Cognition and behavior in motor neuron disease
Raaphorst, J.

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Motor neuron disease (MND) is a devastating neurodegenerative disorder characterized by progressive motor neuron loss, leading to weakness of the muscles of arms and legs, bulbar and respiratory muscles. Depending on the involvement of the lower and the upper motor neuron, amyotrophic lateral sclerosis (ALS; both lower and upper motor neuron affected) and progressive muscular atrophy (PMA; only lower motor neuron affected) are recognized. There is no cure, despite numerous pharmaceutical trials which show promising results in mouse models, and significant advances in the field of genetics and neuropathology. One of the reasons of the failure of pharmaceutical trials is the complexity of the underlying pathophysiology of MND. There is accumulating evidence that in a fair proportion of the MND-patients accompanying non-motor symptoms occur, with an overlap with frontotemporal dementia (FTD) at the end of the spectrum. In order to fully understand the pathophysiology of MND we first need more valid descriptions of the full range of symptoms, signs and the localisation of abnormalities within the nervous system.

Despite descriptions of dementia in ALS patients in the early 20th century, the extent of brain involvement in MND, and the profile of cognitive and behavioral symptoms, is still unknown.

In this thesis we present new evidence of brain dysfunction in two subtypes of MND: ALS and PMA. We show cognitive impairment and prefrontal brain changes in PMA, hippocampus involvement in ALS and present the cognitive and behavioral profiles of MND. We designed and validated new screening instruments to detect these cognitive and behavioral changes in clinical practice. Current research aims to further improve these tests, to search for anatomical substrates by brain imaging and to investigate the effects of non-motor symptoms on survival and quality of life of patients with MND.
Cognition and behavior in motor neuron disease

Joost Raaphorst
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Faculteit der Geneeskunde
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General introduction

Adapted from: Amyotrophic lateral sclerosis and frontotemporal dementia: overlapping characteristics. Nederlands Tijdschrift voor Geneeskunde 2010;154:A631
Chapter 1

GENERAL INTRODUCTION

Progressive muscular atrophy (PMA) and amyotrophic lateral sclerosis (ALS) are collectively known as motor neuron disease (MND). Depending on the clinical involvement of the lower or upper motor neuron (LMN, UMN) a diagnosis of PMA (LMN only) or ALS (LMN and UMN) will be reached. Ninety percent of MND patients are sporadic cases and 10% are familial, often with an autosomal dominant inheritance. The course of the disease is relentlessly progressive ultimately leading to death, in most patients due to respiratory insufficiency. The only effective drug is Riluzole, which has a modest effect on survival (3-6 months). The median survival of ALS is three years, and that of PMA probably between five and eight years, although a proportion of PMA patients show an ALS-like survival predicted by an early decline of vital capacity (a respiratory measure).

Overlap between PMA and ALS

The early decline of the vital capacity as a predictor of survival in PMA, which is similar to findings in ALS, illustrates the clinical overlap between these two conditions. Another observation is that some PMA patients develop UMN signs, which adds to post mortem findings of corticospinal tract involvement in PMA patients who had not developed ALS clinically. Apparently, the corticospinal tract changes in MND may be subclinical and the absence of UMN signs is no guarantee for a relatively benign disease course within the MND spectrum.

Genetic studies, in addition, have shown that some patients with “ALS mutations” such as SOD1 and TARDBP, have a PMA phenotype. These clinical, pathological and genetic similarities between PMA and ALS have fuelled debates between ‘lumpers’ and ‘splitters’ about the question whether PMA and ALS are separate entities or belong to one clinical spectrum of motor neuron disorders. This issue is not just theoretical: if (a proportion of) PMA patients would be regarded as having ALS, this has implications for diagnostic criteria and inclusion in clinical therapeutic trials. Moreover, accurate phenotyping is essential for a valid interpretation of pathological and genetic studies, which are fundamental for the understanding of the disease process and the development of drugs to prevent or cure the disease.

From the early nineties of the last century, new ammunition for the ‘lumpers’ (and
splitters) has become available when ALS was found to be associated with frontotemporal dementia (FTD) or cognitive changes, with prefrontal imaging correlates.⁷⁻⁹

**Frontotemporal dementia (FTD) in ALS**

Progressive behavioral and character changes characterize frontotemporal dementia (FTD). FTD patients have impaired social conduct, inhibition or apathy and a variable degree of cognitive dysfunction, often with sparing of visuoperceptual functions. In addition to the behavioral variant of FTD, two language variants of FTD are recognized, which are beyond the scope of this thesis.¹⁰

In 1932 Braunmuhl, a German physician, described a patient with Pick’s disease (the former denominator for FTD) who developed ALS, and his report was followed by over 100 descriptions of both sporadic and familial cases.¹¹ A considerable clinical variability within families became apparent: different members within one kindred may have either ALS or FTD, or both (ALS-FTD).¹² The cause of this clinical variability is incompletely understood, even after the recent discovery of the C9ORF72 hexanucleotide repeat expansion as a cause of 40% of familial ALS cases (and 30% of familial FTD).¹³ Presumably, environmental factors and modifying genes play a role in the phenotype; the latter, in turn, is not restricted to the familial forms of ALS according to recent studies.¹⁴

The identification of modifying genes and environmental factors is essential for the development of a cure for MND. In order to interpret new genes and the role of environmental factors, we need to know which patients have a pure “motor” form of MND and which patients have “MND-plus”. To establish this, non-motor symptoms need to be detected accurately (phenotyping).

Besides the recognition of FTD in ALS patients, there has been increasing awareness that a proportion of ALS patients have more subtle cognitive and, possibly behavioral disturbances, which can be detected by careful neuropsychological examination. These mild cognitive changes have been associated with imaging changes of predominantly the prefrontal cortex in ALS patients, and are presumed to be a mild manifestation of FTD (based on pathological changes in frontotemporal brain regions), although this has been debated.
FTD, together with mild cognitive and behavioral disturbances are currently known as the “frontotemporal syndrome” of ALS. Again, this association is not just theoretical: cognitive and behavioral impairment in patients with ALS, in particular when severe, may have serious impact on relations with caregivers, adherence to interventions such as non-invasive ventilation, and survival duration.15

The frontotemporal syndrome of ALS in combination with the overlap of PMA and ALS has led to the research presented in this thesis.

AIMS OF THIS THESIS
The primary objective was to investigate whether cognitive impairment is restricted to ALS or also present in MND patients without upper motor neuron involvement. A second objective was to investigate the presence of behavioral changes in MND, based on the reported overlap between ALS and frontotemporal dementia.16 Third, we investigated whether imaging studies could establish structural and functional brain abnormalities beyond the motor cortex in MND patients.

The following research questions were addressed in this thesis:
1. Is cognitive impairment restricted to MND patients with upper motor neuron signs, or also present in PMA?
2. How can we reliably measure behavioral disturbances and the behavioral variant of FTD in ALS patients?
3. Can magnetic resonance imaging further establish the presence of brain dysfunction and structural brain changes in PMA and ALS?

OUTLINE AND HYPOTHESES
Part I. Cognitive impairment in MND: presence, profile and assessment
Cognitive impairment has been found in 30-50% of ALS patients. Verbal fluency deficits have been described consistently.17,18 However, studies addressing other executive functions, memory, language, and in particular visuoperceptive functions have shown heterogeneous and sometimes contradictory findings, in part due to small sample sizes.19,20 A valid description of the cognitive profile may assist
clinicians and neuropsychologists, and may provide directions for the development of cognitive screening instruments. In chapter 2 we report the results of a meta-analysis of neuropsychological studies, which was undertaken to clarify the cognitive profile of ALS.

