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REVIEW ARTICLE

The cognitive profile of amyotrophic lateral sclerosis: A meta-analysis

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Abstract

We aimed to clarify the profile of cognitive impairment in ALS, by meta-analysis of published studies. Criteria for inclusion were: ALS diagnosed according to El Escorial criteria; control group matched for age and education; correction for bias due to motor impairment or dysarthria; no dementia in patients and controls. Effect sizes reflecting a difference in neuropsychological performance between ALS patients and controls were calculated for 12 cognitive domains. The effect of demographic and clinical variables (age, disease duration, site of onset) on cognition was assessed in a moderator analysis. Of 48 eligible articles, 16 studies encompassing 554 ALS patients were included. Significant effect sizes were found for the Mini Mental State Examination ($d=0.8$), immediate verbal memory ($d=0.5$), visual memory ($d=0.4$), fluency ($d=0.5$), psychomotor speed ($d=0.7$), language ($d=0.5$) and executive functioning ($d=0.3$). The results of the latter three domains are less reliable due to the possibility of publication bias. Psychomotor speed, and to a lesser extent fluency, may have been influenced by motor impairment, despite attempts to correct for motor slowness. In conclusion, the diversity of cognitive problems in ALS seems greater than was previously thought. ALS patients may suffer from cognitive impairment in multiple domains, including memory dysfunction.

Key words: *Amyotrophic lateral sclerosis, cognitive impairment, meta-analysis*

Introduction

There is increasing evidence that cerebral regions outside the motor cortex are afflicted in a proportion of ALS patients (1–10). About 5–15% of ALS patients have severe cognitive changes with features consistent with frontotemporal dementia (ALS-FTD) (4). Mild cognitive impairment is found in 33–51% of ALS patients (2,4). A consistent finding is impairment of verbal fluency, a function that heavily taxes prefrontal areas (1,3,5,7,11–14). However, studies addressing other prefrontal functions (5,6,12,15–19) or investigating memory (2,4,7,15,20–25), language (3,5,7,11,12,18,23) or visuospatial functions (2,3,7,22,23), are heterogeneous and often contradictory.

The inconsistency of these findings is probably caused by small sample sizes which may have precluded the detection of subtle cognitive changes,

or by differences in psychometric paradigms such as lack of uniformity in the cognitive tests used and differences in the way neuropsychological testing is adapted to motor impairments of the patients.

Regarding clinical variables, bulbar onset ALS (13,19,26) and disease severity (27) are thought to be associated with cognitive impairment in ALS. The extent to which these disease variables contribute to cognitive dysfunction is less clear (2,16,27).

The main objective of this meta-analysis is to clarify the magnitude and pattern of cognitive impairment in non-demented ALS patients. A second objective is to analyse the effects of clinical variables on the cognitive outcome measures.

Insight into the cognitive functioning of ALS patients will contribute to understanding the disease process. In addition, it may be of use in developing

cognitive screening measures in these patients (13,28).

Methods

Literature search

The search engines of Medline (1966–2008), PsycINFO (1970–2008), EMBASE (1970–2008) and Web of Science (1988–2008) were used to identify all articles suitable for inclusion in the meta-analysis. The following key words were used: ‘amyotrophic lateral sclerosis’ or ‘ALS’ or ‘motor neuron(e) disease’ or ‘MND’ in combination with ‘cognition’, ‘cognitive impairment’, ‘cognitive deficits’, ‘memory’, ‘executive function’, ‘language’ or ‘neuropsychological’. The search was completed in October 2008 and was limited to articles written in English, French and German. Relevant references in articles and reviews were also considered for inclusion.

Inclusion criteria

Included studies had to have a cross-sectional design. From longitudinal studies, only data from the first neuropsychological evaluation were used. For eligibility the studies had to meet the following criteria:

- The diagnosis of ALS was made according to validated clinical criteria (El Escorial criteria (29,30)). If diagnostic criteria were not reported, studies were still considered for inclusion if relevant clinical data were reported that allowed the reviewers to confirm the diagnosis of ALS.
- A control group matched for age and education had to be included, or, when age and education was not matched, normalized test scores (adjusted for age and education) had to be used.
- If the study sample included motor neuron disease (MND) patients, with MND being defined as either lower motor neuron disease or a combination of lower and upper motor neuron involvement, these two patient groups had to be analysed separately.
- To correct for bias due to motor impairment or dysarthria, the neuropsychological tests or test battery had to be adapted, or patients with a severe dysarthria or other severe motor impairment had to be excluded.
- Patients and controls had to be free of dementia. The diagnosis of dementia was made according to standard clinical criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM); American Psychiatric Association, 1994) (31) or when the patients’ performance fell below a cut-off on a screening measure for dementia. If the study

sample included demented and non-demented patients, the results of non-demented patients had to be analysed separately in the original article in order to allow inclusion.

- At least one standardized neuropsychological test had to be used.
- Mean test scores and standard deviations had to be presented for both the patient group and the control group, or other statistics had to be reported that allowed conversion to effect sizes (e.g. *t*-values or *z*-scores).
- When different papers reported data concerning the same group of patients, the study with the largest sample was included in the analysis.

