button with the right index finger as soon as possible when a symbol occurred in one of three target positions of the matrix (positions 3, 7, or 8) irrespective of the geometric form; *Figural Go/NoGo*: Participants had to press a button when one of three symbols occurred (filled downward triangle, open square or filled circle) irrespective of position. *Spatial Working Memory*: A two-back paradigm was used, in which participants had to respond to the present stimulus if its position was identical to the position of the stimulus seen two trials before. *Figural Working Memory*: Here, participants were required to respond to the present stimulus if the symbol was identical to one seen two trials before. Each block started with a training sequence. The total duration of the ERP experiment was around two hours including instructions, application of electrodes and training.

4.4. EEG recording and analysis

Electroencephalography (EEG) signals were registered with a digitization rate of 250 Hz and filtered with a band pass of 0.01–70 Hz. Nineteen tin electrodes mounted in an elastic cap were positioned according to the 10/20 system (Fp1/2, F3/4, C3/4, P3/4, O1/O2, F7/8, T3/4, T5/6, Fz, Cz, Pz). Bio-signals were offline re-referenced to the mean of the activity at the two mastoid processes. Eye movements were recorded in order to allow for later offline correction using the Second Order Blind Identification (SOBI) (Joyce et al., 2004). All electrode impedances (EEG and EOG) were kept below 5 kΩ.

From the continuous signal epochs were created of 1024 ms duration, starting 100 ms prior stimulus onset. These epochs were monitored for remaining artifacts, such as movements or amplifier blocking, by an automated procedure. Trials including artifacts were rejected from further analysis. By averaging the remaining artifact-free epochs per condition the ERPs were derived. Waveforms were quantified by mean amplitude measures in three different time-windows (200 – 400 ms, 400 – 600 ms and 600 – 800 ms). These measures were subjected to repeated measures analysis of variance that crossed the between factor Group (ALS patients vs. control group) and the within factors Memory (2-back vs. Go/NoGo), Task (figural vs. spatial), Stimulus (target vs. non target) and ‘Electrode sites’ (Fz, Cz, Pz). The Greenhouse-Geisser correction for inhomogeneity of covariance was applied whenever an evaluated effect had more than one degree of freedom in the numerator. Reported p-values are corrected.

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