In addition to cognitive impairment in ALS, executive and memory deficits have been shown in a fair proportion of patients with primary lateral sclerosis (PLS, the UMN variant of MND). Whether this also holds true for patients with the lower motor neuron (LMN) variant of MND, i.e. PMA, is unclear. In chapter 3 we examine cognitive dysfunction in PMA patients using a comprehensive neuropsychological battery adapted to motor and speech impairment. We expected to find cognitive impairment in similar domains but possibly to a lesser extent, compared to ALS. Reliable assessment of cognitive functions in MND is of utmost importance as reduced motor speed and speech problems may interfere with cognitive testing. In particular tests of frontal lobe functions are often speed-dependent, and non-adapted tests may lead to false positive results in MND. Despite recommendations by a research workshop in 2007 and a landmark paper by Abrahams et al in 2000, we noticed room for improvement. In chapters 4 and 5 we describe two small studies on valid and reliable assessment of frontal lobe functions in MND.

Part 2. Behavioral disturbances in MND: presence, profile and assessment

The frequency and characteristics of behavioral symptoms, which are the hallmark of FTD, have not been firmly determined in MND. There is debate about the prevalence of behavioral changes (both the behavioral variant of FTD (bvFTD) and mild behavioral changes) and the association of FTD with clinical variables of MND, i.e. bulbar onset and survival. In chapter 6 we systematically reviewed the literature on behavioral changes in MND (PMA, ALS and PLS) in order to estimate the prevalence of FTD and mild behavioral changes in MND. In addition we calculated prevalence rates of FTD symptoms (behavioral, cognitive and psychiatric symptoms) in MND-FTD patients. We expected to find a point-prevalence of FTD below 20% in MND and prevalence rates of behavioral disturbances in MND-FTD patients comparable to those found in FTD patients. The prevalence rates of behavioral variant
FTD symptoms in chapter 3.1 served as an item bank for the development of a new screening instrument for behavioral changes in ALS, which is described in chapter 7. A neuropsychiatric screening instrument is an alternative method to detect behavioral changes, when a detailed family interview (gold standard) is not feasible. The available neuropsychiatric instruments for the assessment of behavioral disturbances have been validated in patients with dementia and traumatic brain injury. These instruments have not been validated in patients with ALS, even though they contain several items that rely on the ability to speak, eat, and move without problems. In chapter 7 we investigate the clinimetric properties of a new screening tool, the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Questionnaire (ALS-FTD-Q), for the detection of bvFTD and mild behavioral disturbances in ALS. We hypothesized that the prevalence of behavioral disturbances would be lower with this new instrument compared to existing screening instruments.

Part 3 Functional and structural imaging correlates of cognitive impairment in MND

The most consistently reported cognitive abnormality in ALS is low performance on letter fluency tests, which has been related to reduced activation in prefrontal and temporal brain regions during functional Magnetic Resonance Imaging (fMRI) and abnormalities in similar regions on Positron Emission Tomography (PET) in ALS patients. Cerebral involvement in PMA is disputed, as generally no cognitive or cerebral imaging changes have been shown in PMA patients, although the patients cohorts were small, precluding firm conclusions. One study showed reduced fractional anisotropy (a diffusion tensor imaging measure) in the white matter of the prefrontal cortex in PMA patients, suggesting non-motor cerebral involvement, although neuropsychological assessments were not performed. In chapter 8 we describe whether cognitive impairment in PMA patients, when present, can be linked to prefrontal changes, similar to findings in ALS patients, using an fMRI fluency task. We hypothesized that PMA patients show non-motor cerebral involvement in frontal brain regions previously associated with fluency performance in ALS.
In addition to the prefrontal cortex, other brain areas are also likely to be involved in ALS, in particular the hippocampus. Post mortem studies have shown neuronal loss and pathological inclusions in the hippocampus of ALS-FTD patients, and to a lesser extent in ALS without FTD. However, most structural and functional imaging studies did not show hippocampal changes in ALS (+/- FTD) patients. In studies that did find hippocampal changes (cerebral blood flow, diffusion tensor imaging) neuropsychological testing had not been performed. Voxel based morphometry (VBM) enables the automated quantification of the grey and white matter volumes of brain regions such as the hippocampus and may be a sensitive measure, in particular in combination with cognitive testing. In chapter 9 we describe structural MRI (VBM) correlates of memory dysfunction in ALS.
Part I

Cognitive impairment in motor neuron disease
The cognitive profile of amyotrophic lateral sclerosis: a meta-analysis

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Wim H Linssen
Rob J de Haan
Ben Schmand

Amyotrophic Lateral Sclerosis 2010;11:27-37
ABSTRACT

Objective
To clarify the profile of cognitive impairment in ALS.

Methods
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.

Results
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.

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.
INTRODUCTION

There is increasing evidence that cerebral regions outside the motor cortex are afflicted in a proportion of ALS patients. About 5-15% of ALS patients have severe cognitive changes with features consistent with frontotemporal dementia (ALS-FTD). Mild cognitive impairment is found in 33-51% of ALS patients. A consistent finding is impairment of verbal fluency, a function that heavily taxes prefrontal areas. However, studies addressing other prefrontal functions or investigating memory, language, or visuospatial functions are heterogeneous and often contradictory. The inconsistency of these findings is most likely 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 and disease severity are thought to be associated with cognitive impairment in ALS. The extent to which these disease variables contribute to cognitive dysfunction is less clear.

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 analyze the effects of clinical variables on the cognitive outcome measures.

Insight in 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.

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
tables 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).\textsuperscript{56, 57} 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)\textsuperscript{58} 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
  analyzed 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. Tests from the individual studies were categorized into the following twelve 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 vs. 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’ $g$\textsuperscript{61} 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.\textsuperscript{62} 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.\textsuperscript{63} 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.\textsuperscript{64}

Heterogeneity of the data was assessed using the chi-square 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.\textsuperscript{65} 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.\textsuperscript{66}

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.\textsuperscript{62} To estimate the number of negative studies which 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. 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 1.

Participant 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 ten 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, Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), ALS severity scale, Norris score). According to these scales most studies had included ALS patients with mild to moderate disease severity.
Table 1. Demographic and clinical characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Study, author, year</th>
<th>N</th>
<th>ALS categories</th>
<th>Onset bulbar/limb</th>
<th>Age, years (SD or range)</th>
<th>Duration (months)</th>
<th>Respiratory dysfunction excl. criterion</th>
<th>Disease severity (mean and range or SD)</th>
<th>Education (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. David (1986)</td>
<td>14</td>
<td>Poss, prob, def.</td>
<td>7/7</td>
<td>53.7 (-)</td>
<td>17.8</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2. Gallassi (1989)</td>
<td>18</td>
<td>Poss</td>
<td>-</td>
<td>57.9 (11.3)</td>
<td>17.2</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3. Ludolph (1992)</td>
<td>17</td>
<td>Poss</td>
<td>13/8*</td>
<td>58.5 (11.3)</td>
<td>-</td>
<td>Yes</td>
<td>Norris: 60-94 (range)</td>
<td>-</td>
</tr>
<tr>
<td>5. Abe (1997)</td>
<td>18</td>
<td>ALS</td>
<td>-</td>
<td>53.7 (36-67)</td>
<td>25.3</td>
<td>Yes</td>
<td>NBS 25, NLS 25</td>
<td>-</td>
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<tr>
<td>6. Abrahams (1997)</td>
<td>52</td>
<td>Poss, prob</td>
<td>24/28</td>
<td>57.2 (-)</td>
<td>22.3</td>
<td>No</td>
<td>-</td>
<td>13.3</td>
</tr>
<tr>
<td>7. Strong (1999)</td>
<td>13</td>
<td>Def</td>
<td>8/5</td>
<td>54.2 (9.6)</td>
<td>21.1</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
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<td>8. Vieregge (1999)</td>
<td>8</td>
<td>Prob, def</td>
<td>7/1</td>
<td>58.4 (43-69)</td>
<td>-</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9. Abrahams (2000)</td>
<td>22</td>
<td>Poss</td>
<td>-</td>
<td>55.8 (10.2)</td>
<td>25.9</td>
<td>Yes</td>
<td>ALS s.s.c. 32 (22-39)</td>
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<td>11. Abrahams (2004)</td>
<td>28</td>
<td>Prob, def</td>
<td>-</td>
<td>57.3 (11.1)</td>
<td>21</td>
<td>Yes</td>
<td>ALS s.s.c. 33</td>
<td>12.7</td>
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<tr>
<td>13. Ringholz (2005)</td>
<td>262</td>
<td>Prob, def</td>
<td>86/156*</td>
<td>58.8 (14.4)</td>
<td>16.5</td>
<td>No</td>
<td>Appel 69 (21)</td>
<td>13.3</td>
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<td>14. Rottig (2006)</td>
<td>15</td>
<td>Prob, def</td>
<td>0/15</td>
<td>60.8 (8)</td>
<td>30.3</td>
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<td>-</td>
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</tbody>
</table>