Outcome measures

Across studies multiple cognitive domains were assessed and many different tests were used for measurement. Therefore, we clustered the neuropsychological tests into functional domains to facilitate interpretation of the data. Categorization of tests into functional domains was based on the description of task characteristics and the corresponding area of cognitive functioning described in two standard textbooks of neuropsychological assessment (32,33). Tests from the individual studies were categorized into the following 12 functional domains: language, immediate verbal memory, delayed verbal memory, visual memory, fluency, executive functioning, attention, verbal intelligence, psychomotor speed, visuoperceptual functions, visuoconstructive skills and global cognitive ability. In the latter domain the Mini Mental State Examination (MMSE) was the only test used.

Appendix 1 lists the tests that were included in each cognitive domain.

Moderator variables

We identified demographic and clinical variables such as age, years of education, bulbar versus limb onset, and disease duration (which is generally the patient’s statement of the number of months after the onset of the first symptom) as moderator variables, and we investigated their influence on cognitive domains using a categorical analysis. For the variables included in moderator analyses, the division of groups was based on a median split (age, disease duration) or a mean split (site of onset), where appropriate. As the reported information about disease severity was heterogeneous and only available in a minority of the studies this moderator was left out of the analyses. The assessment of the effect of respiratory dysfunction on cognitive impairment was not possible due to uncertainty about either the inclusion or exclusion of patients with respiratory dysfunction in the majority of studies.

Calculation of effect sizes and statistical analysis

In each study the effect-size Hedges' g (34) was calculated. Hedges' g is the mean difference between ALS patients and controls divided by the pooled standard deviation (SD). When means and SDs were not presented, effect sizes were calculated from other reported statistics (i.e. z -values or t -values) using the methods described by Rosenthal (35). From the effect sizes obtained in individual studies a pooled d -value, weighted for the sample sizes of the individual studies, was calculated for each of the 12 cognitive domains. By convention, effect sizes of 0.2, 0.5, and 0.8 are considered small, medium and large, respectively (36). A positive direction of effect sizes implies impaired cognitive performance. When studies used more than one measure in a particular cognitive domain, an averaged effect size was computed. Thus, each study added only one effect size to each functional domain for the final analysis. This strategy was used to avoid one study dominating the results of a single domain. Given the diversity of both clinical variables and cognitive assessments, we expected heterogeneity in the results. Consequently, we considered a random-effects model to be appropriate (37). Heterogeneity of the data was assessed using the χ^2 statistic Q and the I^2 index. The I^2 index was calculated using the equation $(Q - df) / Q \times 100\%$, where df means the degrees of freedom ($=$ number of studies $- 1$). The I^2 index reflects the percentage of total variation across studies that is due to heterogeneity rather than chance (38). A value of 0% indicates no heterogeneity. Finally, we calculated in the moderator analyses the Q_w and Q_b statistics. Q_w signifies the degree of heterogeneity of studies within a moderator category, whereas the Q_b statistic refers to a difference in the pooled effect sizes between moderator categories. In all analyses statistical uncertainty was expressed in 95% confidence intervals. Data were analysed in MetaWin, version 2.0 (39).

Publication bias

Because studies with non-significant outcomes are less likely to be published, the use of data from published studies may bias results towards a significant mean effect size (35). To estimate the number of negative studies that would be necessary to render the results non-significant, the fail-safe number (N) was calculated for each pooled effect size, thereby examining the possibility of publication bias (35). The *fail-safe* N is the number of non-significant, unpublished, or missing studies that would need to be added in order to change the results of the meta-analysis from significance to non-significance. In addition, we calculated the tolerance level ($5k + 10$, where k is the number of studies used to calculate the effect size) as a conservative estimate of existing unpublished or unretrieved studies

against which to test a fail-safe calculation. If the *fail-safe* N is large relative to the tolerance level, the observed result is considered a reliable estimate of the true effect.

Results

Identification of studies

The literature search identified 48 neuropsychological studies in ALS patients. Appendix 2 lists the excluded studies and the reasons for exclusion. As a result, 16 studies were eligible for inclusion in the meta-analysis. The demographic and clinical characteristics of these studies are shown in Table I.

Participation and study characteristics

The 16 included studies encompassed a total of 554 non-demented patients with possible, probable or definite ALS (El Escorial criteria). Probable or definite ALS patients were evaluated in 13 studies; possible ALS patients were included in three studies. The mean age was 57.3 years. In 10 studies the proportion of bulbar and limb onset ALS patients was reported. More bulbar than limb onset patients were included in three studies. Eight studies reported information on duration of education. In seven studies disease severity scales or subscales were used measuring bulbar or limb involvement, or both (Appel score (40), Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) (41), ALS severity scale (42), Norris score (43)). According to these scales most studies had included ALS patients with mild to moderate disease severity.

Correction for diminished speech rate or motor speed, or both, was accomplished by several means. ALS patients with severe dysarthria or severe upper limb motor impairment, or both, were excluded in 13 studies from all or some tests (1,3,5,6,11,12,15,19,23,25,44–46). In addition, in five studies a test battery was chosen to minimize effects of impaired motor function (4,7,24,45,46). In three studies a fluency index was presented, which adjusts for slower writing or speaking (7,11,19). Severe depression may influence cognitive performance. None of the mean depression scores presented in nine of the 16 studies included in this meta-analysis showed values corresponding to clinically relevant depression (3,4,7,11,12,19,23–25). The small proportion of studies (5/16) providing useful statistics of depression scales, precluded a moderator analysis of depression as a clinical variable. Seven studies did not report on medication use in their patient groups (4,6,11,12,15,45,47). The use of psychoactive medication was an exclusion criterion in six studies (1,5,7,19,23,25). In two studies amitriptyline (3), and benzodiazepines and anti-depressants (24) were

Table I. Demographic and clinical characteristics of studies included in the meta-analysis.

Study, ref.	<i>n</i>	ALS categories	Onset bulbar/limb	Age, years (SD or range)	Duration (months)	Respiratory dysfunction as exclusion criterion	Disease severity (mean and range or SD)	Education (years)
1. David (1986), 15	14	Poss, prob, def.	7/7	53.7 (–)	17.8	No	–	–
2. Gallassi (1989), 1	18	Poss	–	57.9 (11.3)	17.2	No	–	–
3. Ludolph (1992), 12	17	Poss	13/8*	58.5 (11.3)	–	Yes	Norris: 60–94 (range)	–
4. Kew (1993), 5	16	Prob, def	–	59.1 (37–71)	21.4	No	–	–
5. Abe (1997), 6	18	ALS	–	53.7 (36–67)	25.3	Yes	NBS 25, NLS 25	–
6. Abrahams (1997), 19	52	Poss, prob	24/28	57.2 (–)	22.3	No	–	13.3
7. Strong (1999), 3	13	Def	8/5	54.2 (9.6)	21.1	Yes	–	–
8. Vieregge (1999), 25	8	Prob, def	7/1	58.4 (43–69)	–	No	–	–
9. Abrahams (2000), 11	22	Poss	–	55.8 (10.2)	25.9	Yes	ALS s.sc. 32 (22–39)	14.1
10. Hanagasi (2002), 23	20	Prob, def	0/20	53 (11)	18.3	No	ALSFRS 33 (29–36)	8.7
11. Abrahams (2004), 7	28	Prob, def	–	57.3 (11.1)	21	Yes	ALS s.sc. 33	12.7
12. Kilani (2004), 24	19	Prob, def	2/17	58.5 (10.1)	24	No	NBS 43 NLS 33	12
13. Ringholz (2005), 4	262	Prob, def	86/156*	58.8 (14.4)	16.5	No	Appel 69 (21)	13.3
14. Rottig (2006), 45	15	Prob, def	0/15	60.8 (8)	30.3	Yes	–	–
15. Gibbons (2007), 47	16	Prob, def	3/13	62 (10)	24	Yes	–	13
16. Mezzapesa (2007), 46	16	Prob, def	–	58.6 (10.2)	38.1	No	–	8.7

n = number of patients reported in the studies. ALS categories: poss = possible; prob = probable; def = definite ALS; according to El Escorial criteria (Brooks, 1994; Brooks et al., 2000) (<http://www.wfnals.org/guidelines/1998elescorial/elescorial1998.htm>). No, or – = no information presented. Disease severity scales: Norris: maximum = 100. NBS = Norris bulbar scale normal value 63; NLS = Norris limb Scale: normal value 39. ALS s.sc. = ALS severity scale: low scores represent functional impairment; maximum = 40. ALSFRS = ALS functional rating scale maximum score 48, minimum score 0 (= maximum dysfunction); respiratory, limb and bulbar items are included. Appel = Appel ALS rating scale: normal function = score 30, maximum dysfunction = score 164.

* In these two studies the proportion of bulbar and limb onset was presented for the complete sample while neuropsychological examinations were performed in 81% (Ludolph et al., 1992) or 96% (Ringholz et al., 2005) of the complete patient sample.

used by a majority of the patients, of whom none had a psychiatric diagnosis.

Effect sizes

Effect sizes could be calculated from means and SDs in 13 studies (87%). In three studies (1,3,46) effect sizes were calculated from *z*- or *p*-values. Pooled effect sizes (*d*-values) for each cognitive domain are shown in Table II and Figure 1.

A large, statistically significant effect size was found for the MMSE (0.8). Six domains showed significant medium effect sizes, i.e. immediate verbal memory (0.5), visual memory (0.4), fluency (0.5), psychomotor speed (0.7), language (0.5), and executive functioning (0.3). The effect sizes of the other cognitive domains were not significantly different from controls.

Publication bias

The *fail-safe N* and the tolerance level were calculated for cognitive domains that showed a significant difference between ALS patients and controls (Table II). Except for language, executive functioning and psychomotor speed, the *fail-safe N* exceeded the estimate of unpublished studies, indicating that the

observed effects cannot be explained by publication bias.

Influence of moderator variables

Owing to insufficient information from some of the studies, the number of studies available for calculating the influence of the moderator variables on some of the cognitive domains (see Tables III, IV and V) was fairly small or calculation was not possible.

The influence of the moderator variables was calculated in the domains that showed significant changes in the primary analysis. Visual memory impairment in ALS patients was related to age (Q_B significantly different between groups), with more impairment in the elderly patients (effect size larger for older group). Data derived from six studies showed that the MMSE was lower in younger patients. In other cognitive domains no effect of age on effect sizes was shown (Table III). Seven studies provided information on years of education of their patient and control samples. In the cognitive domains for which calculation of the influence of education on cognitive performance was possible (MMSE, immediate verbal memory and executive functioning), no influence was shown.

Table II. Pooled weighted effect sizes, confidence intervals and heterogeneity statistics for each domain of cognitive functioning.