N = Number of patients. ALS categories: poss = possible; prob = probable; def = definite ALS; according to El Escorial criteria. excl. = exclusion. No = 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.s.c. = ALS severity scale: low scores represent functional impairment; maximum = 40. ALSFRS = ALS functional rating scale: maximum score 48, minimum score 0 (= maximal dysfunction). 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% or 96% of the complete patient sample.
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.\textsuperscript{8, 18, 19, 22, 36, 40, 43, 46, 50, 52, 71-73} In addition, in five studies a test battery was chosen to minimize effects of impaired motor function.\textsuperscript{20, 35, 51, 72, 73} In three studies a \textit{fluency index} was presented, which adjusts for slower writing or speaking.\textsuperscript{18, 20, 46} Severe depression may influence cognitive performance. None of the mean depression scores presented in nine of the 16 the studies included in this meta-analysis showed values corresponding to clinically relevant depression.\textsuperscript{18-20, 35, 40, 46, 50-52} 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.\textsuperscript{18, 35, 36, 40, 43, 71, 72} The use of psychoactive medication was an exclusion criterion in 6 studies.\textsuperscript{8, 20, 22, 46, 50, 52} In two studies amitriptyline\textsuperscript{19}, and benzodiazepines and anti-depressants\textsuperscript{51} were 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 effect sizes were calculated from z- or p- values.\textsuperscript{1, 3, 46} Pooled effect sizes (\textit{d}-values) for each cognitive domain are shown in table 2 and figure 1.

A large, statistical 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 \textit{fail-safe N} and the tolerance level were calculated for cognitive domains that showed a significant difference between ALS patients and controls (table 2). Except for language, executive functioning and psychomotor speed, the \textit{fail-safe N} exceeded the estimate of unpublished studies, indicating that the observed effects can not be explained by publication bias.
Table 2. Pooled weighted effect sizes, confidence intervals and heterogeneity statistics for each domain of cognitive functioning

<table>
<thead>
<tr>
<th>Domain</th>
<th>k</th>
<th>Patients (n)</th>
<th>Nd</th>
<th>D</th>
<th>95% CI</th>
<th>Q</th>
<th>p (Q)</th>
<th>I²</th>
<th>Fail-safe N</th>
<th>Tolerance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>6</td>
<td>350</td>
<td>6</td>
<td>0.82a</td>
<td>0.24 to 1.40</td>
<td>6.62</td>
<td>0.25</td>
<td>9</td>
<td>113</td>
<td>40</td>
</tr>
<tr>
<td>Language</td>
<td>7</td>
<td>155</td>
<td>10</td>
<td>0.53a</td>
<td>0.09 to 0.97</td>
<td>6.42</td>
<td>0.38</td>
<td>7</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>5</td>
<td>105</td>
<td>5</td>
<td>0.25</td>
<td>-0.17 to 0.68</td>
<td>1.26</td>
<td>0.87</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Immediate verbal memory</td>
<td>12</td>
<td>497</td>
<td>17</td>
<td>0.51a</td>
<td>0.16 to 0.86</td>
<td>6.75</td>
<td>0.82</td>
<td>0</td>
<td>196</td>
<td>70</td>
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<tr>
<td>Delayed verbal memory</td>
<td>7</td>
<td>371</td>
<td>8</td>
<td>0.47</td>
<td>-0.02 to 0.97</td>
<td>3.47</td>
<td>0.84</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Visual memory</td>
<td>11</td>
<td>446</td>
<td>16</td>
<td>0.43a</td>
<td>0.01 to 0.84</td>
<td>4.35</td>
<td>0.93</td>
<td>0</td>
<td>146</td>
<td>65</td>
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<tr>
<td>Fluency</td>
<td>12</td>
<td>213</td>
<td>22</td>
<td>0.52a</td>
<td>0.31 to 0.73</td>
<td>9.35</td>
<td>0.59</td>
<td>0</td>
<td>133</td>
<td>70</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>11</td>
<td>194</td>
<td>19</td>
<td>0.34a</td>
<td>0.12 to 0.56</td>
<td>9.36</td>
<td>0.50</td>
<td>0</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>6</td>
<td>99</td>
<td>8</td>
<td>0.68a</td>
<td>0.30 to 1.06</td>
<td>2.16</td>
<td>0.83</td>
<td>0</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>Attention</td>
<td>5</td>
<td>116</td>
<td>15</td>
<td>0.58</td>
<td>-0.22 to 1.40</td>
<td>4.82</td>
<td>0.31</td>
<td>17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Visuoperceptual functions</td>
<td>4</td>
<td>93</td>
<td>6</td>
<td>0.17</td>
<td>-0.36 to 0.70</td>
<td>4.14</td>
<td>0.39</td>
<td>28</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Visuoconstructive skills</td>
<td>4</td>
<td>67</td>
<td>5</td>
<td>0.40</td>
<td>-0.47 to 1.27</td>
<td>3.40</td>
<td>0.33</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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%].
a p < 0.05. b Tolerance level (i.e. estimated number of existing unpublished studies, 5k + 10). 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. 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.
Figure 1. Pooled weighted effect sizes and 95% confidence intervals of the cognitive domains

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.

Influence of moderator variables

Due 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 3-5) 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 primarily 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 (appendix 3). 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. 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 (appendix 3). 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 (appendix 3).

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 the effect sizes the following domains are impaired in ALS patients: MMSE, psychomotor speed, fluency, language, visual memory, immediate verbal memory and executive functioning. No impairments were found for verbal IQ, delayed verbal memory, attention, visuoperceptual and visuoconstructive 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 profile of ALS: a meta-analysis

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 was stated earlier, 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, this finding needs to be interpreted cautiously.