Domain	K	n patients	Nd	D	95% CI	Q	p (Q)	I ²	Fail-safe N	Tolerance level‡
MMSE	6	350	6	0.82*	0.24 to 1.40	6.62	0.25	9	113	40
Language	7	155	10	0.53*	0.09 to 0.97	6.42	0.38	7	40	45
Verbal IQ	5	105	5	0.25	0.17 to 0.68	1.26	0.87	0	–	–
Immediate verbal memory	12	497	17	0.51*	0.16 to 0.86	6.75	0.82	0	196	70
Delayed verbal memory	7	371	8	0.47	–0.02 to 0.97	3.47	0.84	0	–	–
Visual memory	11	446	16	0.43*	0.01 to 0.84	4.35	0.93	0	146	65
Fluency	12	213	22	0.52*	0.31 to 0.73	9.35	0.59	0	133	70
Executive functioning	11	194	19	0.34*	0.12 to 0.56	9.36	0.50	0	40	65
Psychomotor speed	6	99	8	0.68*	0.30 to 1.06	2.16	0.83	0	38	40
Attention	5	116	15	0.58	–0.22 to 1.40	4.82	0.31	17	–	–
Visuo-perceptual functions	4	93	6	0.17	–0.36 to 0.70	4.14	0.39	28	–	–
Visuoconstructive skills	4	67	5	0.40	–0.47 to 1.27	3.40	0.33	12	–	–

k=number of studies; Nd=number of effect sizes; d=mean weighted effect size; CI=confidence interval; Q=within domain heterogeneity; p (Q)=p-value for heterogeneity; I²=percentage of heterogeneity due to study differences [(Q – df)/Q x 100%]. ‡ Tolerance level (i.e. estimated number of existing unpublished studies, 5k + 10; Rosenthal, 1991). A random effects model was used to produce pooled effect sizes. † Negative I² values are set equal to zero as recommended by Higgins et al. (2005). * p < 0.05. If the Fail-safe N is large compared to the tolerance level the effect can be considered a reliable estimate with respect to publication bias due to unpublished, not significant studies.

ALS patients with a longer disease duration showed better results on immediate verbal and visual memory compared to patients with shorter disease duration. No influence of disease duration was found for the MMSE, language, fluency, psychomotor speed and executive function (Table V). If the proportion of bulbar patients per study cohort was taken into account, performance in the following domains was worse in studies with a lower number of bulbar onset ALS patients: immediate verbal memory, visual memory and executive functioning (Table IV).

Discussion

This meta-analysis confirms that non-demented ALS patients may suffer from decreased cognitive abilities. Our findings corroborate previous observations that motor neuron disease is not solely confined to the upper and lower motor neuron tracts per se. Apparently, cognitive domains subserved by non-motor zones in the cerebral cortex are affected in ALS patients as well. In decreasing order of effect sizes the following domains are impaired in ALS patients: MMSE, psychomotor speed, fluency,

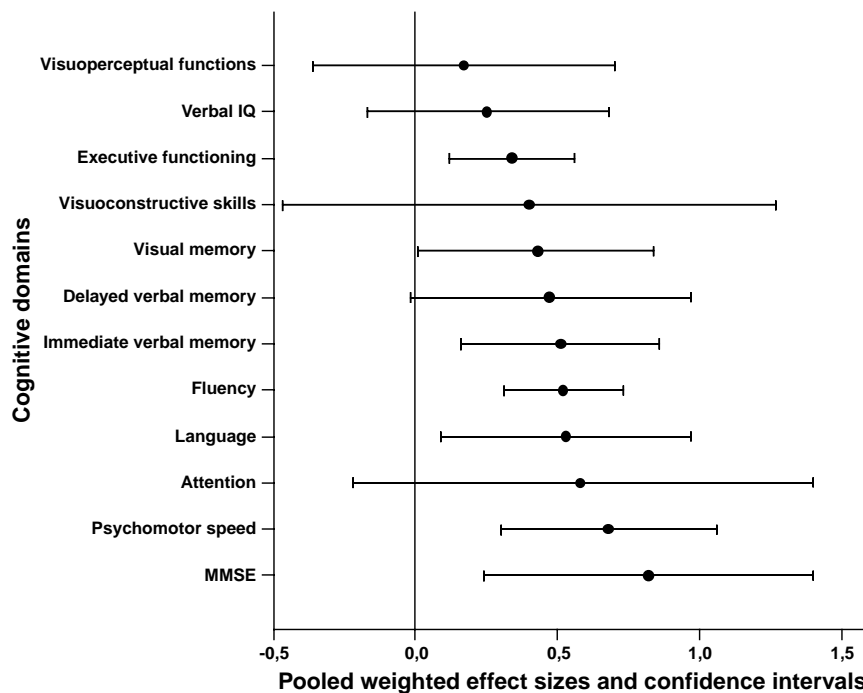


Figure 1. Pooled weighted effect sizes (●) and 95% confidence intervals of the cognitive domains calculated from available studies. A positive effect size indicates a worse cognitive performance of ALS patients compared to controls for that domain. If the horizontal line does not bracket the vertical bar (0), the effect is significant at the 0.05 level.

Table III. The influence of age on effect sizes.

Domain	Age (years)	k	Samples size	<i>d</i>	95% CI	Q _w	Q _B
MMSE	<57.3	2	38	1.26	-2.04 to 4.56	7.10*	
	≥57.3	4	322	0.68	0.37 to 0.99	5.21	4.33*
Language	<57.3	2	42	0.81	2.21 to 3.83	3.87*	
	≥57.3	5	97	0.38	0.01 to 0.78	6.55	2.39
Immediate verbal memory	<57.3	3	83	0.43	0.33 to 1.18	6.35*	
	≥57.3	9	398	0.80	0.61 to 0.91	28.55#	3.67
Visual memory	<57.3	3	72	0.33	-0.46 to 1.11	0.46	
	≥57.3	8	390	0.80	0.60 to 1.00	43.83†	5.48§
Fluency	<57.3	4	95	0.51	0.03 to 1.00	2.76	
	≥57.3	8	134	0.52	0.24 to 0.81	6.59	0.003
Executive functioning	<57.3	3	68	0.35	0.44 to 1.15	4.88	
	≥57.3	8	126	0.34	0.05 to 0.62	4.48	0.01

k = Number of studies; *d* = mean weighted effect size; CI = confidence interval; Q_w = heterogeneity within a class of studies examining the same domain (df = k-1); Q_B = heterogeneity between categories (df = 1). * *p* < 0.05; § *p* < 0.01; # *p* < 0.001; † *p* < 0.0001. Groups are based on a median split.

language, visual memory, immediate verbal memory and executive functioning. No impairments were found for verbal IQ, delayed verbal memory, attention, visuo-perceptual and visuo-constructive functions. The heterogeneity between studies was fairly low, indicating that the observed pooled effects are reliable estimates. With the exception of the domains of language, psychomotor speed and executive functioning, we could not demonstrate clear indications for publication bias. The results of the fluency and psychomotor speed domains may have been influenced by slight motor impairment.

Cognitive dysfunction: MMSE

Across the various cognitive domains, the extent of cognitive deficits in ALS patients in our meta-analysis varies. The MMSE showed the largest effect size. As stated earlier (48), one should be cautious when comparing effect sizes from different cognitive domains. The MMSE is a global cognitive screening measure with a ceiling effect in the normal population. Therefore, nearly all cognitively normal people perform good or excellent on the MMSE, resulting in little variation in the scores of mentally normal people. This will generate artificially large effect sizes

when comparing those subjects with cognitively impaired patients. As a result, the large effect size for the MMSE in our meta-analysis merely indicates diffuse mild cognitive deficits in ALS patients compared with healthy subjects. The finding from the moderator analysis that the MMSE was lower in younger patients might be unexpected, as in general cognitive performance is lower in elderly subjects. As the size of the lower age group is relatively small and based on two studies only (38), this finding needs to be interpreted cautiously.

Cognitive dysfunction: language

Both non-fluent aphasia (49) and a severely impaired comprehension of verbs with sparing of nouns and adjectives (50) have been described in ALS, with or without behavioural abnormalities typical of FTD (motor neuron disease-aphasia-dementia syndrome) (51). In our meta-analysis of non-demented ALS patients, a significant medium effect size was found for language deficits (mostly naming of objects), whereas in individual studies of non-demented ALS patients language problems were found inconsistently (3,5,7,11,12,18,23). This may well be the result of the small sample sizes of the

Table IV. The influence of site of onset on effect sizes.

Domain	Site of onset bulbar¶	k	Samples size	D	95% CI	Q _w	Q _B
Immediate verbal memory	<40	5	358	0.99	0.72 to 1.26	13.12*	15.70†
	≥40	4	79	0.24	-0.28 to 0.76	2.43	
Visual memory	<40	4	316	1.04	-0.72 to 1.36	21.48†	11.26#
	≥40	3	68	0.34	-0.44 to 1.13	0.68	
Fluency	<40	3	51	0.73	-0.19 to 1.66	0.06	0.23
	≥40	4	81	0.60	0.08 to 1.12	2.54	
Executive functioning	<40	3	54	0.77	-0.12 to 1.67	1.05	5.30*
	≥40	4	73	0.16	-0.38 to 0.69	0.93	

¶ <40: less than 40% of the patients in these studies had bulbar onset ALS; k = number of studies; *d* = mean weighted effect size; CI = confidence interval; Q_w = heterogeneity within a class of studies examining the same domain (df = k-1); Q_B = heterogeneity between categories (df = 1). * *p* < 0.05; § *p* < 0.01; # *p* < 0.001; † *p* < 0.0001. Percentages of bulbar patients were calculated for each study. The two groups are based on a mean split of these percentages.

Table V. The influence of disease duration on effect sizes.

Domain	Duration (months)	k	Samples size	<i>d</i>	95% CI	Q _w	Q _B
MMSE	<23.1	2	282	0.70	−0.63 to 2.02	15.44#	1.07
	≥23.1	4	68	0.92	0.33 to 1.51	0.12	
Language	<23.1	4	54	0.59	0.23 to 1.40	0.75	2.52
	≥23.1	3	57	0.43	0.08 to 0.94	6.42	
Immediate verbal memory	<23.1	6	375	0.88	0.65 to 1.11	27.47†	11.67#
	≥23.1	4	99	0.41	0.09 to 0.92	1.20	
Visual memory	<23.1	6	357	0.92	0.69 to 1.15	29.54†	19.49#
	≥23.1	4	89	0.13	−0.36 to 0.62	0.63	
Fluency	<23.1	5	92	0.46	0.06 to 0.86	4.75	0.08
	≥23.1	5	112	0.52	0.14 to 0.90	3.60	
Executive functioning	<23.1	5	84	0.26	−0.15 to 0.67	5.72	0.92
	≥23.1	4	85	0.47	−0.03 to 0.96	1.67	
Psychomotor speed	<23.1	2	32	0.89	−2.58 to 4.35	0.04	0.46
	≥23.1	3	49	0.66	−0.14 to 1.47	0.47	

k = number of studies; *d* = mean weighted effect size; CI = confidence interval; Q_w = heterogeneity within a class of studies examining the same domain (df = k−1); Q_B = heterogeneity between categories (df = 1). * *p* < 0.05; § *p* < 0.01; # *p* < 0.001; † *p* < 0.0001. Groups are based on a median split.