Cognitive dysfunction: language

Both non-fluent-aphasia and a severely impaired comprehension of verbs with sparing of nouns and adjectives have been described in ALS, with or without behavioral abnormalities typical of FTD (motor neuron disease-aphasia-dementia syndrome). 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. This may well be the result of the small sample sizes of the 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. 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. As memory dysfunction has been inconsistently found in various studies there is uncertainty whether it is an integral part of the cognitive profile in ALS. 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, opposed 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 2) 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. Conversely, immediate memory deficits may be explained by executive problems due to pathology in the frontal cortex. 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\textsuperscript{8, 32, 40, 81-86} as well as, to a lesser extent, of regions in the temporal lobe, including the medial part.\textsuperscript{30, 37, 84, 87} The presence of memory dysfunction in ALS is further enhanced by the significant visual memory deficits. Opposed to verbal memory tests, visual memory tests rely very little on motor performance, 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 prefrontal 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.\textsuperscript{20} Clinical implications of this test are suggested in one study showing a correlation between verbal fluency deficits and decreased abilities of abstract reasoning and judgment, which both are relevant when one has to discuss treatment interventions and end-of-life issues with the patient and his family.\textsuperscript{55}

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\textsuperscript{41} 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 co-existing dementia or mild
cognitive impairment.\textsuperscript{41, 46} In contrast, other studies including two large cohort studies did not show this association.\textsuperscript{17, 35, 44, 54} 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)\textsuperscript{88, 89} 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).\textsuperscript{90} 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.\textsuperscript{91} 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 PCO\textsubscript{2} 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. 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 visuoperceptual and
visuoconstructive functions in ALS patients due to the relatively small number of
patients who underwent visuoperceptual 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 for 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 for 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 twelve 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 variation of cognitive test results due to motor impairments.
## Appendix 1. Cognitive domains and corresponding tests

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>k</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive ability</td>
<td>MMSE</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>Mill Hill vocabulary scale</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>WAIS-R</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>MWT-B</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Language</td>
<td>Boston Naming Test</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Analogies</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Graded Naming Test</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Picture Naming Test</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Immediate Verbal Memory</td>
<td>Auditory Verbal Learning Test (AVLT)</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>California Verbal Learning Test (CVLT)</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Hopkins verbal learning task (verbal learning)</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>WMS Paired Associative Learning Test</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>WMS Logical Memory</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Ass. Learning Warrington Recognition Test Words</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Delayed Verbal Memory</td>
<td>AVLT</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Hopkins verbal learning task</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>WMS Logical Memory</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Delayed recognition Test</td>
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<tr>
<td></td>
<td>Spinler Prose Memory Test</td>
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<td>Visual Memory</td>
<td>Warrington Recognition Test Faces</td>
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<tr>
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<td>Benton’s Visual Retention Test</td>
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<td>Benton’s Facial Recognition Test</td>
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<td>Reproduction of Figure of Rey Osterrieth</td>
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<td>Kendrick Object Learning Test</td>
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<td></td>
<td>WAIS visual reproduction (imm., del.)</td>
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<td>Immediate Visual Memory</td>
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<tr>
<td></td>
<td>Picture recall/recognition</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Brown-Peterson Interference Test</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Fluency</td>
<td>COWAT letter fluency</td>
<td>8</td>
<td>50</td>
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<tr>
<td></td>
<td>Milner written letter fluency</td>
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<td>Category fluency</td>
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<td></td>
<td>Alternating Fluency</td>
<td>1</td>
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</tr>
<tr>
<td></td>
<td>Design fluency</td>
<td>2</td>
<td>13</td>
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<tr>
<td>Executive functioning</td>
<td>(Modified) Wisconsin Card Sorting Test</td>
<td>4</td>
<td>25</td>
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<td></td>
<td>Stroop test part C (interference)</td>
<td>7</td>
<td>44</td>
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<td></td>
<td>Trail B (B-A)</td>
<td>2</td>
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<tr>
<td></td>
<td>Temporal Rules Induction</td>
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<td>6</td>
</tr>
<tr>
<td>Attention</td>
<td>Digit span forward &amp; backward</td>
<td>4</td>
<td>25</td>
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<tr>
<td></td>
<td>PASAT</td>
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<td>6</td>
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<tr>
<td></td>
<td>Counting Test of Wilkins</td>
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<td>6</td>
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<td></td>
<td>Continuous Performance Test</td>
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<tr>
<td></td>
<td>Serial Digit Learning Test</td>
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<td>6</td>
</tr>
<tr>
<td></td>
<td>Stroop A, B</td>
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<td>6</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>Trail A</td>
<td>3</td>
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<tr>
<td></td>
<td>Symbol Digit Modalities Test</td>
<td>2</td>
<td>13</td>
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<td></td>
<td>Kendrick Digit Copying Test</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Stroop words, colors</td>
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<td>6</td>
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## Domain

<table>
<thead>
<tr>
<th>Test</th>
<th>k</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Judgment of Line Orientation</td>
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<tr>
<td>Little Men (right left orientation)</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Money road map (spatial representation)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Fragmented figures (object perception)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Motor Free Visual Perception Test</td>
<td>1</td>
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</tr>
<tr>
<td>VOSP (spatial subtests or &quot;object decision&quot;)</td>
<td>2</td>
<td>13</td>
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<tr>
<td><strong>Visuoconstructive skills</strong></td>
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<td>WAIS Block Design</td>
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<td>13</td>
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<td>Copy design</td>
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<tr>
<td>Copy of figure of Rey Osterrieth</td>
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</tbody>
</table>

k = number of studies; % = percentage of articles in the meta-analysis that included the test; MMSE = Mini Mental State Examination; MWT-B = Mehrfachwahl Wortschatz-Intelligenztest. WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale; RBMT = Rivermead Behavioral 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

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal, year of publication</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poloni</td>
<td>Acta Neurol Scand 1986</td>
<td>Did not meet WFN El Escorial criteria</td>
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<tr>
<td>Iwasaki</td>
<td>Acta Neurol Scand 1990</td>
<td>Did not meet WFN El Escorial criteria</td>
</tr>
<tr>
<td>Iwasaki</td>
<td>Int J Neurosci 1990</td>
<td>Did not meet WFN El Escorial criteria</td>
</tr>
<tr>
<td>Hartikainen</td>
<td>J Neural Transm Park Dis 1993</td>
<td>Did not meet WFN El Escorial criteria</td>
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<tr>
<td>Frank</td>
<td>Clin Neurology Neurosurg 1997</td>
<td>Did not meet WFN El Escorial criteria</td>
</tr>
<tr>
<td>Cobble</td>
<td>J Neurol Sci 1998</td>
<td>Did not meet WFN El Escorial criteria</td>
</tr>
<tr>
<td>Moretti</td>
<td>Dement Geriatr Cogn Disord 2002</td>
<td>Did not meet WFN El Escorial criteria</td>
</tr>
<tr>
<td>Gil</td>
<td>Arch Neurol 1995</td>
<td>No standardized neuropsychological tests</td>
</tr>
<tr>
<td>Munte</td>
<td>Acta Neurol Scand 1998</td>
<td>No standardized neuropsychological tests</td>
</tr>
<tr>
<td>Papps</td>
<td>Neuropsychologia 2005</td>
<td>No standardized neuropsychological tests</td>
</tr>
<tr>
<td>Abrahams</td>
<td>J Neurol Sci 1995</td>
<td>Same patient group included in ref. 19</td>
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<tr>
<td>Abrahams</td>
<td>Neurology 2005</td>
<td>Same patient group included in ref. 7</td>
</tr>
<tr>
<td>Gallassi</td>
<td>Acta Neurol Scand 1985</td>
<td>Same patient group included in ref. 7</td>
</tr>
<tr>
<td>Abrahams</td>
<td>J Neurol 2005</td>
<td>Same patient group included in ref. 7</td>
</tr>
<tr>
<td>Talbot</td>
<td>J Neurol Neurosurg Psychiatry 1995</td>
<td>Effect size calculation not possible</td>
</tr>
<tr>
<td>Chari</td>
<td>Neuropsychologia 1995</td>
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<td>Rippon</td>
<td>Arch Neurol 2006</td>
<td>Effect size calculation not possible</td>
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<td>Dary-Auriol</td>
<td>Rev Neurol (Paris) 1997</td>
<td>PSMA patients included in patient group</td>
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<td>Massman</td>
<td>J Neurol Neurosurg Psychiatry 1995</td>
<td>Uncontrolled study</td>
</tr>
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<td>Rakowicz</td>
<td>J Neurol Neurosurg Psychiatry 1998</td>
<td>Uncontrolled study</td>
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<td>McCullagh</td>
<td>J Neurol Sci 1999</td>
<td>Uncontrolled study</td>
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<td>Portet</td>
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<td>Uncontrolled study</td>
</tr>
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<td>Mantovan</td>
<td>Eur J Neurol 2003</td>
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<td>Lomen-Hoerth</td>
<td>Neurology 2003</td>
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<td>Robinson</td>
<td>J Neurol Neurosurg Psychiatry 2006</td>
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<td>Flaherty-Craig</td>
<td>Neurology 2006</td>
<td>Uncontrolled study</td>
</tr>
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<td>Gordon</td>
<td>Amyotroph Lateral Scler 2007</td>
<td>Uncontrolled study</td>
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<td>Murphy</td>
<td>Arch Neurol 2007</td>
<td>Uncontrolled study</td>
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<tr>
<td>Pinkhardt</td>
<td>J Neurol 2008</td>
<td>Control group not matched for education</td>
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## Appendix 3. Influence of moderator variables on effect sizes

### Table 3. The influence of age on effect sizes

<table>
<thead>
<tr>
<th>Domain</th>
<th>Age (years)</th>
<th>k</th>
<th>Samples size</th>
<th>d</th>
<th>95%CI</th>
<th>Qw</th>
<th>QB</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>&lt; 57.3</td>
<td>2</td>
<td>38</td>
<td>1.26</td>
<td>-2.04 to 4.56</td>
<td>7.10a</td>
<td>4.33a</td>
</tr>
<tr>
<td></td>
<td>≥ 57.3</td>
<td>4</td>
<td>322</td>
<td>0.81</td>
<td>0.37 to 0.99</td>
<td>5.21</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>&lt; 57.3</td>
<td>2</td>
<td>42</td>
<td>0.38</td>
<td>2.21 to 3.83</td>
<td>3.87a</td>
<td>2.39</td>
</tr>
<tr>
<td></td>
<td>≥ 57.3</td>
<td>5</td>
<td>97</td>
<td>0.81</td>
<td>0.01 to 0.78</td>
<td>6.55</td>
<td></td>
</tr>
<tr>
<td>Immediate verbal memory</td>
<td>&lt; 57.3</td>
<td>3</td>
<td>83</td>
<td>0.33</td>
<td>0.33 to 1.18</td>
<td>6.35a</td>
<td>3.67</td>
</tr>
<tr>
<td></td>
<td>≥ 57.3</td>
<td>9</td>
<td>398</td>
<td>0.80</td>
<td>0.61 to 0.91</td>
<td>28.55c</td>
<td></td>
</tr>
<tr>
<td>Visual memory</td>
<td>&lt; 57.3</td>
<td>3</td>
<td>72</td>
<td>0.33</td>
<td>-0.46 to 1.11</td>
<td>0.46</td>
<td>5.48d</td>
</tr>
<tr>
<td></td>
<td>≥ 57.3</td>
<td>8</td>
<td>390</td>
<td>0.80</td>
<td>0.60 to 1.00</td>
<td>43.83d</td>
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<tr>
<td>Fluency</td>
<td>&lt; 57.3</td>
<td>4</td>
<td>95</td>
<td>0.51</td>
<td>0.03 to 1.00</td>
<td>2.76</td>
<td>0.003</td>
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<tr>
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<td>≥ 57.3</td>
<td>8</td>
<td>134</td>
<td>0.50</td>
<td>0.24 to 0.81</td>
<td>6.59</td>
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</tr>
<tr>
<td>Executive functioning</td>
<td>&lt; 57.3</td>
<td>3</td>
<td>68</td>
<td>0.35</td>
<td>0.44 to 1.15</td>
<td>4.88</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>≥ 57.3</td>
<td>8</td>
<td>126</td>
<td>0.34</td>
<td>0.05 to 0.62</td>
<td>4.48</td>
<td></td>
</tr>
</tbody>
</table>

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

### Table 4. The influence of site of onset on effect sizes

<table>
<thead>
<tr>
<th>Domain</th>
<th>Site of onset</th>
<th>k</th>
<th>Samples size</th>
<th>d</th>
<th>95%CI</th>
<th>Qw</th>
<th>QB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate verbal memory</td>
<td>&lt; 40</td>
<td>5</td>
<td>358</td>
<td>0.99</td>
<td>0.72 to 1.26</td>
<td>13.12b</td>
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<tr>
<td></td>
<td>≥ 40</td>
<td>4</td>
<td>79</td>
<td>0.24</td>
<td>-0.28 to 0.76</td>
<td>2.43</td>
<td>15.7d</td>
</tr>
<tr>
<td>Visual memory</td>
<td>&lt; 40</td>
<td>4</td>
<td>316</td>
<td>1.04</td>
<td>-0.72 to 1.36</td>
<td>21.48d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 40</td>
<td>3</td>
<td>68</td>
<td>0.34</td>
<td>-0.44 to 1.13</td>
<td>0.68</td>
<td>11.26c</td>
</tr>
<tr>
<td>Fluency</td>
<td>&lt; 40</td>
<td>3</td>
<td>51</td>
<td>0.73</td>
<td>-0.19 to 1.66</td>
<td>0.06</td>
<td>0.23</td>
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<tr>
<td></td>
<td>≥ 40</td>
<td>4</td>
<td>81</td>
<td>0.60</td>
<td>0.08 to 1.12</td>
<td>2.54</td>
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</tr>
<tr>
<td>Executive functioning</td>
<td>&lt; 40</td>
<td>3</td>
<td>54</td>
<td>0.77</td>
<td>-0.12 to 1.67</td>
<td>1.05</td>
<td>5.30b</td>
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<tr>
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<td>≥ 40</td>
<td>4</td>
<td>73</td>
<td>0.16</td>
<td>-0.38 to 0.69</td>
<td>0.93</td>
<td></td>
</tr>
</tbody>
</table>

*a<40: less than 40 percent of the patients in these studies had bulbar onset ALS; **p < 0.05; ***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. For other abbreviations see legend above.
Table 5. The influence of disease duration on effect sizes

<table>
<thead>
<tr>
<th>Domain</th>
<th>Duration (months)</th>
<th>k</th>
<th>Sample size</th>
<th>d</th>
<th>95%CI</th>
<th>Qw</th>
<th>QB</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>&lt; 23.1</td>
<td>2</td>
<td>282</td>
<td>0.70</td>
<td>-0.63 to 2.02</td>
<td>15.44(^a)</td>
<td>1.07</td>
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<tr>
<td></td>
<td>≥ 23.1</td>
<td>4</td>
<td>68</td>
<td>0.92</td>
<td>0.33 to 1.51</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>&lt; 23.1</td>
<td>4</td>
<td>54</td>
<td>0.59</td>
<td>0.23 to 1.40</td>
<td>0.75</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td>≥ 23.1</td>
<td>3</td>
<td>57</td>
<td>0.43</td>
<td>0.08 to 0.94</td>
<td>6.42</td>
<td></td>
</tr>
<tr>
<td>Immediate verbal memory</td>
<td>&lt; 23.1</td>
<td>6</td>
<td>375</td>
<td>0.88</td>
<td>0.65 to 1.11</td>
<td>27.47(^b)</td>
<td>11.67(^a)</td>
</tr>
<tr>
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<td>≥ 23.1</td>
<td>4</td>
<td>99</td>
<td>0.41</td>
<td>0.09 to 0.92</td>
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<tr>
<td>Visual memory</td>
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<td>357</td>
<td>0.92</td>
<td>0.69 to 1.15</td>
<td>29.54(^b)</td>
<td>19.49(^a)</td>
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<tr>
<td></td>
<td>≥ 23.1</td>
<td>4</td>
<td>89</td>
<td>0.13</td>
<td>-0.36 to 0.62</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Fluency</td>
<td>&lt; 23.1</td>
<td>5</td>
<td>92</td>
<td>0.46</td>
<td>0.06 to 0.86</td>
<td>4.75</td>
<td>0.08</td>
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<td>0.52</td>
<td>0.14 to 0.90</td>
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<tr>
<td>Executive functioning</td>
<td>&lt; 23.1</td>
<td>5</td>
<td>84</td>
<td>0.26</td>
<td>-0.15 to 0.67</td>
<td>5.72</td>
<td>0.92</td>
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<td>≥ 23.1</td>
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<td>85</td>
<td>0.47</td>
<td>-0.03 to 0.96</td>
<td>1.67</td>
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<tr>
<td>Psychomotor speed</td>
<td>&lt; 23.1</td>
<td>2</td>
<td>32</td>
<td>0.89</td>
<td>-2.58 to 4.35</td>
<td>0.04</td>
<td>0.46</td>
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<tr>
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<td>49</td>
<td>0.66</td>
<td>-0.14 to 1.47</td>
<td>0.47</td>
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</tbody>
</table>