studies. Alternatively, the possibility of an underlying disease process with abnormalities in different cerebral networks involved in language processes, resulting in heterogeneity of the presentation of the disorder, should be taken into consideration (7,52). We cannot rule out publication bias in the language domain, and therefore we cannot definitely conclude that the results of this meta-analysis suggest that ALS patients suffer from language deficits.

Cognitive dysfunction: memory

A remarkable finding in this meta-analysis is the presence of visual and verbal memory impairments in ALS patients. Although an exact cognitive profile in ALS has not yet been defined, most authors suggest a frontal lobe type of cognitive impairment with verbal fluency deficits, and other executive problems (11–13). As memory dysfunction has been inconsistently found in various studies (2,4,7,15,20–25), there is uncertainty whether it is an integral part of the cognitive profile in ALS (11,53). We found a medium effect for fluency and a smaller effect for other executive functions. The observed effects for both verbal (immediate and delayed) and visual memory impairments were in the same range as the effects for fluency deficits. In this meta-analysis, the visual memory domain includes both immediate and delayed memory tests, in contrast to the separate domains for immediate and delayed verbal memory. The low number of delayed visual memory tests in the included studies precluded separate calculations of the delayed memory tests. The statistic *Q* (Table II) shows that the heterogeneity of the visual memory domain is low and therefore the results of this domain are reliable. In the verbal memory domain, the separate results for the immediate and delayed memory tests may help to elucidate whether the memory impairments

in our meta-analysis reflect either frontal or medial temporal lobe involvement. In general, medial temporal lobe involvement results in delayed memory deficits (54). Conversely, immediate memory deficits may be explained by executive problems due to pathology in the frontal cortex (32). Our meta-analysis shows a significant effect for executive problems in ALS patients. However, the possibility of publication bias weakens the conclusions for this domain. Although we found no significant impairment of delayed (verbal) memory, the effect size of the delayed memory domain is in the same range as the effect size of the immediate verbal memory domain and it is borderline significant as the lower border of the confidence interval (CI) is very close to zero (−0.02). This wider CI of the delayed memory domain is possibly the result of a substantial lower number of patients in this domain compared to the immediate verbal memory domain. In conclusion, the memory impairments shown in our meta-analysis probably reflect frontal lobe involvement – although temporal lobe involvement cannot be ruled out as a large effect size of delayed memory tests was found, albeit not significant. This is in line with pathology and imaging studies in both demented and non-demented ALS patients that have shown involvement of prefrontal cortical regions (5,12,55–61) as well as, to a lesser extent, of regions in the temporal lobe, including the medial part (8,59,62,63). The presence of memory dysfunction in ALS is further enhanced by the significant visual memory deficits. In contrast to verbal memory tests, visual memory tests rely very little on motor performance, and thus the chance of bias due to paresis or dysarthria is negligible in the visual memory domain.

Cognitive dysfunction: fluency

The greatest part of the fluency domain consists of the letter fluency tests (Appendix 1). The large effect

size for fluency deficits was not unexpected as letter fluency impairment is the most consistently found cognitive deficit in ALS patients with mild cognitive impairment. An explanation for this finding may be the sensitivity of the letter fluency test. The test results are dependent on the function of the pre-frontal cortex, the anterior cingulate and parts of the temporal cortex. During a letter fluency task in non-demented ALS patients, functional magnetic resonance imaging has shown decreased activation of the middle and inferior frontal gyri and of the anterior cingulate gyrus, but also of regions in the temporal and parietal lobes (7). Clinical implications of this test are suggested in one study showing a correlation between verbal fluency deficits and decreased abilities of abstract reasoning and judgement, which both are relevant when one has to discuss treatment interventions and end-of-life issues with the patient and their family (28).

One might argue that the fluency test would be a candidate to serve as a screening measure for cognitive impairment in ALS. However, normal fluency does not exclude a diagnosis of FTD (13), and our meta-analysis showed substantial diversity of the cognitive problems in ALS. Therefore, a single test covering one cognitive domain is probably not suitable as a screening measure to detect cognitive deficits or FTD in ALS.

Clinical variables: site of onset

Several studies suggested that bulbar onset ALS patients compared to limb onset individuals are more frequently suffering from a coexisting dementia or mild cognitive impairment (13,19,26). In contrast, other studies including two large cohort studies did not show this association (2,4,16,27). On the basis of our moderator analysis we were not able to support the suggested relation between bulbar ALS and cognitive deficits.