Groups are based on a median split. \(^a\)p < 0.001; \(^b\)p < 0.0001. For abbreviations see legend Table 3.
Cognitive dysfunction in lower motor neuron disease:
executive and memory deficits in progressive muscular atrophy

Joost Raaphorst
Marianne de Visser
Marie-José van Tol
Wim H Linssen
Anneke J van der Kooi
Rob J de Haan
Leonard H van den Berg
Ben Schmand

ABSTRACT

Objective
In contrast to findings in ALS, cognitive impairments have as yet not been shown in the lower motor neuron variant of motor neuron disease, progressive spinal muscular atrophy (PMA). Our objective was to investigate cognitive function in PMA and to compare the cognitive profile with that of ALS. In addition, we assessed visuospatial functions comprehensively; these tests are underrepresented in earlier neuropsychological investigations in ALS.

Methods
Twenty-three PMA and 30 ALS patients (vital capacity >70% of predicted value) underwent a neuropsychological assessment adapted to motor impairments: global cognitive and executive functioning, psychomotor speed, memory, language, attention and visuospatial skills. The results were compared with age, education and sex-matched controls and with normative data.

Results
Compared to controls PMA patients performed worse on attention/working memory (digit span backward), category fluency and the mini-mental state examination. Compared with normative data, PMA most frequently showed impairment on three measures: letter-number sequencing, immediate and delayed story recall. Seventeen percent of PMA patients showed cognitive impairment, defined as performance below two standard deviations from the mean of normative data on at least three neuropsychological tests. In ALS similar but more extensive cognitive deficits were found. Visuospatial dysfunction was not found in PMA and ALS patients.

Conclusion
Seventeen percent of PMA patients have executive and memory impairments. PMA with cognitive impairment adds a formerly unknown phenotype to the existing classification of motor neuron diseases.
INTRODUCTION
Cognitive impairments have been found in motor neuron disease patients with upper motor neuron (UMN) involvement: 30% of patients with amyotrophic lateral sclerosis (ALS), and a fair proportion of patients with primary lateral sclerosis have executive and memory deficits. Whether this holds true for patients with only lower motor neuron (LMN) signs is unclear. Progressive spinal muscular atrophy (PMA) is an adult-onset progressive LMN disorder. There is still debate on whether PMA is a distinct disease entity or whether it represents one end of the spectrum of motor neuron diseases. In favor of the latter claim are the clinical, genetic and pathologic features that PMA shares with ALS. We therefore hypothesize that PMA patients may exhibit cognitive impairments in similar domains compared to ALS. PMA seldom starts in bulbar neurons. As cognitive impairments have been found to be related to bulbar-onset ALS in some studies, cognitive impairment may not be encountered as frequently in PMA compared to ALS.

The main objective of this study was to explore the occurrence of cognitive dysfunction and its clinical correlates in PMA in comparison with that of ALS. In addition, we aimed to further define the cognitive profile of ALS by measuring visuospatial functions. Visuospatial test are underrepresented in earlier neuropsychological investigations in ALS and thus the presence of visuospatial deficits is unclear. Visuospatial dysfunction may be suspected in ALS, as patients with other disorders affecting the motor system (e.g. Parkinson's disease or dystonia) have shown visuospatial deficits.

METHODS
Subjects
Patients were recruited between January 2007 and January 2009 from the out-patient clinics of the Academic Medical Centre, Amsterdam and University Medical Centre Utrecht. Spouses and friends of patients were asked to participate as controls. We chose this control group to ensure that it would be matched for education and age, which are important variables that may influence cognitive measures. The medical ethical committees of the hospitals approved the study. Written informed consent was obtained from all participants. Included were PMA patients who fulfilled the criteria...
as earlier described: (1) a disease duration of less than 5 years from the time of
diagnosis, (2) clinical and electrophysiological evidence of LMN involvement in two or
more of four regions (bulbar, cervical, thoracic and lumbosacral), (3) no conduction
blocks on nerve conduction studies, and (4) no clinical UMN-signs and symptoms,
including forced yawning, crying and laughing, clonus of masseter reflex, (sub)clonic
myotatic reflexes, Hoffmann-Trömner sign, extensor plantar response, or spasticity.\(^3\)
All patients with ALS included in the study could be classified as probable or definite
according to the revised El Escorial criteria.\(^5\) Patients and controls were excluded if
they had dementia according to consensus criteria (Diagnostic and Statistical Manual
of Mental Disorders (DSM), American Psychiatric Association, 1994 and Lund-
Manchester Criteria,\(^10\) a history of another neurological disorder associated with
cognitive impairment, a vital capacity lower than 70% of the predicted value (to
prevent bias of respiratory compromise on cognitive measures),\(^9\) severe dysarthria
or anarthria, or if they were unable to push a button with the index or middle finger of
their dominant hand. Patients had to speak Dutch fluently and they had to be free of
psycho-active medication.

**Clinical assessment**

The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) was used to
evaluate the functional status of the patients.\(^6\) To assess upper motor neuron
involvement an unvalidated scale was used that summated myotatic and pathological
UMN reflexes and pseudobulbar affect. The scale is a modification of the scale used by
Ellis et al. (table 1).\(^9\)

In addition the following clinical variables were assessed: site of onset (bulbar of
limb); degree of bulbar involvement (defined as a score below 4 on 1 or more of the
bulbar items of the ALSFRS-R); disease duration (defined as the time between the first
symptom and the neuropsychological assessment); vital capacity (percentage of
predicted value: predVC) and the years of formal education.
Table 1. Upper motor neuron scale

<table>
<thead>
<tr>
<th>Reflex, symptoms</th>
<th>absent</th>
<th>barely visible</th>
<th>clearly hypoactive</th>
<th>slightly hypoactive</th>
<th>normal</th>
<th>slightly hyperactive</th>
<th>clearly hyperactive</th>
<th>subclonic</th>
<th>hyperactive or preserved</th>
<th>reflex wasted muscle</th>
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<tr>
<td>Hoffmann signs</td>
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<td></td>
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</tr>
<tr>
<td>Extensor plantar responses</td>
<td>absent</td>
<td></td>
<td></td>
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<tr>
<td>Clonus of masseter reflex</td>
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<td></td>
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</tr>
<tr>
<td>pseudobulbar affect*</td>
<td>one or more present</td>
<td></td>
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<tr>
<td></td>
<td>all absent</td>
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</tr>
</tbody>
</table>

*Pseudobulbar affect: forced crying, laughing or yawning

Neuropsychological assessment

Neuropsychological tests were administered in a fixed order with rest periods if needed. To further avoid a negative effect of fatigue the testing was done in an outpatient clinic in the vicinity of the patients’ homes.

Premorbid intellectual ability (National Adult Reading Test, Dutch version, DART), global cognitive functioning (MMSE) and six cognitive domains were tested: attention and working memory, executive functions, psychomotor speed, memory, language and visuospatial abilities (for neuropsychological tests and references, see appendix 1). Five tests relied on speed: Stroop test parts A (word naming), B (color naming) and C (word interference on color naming), category and letter fluency. The Stroop test part A was used to control for a possible negative effect of dysarthria on the fluency tests, by generating the measure fluency-motor speed corrected, according to the following formula (for letter fluency):
Letter fluency-motor speed corrected =

\[
\frac{(180 \times \text{time per word for Stroop part A}) \times \text{fluency score}}{\text{fluency score}}
\]

*Fluency score* = total amount of produced words with letters K, O and M in 180 seconds (60 per letter). *Time per word for Stroop part A* = mean time (in seconds) it took the subject to pronounce a color-word. A similar formula for category fluency was used.

The Stroop test part B (color naming) and C (word interference on color naming) were not accommodated for motor impairment. These tests were used to calculate the Stroop interference time (Stroop C – Stroop B, not motor speed dependent). The mental rotation task is described in detail in appendix 2. The Hospital Anxiety and Depression Scale (HADS) was used to examine symptoms of depression or anxiety.99

**Statistical analyses**

Differences in demographic and clinical characteristics between the PMA and ALS patients, respectively, and the control group were analyzed with a two group t-test. When data and their log or inverse transformations were not normally distributed, non parametric Mann-Whitney *U* tests were used to analyze differences between groups. The \( \chi^2 \) test was used to analyze nominal variables. Differences between the scores of neuropsychological measures of PMA and ALS patients, respectively, and the control group were expressed in Hedge’s *g* effect size. By convention, effect sizes of 0.2, 0.5 and 0.8 are considered small, moderate and large, respectively.63 A second set of analyses was done to examine the cognitive deficits in a manner similar to clinical practice. Standard scores, either scaled scores (mean 10; SD 3) or T-scores (mean 50; SD 10) were derived from available normative data in test manuals. Normative scores were taken from the following sources: Stroop Color Word Test and RBMT, www.psynip.nl,100 COWAT and category fluency,101 BNT,102 MWCST.103

**Frequency of cognitive dysfunction**

A test score was considered impaired if more than two standard deviations (SD) below the mean score of the normative sample, after correction for age, gender, and if possible, education. Cognitive dysfunction was considered to be present if
performance on more than two neuropsychological tests was impaired (measures without adjustment for motor impairment (Stroop test parts A, B and C) were excluded from this analysis). This criterion ensured that less than 5% of the control subjects would be impaired. In addition, the criterion minimizes the possibility that impaired performance reflects a chance finding due to the large number of measures employed.

**Demographic and clinical variables associated with cognitive impairment**

To identify variables associated with cognitive impairment, ALS and PMA patients with and without cognitive impairment were compared using the following variables: age; education; HADS total score and subscores; disease duration; ALSFRS-R (including a bulbar sum-score); site of onset and predVC. A possible relation of UMN-signs with cognitive impairment was explored in three ways: firstly, performance of the PMA and ALS patient groups on the neuropsychological tests were compared. Secondly, in the PMA and ALS patients together (MND patients), the UMN-score was compared between MND patients with and without cognitive impairment. Thirdly, within MND patients correlations between the UMN-score and performance on the neuropsychological tests were analyzed.

**RESULTS**

**Demographic and clinical characteristics**

Twenty-three PMA patients, 30 ALS patients and 24 age, sex and education matched controls were included. Age, sex distribution, years of education, DART-IQ estimate, HADS-scores and the ALSFRS-R were not significantly different in patients and controls (PMA vs. controls; ALS vs. controls and PMA vs. ALS, table 2). The median sum-score of the three ALSFRS-R bulbar items (normal score = 12) was 10 (range 6-11) in ALS patients and 12 (range 9-12) in PMA patients (p<0.05), respectively. The UMN-score was higher in ALS compared to PMA patients (p<0.001).

**Neuropsychological performance of PMA and ALS patients and control subjects**

Compared to controls, PMA patients performed worse on an attention/working memory test (digit span backward), category fluency and the MMSE. Compared to
controls, ALS patients showed impaired performance on attention/working memory (letter-number sequencing), category and letter fluency, Stroop test part B (not corrected for motor impairment), visual memory and naming (table 3). Effect sizes ranged from negligible to moderate (table 3). There were no statistical differences in performance on the neuropsychological tests between the PMA and ALS patient groups. Not all patients completed the neuropsychological battery: two visuospatial tests were not performed by some patients due to fatigue, technical problems (1 ALS patient, 1 control) and disease progression (not being able to push a button) between the moment the patient decided to participate and the neuropsychological investigation (2 ALS patients, 1 PMA patient).

Table 2. Demographic and clinical characteristics of patients and controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PMA (n=23)</th>
<th>ALS (n=30)</th>
<th>HC (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>17 / 6</td>
<td>18 / 12</td>
<td>12 / 12</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62.0 (9.3)</td>
<td>61.2 (11.8)</td>
<td>59.8 (11.8)</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>99.3 (16.2)</td>
<td>103.5 (15.6)</td>
<td>108.2 (18.2)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>13.6 (2.5)</td>
<td>13.8 (2.6)</td>
<td>13.9 (2.1)</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>4.4 (2.6)</td>
<td>4.2 (2.8)</td>
<td>4.6 (2.9)</td>
</tr>
<tr>
<td>HADS depression</td>
<td>4.1 (2.5)</td>
<td>4.4 (3.5)</td>
<td>3.5 (3.8)</td>
</tr>
<tr>
<td>HADS total</td>
<td>8.4 (4.8)</td>
<td>8.6 (5.8)</td>
<td>8.1 (6.1)</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>27.5 (18.0)</td>
<td>21.5 (11.2)</td>
<td>-</td>
</tr>
<tr>
<td>ALSFRS-R (max. 48)</td>
<td>41.6 (3.8)</td>
<td>40.3 (4.6)</td>
<td>-</td>
</tr>
<tr>
<td>Bulbar onset, No. (%)</td>
<td>0</td>
<td>10 (30)</td>
<td>-</td>
</tr>
<tr>
<td>Bulbar region affected, No. (%)</td>
<td>5 (22)</td>
<td>19 (57)</td>
<td>-</td>
</tr>
<tr>
<td>UMN-scoreb</td>
<td>14.7 (4.6)</td>
<td>29.7 (5.7)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless stated otherwise. HC: Healthy controls. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. HADS: Hospital Anxiety and Depression Scale. aBulbar region affected was defined as a score below 4 on 1 of the bulbar items of the ALSFRS-R. bUMN-score: sum score of myotatic and pathological UMN reflexes and pseudobulbar affect (range 0-48, normal score is 16, table 1).
Table 3. Neuropsychological test results: raw scores and effect sizes