Clinical variables: respiration

In ALS patients, nocturnal hypoventilation, sleep disturbance and hypercapnia may occur due to weakness of the respiratory muscles. Both in patients with obstructive sleep apnoea syndrome (OSAS) (64,65) and in ALS patients with respiratory dysfunction, fluency deficits and memory impairments were found, of which the latter were partially reversible after the start of non-invasive positive pressure ventilation (NIPPV) (66). When ALS patients with a vital capacity (VC) lower than 80% and those with a VC higher than 80% of the predicted value were compared, the patients with a lower VC performed worse on memory retention, retrieval efficacy and spoken verbal fluency (67). Patients with respiratory dysfunction (RD) were excluded in seven studies in this meta-analysis (i.e.

a vital capacity below 70% of the predicted value, or abnormal arterial PCO₂ levels). The lack of information on whether patients with RD were included or excluded in the remaining nine studies did not allow a valid assessment of the effect of RD on the cognitive domains. However, we tried to generate more insight in the data by performing two exploratory analyses (data not shown). First, the calculation of the effect sizes was repeated excluding the nine studies that did not present information on RD, showing that fluency is the only cognitive measure with a significant effect size (0.5, 95% C.I. 0.2–0.9) in the seven remaining studies. The domains language, immediate and delayed verbal memory, visual memory and the MMSE still showed positive effect sizes; however, the confidence intervals did not yield significance. In this analysis, only two studies contributed to the effect size of the MMSE and the number of studies was too small to perform this calculation for psychomotor speed. We also assessed the possible effect of RD on effect sizes comparing two groups using a moderator analysis: the seven studies in which patients with RD were excluded were compared with the nine studies in which this information was lacking. More visual and immediate verbal memory impairments were found in the latter group. Whether this latter group of studies without information on respiratory dysfunction in their patients included a different number of patients with respiratory dysfunction compared to the first group remains unknown. In conclusion, because of the lack of data in nine studies, we cannot rule out the possibility that some of the results of this meta-analysis might be biased because of RD in a proportion of the patients.

Limitations

There are some limitations to this meta-analysis. From some studies only one or two cognitive domains could be included, thus limiting the number of studies that could be used per domain in our meta-analysis. Information on clinical variables was incomplete in some studies (1,5–7,11,12,25). The results of the moderator analysis for the bulbar versus limb onset ALS patients, for example, are based on relatively small numbers of studies and could not be computed for all domains that showed significant changes. No definite conclusions can be drawn regarding the visuo-perceptual and visuo-constructive functions in ALS patients due to the relatively small number of patients who underwent visuo-perceptual testing and the heterogeneous results between studies for this domain. Effect sizes could be calculated from means and SDs in the majority of the studies (82%). The most accurate way to calculate an effect size is by using the mean and the SD, compared to extracting the effect size from other statistics from the original studies.

i.e. z - or p -values. The latter method was used in three studies. Tests from these studies were included in nine domains (75%). In nearly all these domains the three studies contributed 25% or less to the general effect size for the particular domain. Therefore, the less accurate method of calculating the effect sizes by z - or p -values has had a limited effect on the reliability of our results.

Progressive limb weakness and dysarthria, the clinical hallmarks of ALS, may interfere with cognitive testing. We tried to diminish the influence of these impairments on the results of our meta-analysis. Studies in which no adjustment of the neuropsychological test battery, or exclusion of severely motor impaired or dysarthric patients had been achieved, were excluded. As no consensus exists on the extent of severity as a measure for exclusion, there remains some subjectivity here. Mild upper extremity motor impairment, which may influence the results of cognitive tests relying a great deal on motor speed, may still have been present in some patients included in the studies. The results of the domains psychomotor speed and, to a lesser extent, fluency, could have been affected by this. The domain psychomotor speed measures the speed of mental processing in combination with motor speed; it does not measure mental processing speed in itself. The medium effect size of this domain is not unexpected, taking into account the possible mild motor impairments of the patients and the absence of a (motor) control condition in the tests that were included in this domain. Three out of the 12 studies contributing to the effect size of the fluency measure included a fluency index, which controls for motor impairment. In the remaining nine studies no such control condition was included and thus slightly motor impaired, or mildly dysarthric, patients may have shown lower fluency scores. Unlike many executive/frontal lobe tests, the MMSE and the great majority of the memory and language tests in this meta-analysis are not time-paced with respect to the mode of responding, implying that if any effect of motor impairment on cognitive deficits exists in our meta-analysis, it does not concern the MMSE or the memory and language domains.

In conclusion, the diversity of cognitive problems in ALS seems to be more extensive than was previously thought. This meta-analysis of cognitive dysfunction in non-demented ALS patients shows a lower MMSE, fluency deficits, memory impairments, language problems, pure executive deficits and a lower psychomotor speed. Publication bias should be taken into account regarding the executive deficits, psychomotor speed and language problems. Also, more studies are needed to quantify the effect of disease severity, site of onset and respiratory dysfunction on cognitive impairment and to evaluate the presence of visuospatial deficits. Finally, future neuropsychological studies need to minimize varia-

tion of cognitive test results due to motor impairments.

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Appendix 1: Cognitive domains and corresponding tests.

Domain	Test	k	%
Global cognitive ability	MMSE	6	38
Verbal IQ	Mill Hill vocabulary scale	1	6
	WAIS-R	3	19
	MWT-B	1	7
Language	Boston Naming Test	4	25
	Analogies	2	13
	Graded Naming Test	2	13
	Picture Naming Test	1	6
Immediate Verbal Memory	Auditory Verbal Learning Test (AVLT)	5	31
	California Verbal Learning Test (CVLT)	2	13
	Hopkins verbal learning task (verbal learning)	4	25
	WMS Paired Associative Learning Test	1	6
	WMS Logical Memory	1	6
	Ass. Learning Warrington Recognition Test Words	4	25
Delayed Verbal Memory	AVLT	3	19
	Hopkins verbal learning task	1	6
	WMS Logical Memory	1	6
	Delayed recognition Test	4	25
	Spinler Prose Memory Test	1	7
Visual Memory	Warrington Recognition Test Faces	4	25
	Benton's Visual Retention Test	1	6
	Benton's Facial Recognition Test	1	6
	Reproduction of Figure of Rey Osterrieth	1	6
	Kendrick Object Learning Test	3	19
	WAIS visual reproduction (imm., del.)	1	6
	Immediate Visual Memory	1	6
	Picture recall/recognition	1	6
	Brown-Peterson Interference Test	1	6
Fluency	COWAT letter fluency	8	50
	Milner written letter fluency	4	25
	Category fluency	5	31
	Alternating Fluency	1	6
	Design fluency	2	13
Executive functioning	(Modified) Wisconsin Card Sorting Test	4	25
	Stroop test part C (interference)	7	44
	Trail B (B-A)	2	13
	Temporal Rules Induction	1	6
Attention	Digit span forward & backward	4	25
	PASAT	1	6
	Counting Test of Wilkins	1	6
	Continuous Performance Test	1	6
	Serial Digit Learning Test	1	6
	Stroop A, B	1	6
Psychomotor speed	Trail A	3	19
	Symbol Digit Modalities Test	2	13
	Kendrick Digit Copying Test	1	6
	Stroop words, colours	1	6
Visuoperceptual functions	Judgment of Line Orientation	2	13
	Little Men (right left orientation)	1	6
	Money road map (spatial representation)	1	6
	Fragmented figures (object perception)	1	6
	Motor Free Visual Perception Test	1	6
	VOSP (spatial subtests or object decision)	2	13
Visuoconstructive skills	WAIS Block Design	2	13
	Copy design	1	6
	Copy of figure of Rey Osterrieth	1	6

k: number of studies; %: percentage of articles in the meta-analysis that included the test; MMSE: Mini Mental State Examination; MWT-B: B Mehrfachwahl Wortschatz-Intelligenztest. WAIS: Wechsler Adult Intelligence Scale; WMS: =Wechsler Memory Scale; RBMT: Rivermead Behavioural Memory Test; COWAT: Controlled Oral Word Association Test; PASAT: Paced Auditory Serial Addition Test; VOSP: Visual Object and Space Perception Test.

Appendix 2: Studies excluded from the meta-analysis.

First author	Journal, year of publication	Reason for exclusion*
Poloni	Acta Neurol Scand 1986	Did not meet WFN El Escorial criteria
Iwasaki	Acta Neurol Scand 1990	Did not meet WFN El Escorial criteria
Iwasaki	Int J Neurosci 1990	Did not meet WFN El Escorial criteria
Hartikainen	J Neural Transm Park Dis 1993	Did not meet WFN El Escorial criteria
Frank	Clin Neurology Neurosurg 1997	Did not meet WFN El Escorial criteria
Cobble	J Neurol Sci 1998	Did not meet WFN El Escorial criteria
Moretti	Dement Geriatr Cogn Disord 2002	Did not meet WFN El Escorial criteria
Gil	Arch Neurol 1995	No standardised neuropsychological tests
Munte	Acta Neurol Scand 1998	No standardised neuropsychological tests
Papps	Neuropsychologia 2005	No standardised neuropsychological tests
Abrahams	J Neurol Sci 1995	The same patient group was included in ref. 19
Abrahams	Neurology 2005	The same patient group was included in ref. 7
Gallassi	Acta Neurol Scand 1985	The same patient group was included in ref. 1
Abrahams	J Neurol 2005	The same patient group was included in ref. 7
Talbot	J Neurol Neurosurg Psychiatry 1995	Effect size calculation not possible
Chari	Neuropsychologia 1995	Effect size calculation not possible
Rippon	Arch Neurol 2006	Effect size calculation not possible
Dary-Auriol	Rev Neurol (Paris) 1997	PSMA patients included in patient group
Massman	J Neurol Neurosurg Psychiatry 1995	Uncontrolled study
Rakowicz	J Neurol Neurosurg Psychiatry 1998	Uncontrolled study
Verceletto	Rev Neurol (Paris) 1999	Uncontrolled study
McCullagh	J Neurol Sci 1999	Uncontrolled study
Portet	Amyotroph Lateral Scler 2001	Uncontrolled study
Mantovan	Eur J Neurol 2003	Uncontrolled study
Lomen-Hoerth	Neurology 2003	Uncontrolled study
Schreiber	J Neurol 2005	Uncontrolled study
Robinson	J Neurol Neurosurg Psychiatry 2006	Uncontrolled study
Flaherty-Craig	Neurology 2006	Uncontrolled study
Gordon	Amyotroph Lateral Scler 2007	Uncontrolled study
Murphy	Arch Neurol 2007	Uncontrolled study
Pinkhardt	J Neurol 2008	Control group not matched for education
Zimmerman	Cogn Behav Neurol 2007	Patients with dementia included

*See section: 'Methods, inclusion criteria' for details.