<table>
<thead>
<tr>
<th>Test</th>
<th>PMA (n=23)</th>
<th>ALS (n=30)</th>
<th>HC (n=24)</th>
<th>Effect size</th>
<th>PMA</th>
<th>ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>28.1 (1.5)</td>
<td>28.3 (1.5)</td>
<td>29.0 (1.0)</td>
<td>-0.70</td>
<td>-0.53</td>
<td></td>
</tr>
<tr>
<td><strong>Attention/working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits forward raw score</td>
<td>7.4 (2.0)</td>
<td>7.7 (2.4)</td>
<td>8.4 (2.2)</td>
<td>-0.47</td>
<td>-0.30</td>
<td></td>
</tr>
<tr>
<td>Digits backward raw score</td>
<td>4.4 (1.9)</td>
<td>5.2 (1.7)</td>
<td>5.8 (1.7)</td>
<td>-0.76</td>
<td>-0.35</td>
<td></td>
</tr>
<tr>
<td>Number letter sequencing</td>
<td>9.4 (2.6)</td>
<td>9.1 (2.9)</td>
<td>10.3 (1.5)</td>
<td>-0.42</td>
<td>-0.49</td>
<td></td>
</tr>
<tr>
<td>span</td>
<td>5.1 (1.1)</td>
<td>4.9 (1.1)</td>
<td>5.5 (0.7)</td>
<td>-0.43</td>
<td>-0.62</td>
<td></td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop C time (s)</td>
<td>107.1 (35.6)</td>
<td>121.4 (57.8)</td>
<td>103.3 (31.7)</td>
<td>-0.11</td>
<td>-0.37</td>
<td></td>
</tr>
<tr>
<td>Stroop (interference)</td>
<td>52.0 (25.0)</td>
<td>52.7 (40.2)</td>
<td>47.8 (27.4)</td>
<td>-0.16</td>
<td>-0.14</td>
<td></td>
</tr>
<tr>
<td>WCST categories</td>
<td>5.6 (1.1)</td>
<td>5.3 (1.2)</td>
<td>5.5 (0.8)</td>
<td>0.10</td>
<td>-0.19</td>
<td></td>
</tr>
<tr>
<td>perseverative errors</td>
<td>7.3 (6.5)</td>
<td>8.2 (6.3)</td>
<td>6.8 (5.9)</td>
<td>-0.08</td>
<td>-0.23</td>
<td></td>
</tr>
<tr>
<td>non. pers. Errors</td>
<td>2.1 (3.3)</td>
<td>3.0 (4.1)</td>
<td>1.9 (2.0)</td>
<td>-0.07</td>
<td>-0.32</td>
<td></td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category time/item (s)</td>
<td>2.0 (1.1)</td>
<td>2.0 (1.0)</td>
<td>1.6 (0.5)</td>
<td>-0.46</td>
<td>-0.48</td>
<td></td>
</tr>
<tr>
<td>Letter time/item (s)</td>
<td>4.1 (1.9)</td>
<td>4.3 (1.8)</td>
<td>3.4 (0.9)</td>
<td>-0.47</td>
<td>-0.60</td>
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<tr>
<td><strong>Psychomotor speed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop A time(s)</td>
<td>43.3 (7.8)</td>
<td>54.2 (25.5)</td>
<td>44.7 (5.9)</td>
<td>0.20</td>
<td>-0.50</td>
<td></td>
</tr>
<tr>
<td>Stroop B time (s)</td>
<td>55.1 (14.2)</td>
<td>68.7 (27.0)</td>
<td>55.4 (8.7)</td>
<td>0.03</td>
<td>-0.62</td>
<td></td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doors A</td>
<td>10.3 (2.1)</td>
<td>9.6 (1.6)</td>
<td>9.8 (1.8)</td>
<td>0.25</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>Doors B</td>
<td>6.1 (2.0)</td>
<td>6.0 (2.6)</td>
<td>7.4 (2.4)</td>
<td>-0.58</td>
<td>-0.55</td>
<td></td>
</tr>
<tr>
<td>15 words test direct recall</td>
<td>39.0 (12.6)</td>
<td>43.1 (10.9)</td>
<td>43.3 (7.7)</td>
<td>-0.41</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>delayed recall</td>
<td>7.4 (3.8)</td>
<td>9.0 (3.5)</td>
<td>8.6 (2.7)</td>
<td>-0.36</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>recognition</td>
<td>13.8 (1.2)</td>
<td>13.8 (1.7)</td>
<td>14.0 (1.4)</td>
<td>-0.15</td>
<td>-0.12</td>
<td></td>
</tr>
<tr>
<td>RBMT immediate recall</td>
<td>16.6 (5.5)</td>
<td>16.3 (6.6)</td>
<td>16.7 (4.6)</td>
<td>0.02</td>
<td>-0.07</td>
<td></td>
</tr>
<tr>
<td>delayed recall</td>
<td>12.2 (5.0)</td>
<td>13.1 (6.3)</td>
<td>12.9 (4.5)</td>
<td>-0.14</td>
<td>0.04</td>
<td></td>
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<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston naming test</td>
<td>54.3 (5.9)</td>
<td>53.7 (5.5)</td>
<td>56.6 (1.6)</td>
<td>-0.53</td>
<td>-0.67</td>
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</tr>
</tbody>
</table>
Table 3 continued

<table>
<thead>
<tr>
<th>Visuospatial functions</th>
<th>PMA (n=23)</th>
<th>ALS (n=30)</th>
<th>HC (n=24)</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOLO</td>
<td>26.2 (4.4)</td>
<td>24.8 (4.5)</td>
<td>26.1 (4.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>DAT space relations&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27.7</td>
<td>24.7</td>
<td>26.1</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(18.2)</td>
<td>(20.1)</td>
<td>(4.0)</td>
<td></td>
</tr>
<tr>
<td>Mental rotation&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hand (ms)</td>
<td>1937</td>
<td>1808</td>
<td>1897</td>
<td>-0.04</td>
</tr>
<tr>
<td></td>
<td>(1017)</td>
<td>(625)</td>
<td>(936)</td>
<td></td>
</tr>
<tr>
<td>letter R (ms)</td>
<td>932</td>
<td>910</td>
<td>841</td>
<td>-0.37</td>
</tr>
<tr>
<td></td>
<td>(298)</td>
<td>(329)</td>
<td>(193)</td>
<td></td>
</tr>
</tbody>
</table>

Legend: values are mean (SD). P-values of <0.05 are considered significant (two group t-test), shown in bold. Negative effect sizes reflect impaired performance compared to controls. (ms)= (milli)seconds. MMSE: Mini-mental state examination; MWCST: Modified Wisconsin Card Sorting Test. RBMT: Rivermead Behavioral Memory Test; JOLO: judgment of line orientation; DAT: Differential Aptitude Test.

<sup>a</sup>speed dependent tests, not motor speed corrected, <sup>b</sup>n = 19,26,22 in PMA, ALS and HC, <sup>c</sup>n= 16,23,21 in PMA, ALS and HC

**Frequency of cognitive dysfunction**

Individual performance compared with normative data showed three measures that were most frequently impaired in PMA and ALS patients: letter-number sequencing, and immediate and delayed story recall. In the remaining tests the frequency of impairment was 10 percent or lower (figure 1).

Seventeen percent of PMA patients, 27 % of ALS patients and 4% of controls, respectively, displayed cognitive impairment defined as a score > 2 SD below the mean of normative data on at least three neuropsychological tests (table 4). Except for the Stroop interference condition and the RAVLT recognition, impairments on all tests were observed in one or more of the 8 cognitively impaired ALS patients. Tests that showed impairments in at least 50% of the cognitively impaired PMA and ALS patients were: letter-number sequencing, immediate and delayed story recall.

**Clinical variables associated with cognitive impairment**

The cognitively impaired ALS patients more often had bulbar onset, compared to the ALS patients without cognitive impairment (p <0.05). None of the PMA patients had bulbar onset.
One of the 4 cognitively impaired PMA patients and 6 of the 8 cognitively impaired ALS patients had bulbar involvement (not significant). Cognitively impaired ALS and PMA patients, respectively, did not differ from patients without cognitive dysfunction with respect to age, education, HADS total score and subscores, disease duration, ALSFRS-R, predVC and UMN-score. When PMA and ALS patients were analyzed together (n=53), the UMN-score did not differ between patients with and without cognitive impairment, nor did the UMN-score correlate to any neuropsychological test score.

Figure 1. Percentages of patients and controls with abnormal scores: lower than 2 SD below the population mean; tests with abnormal scores in <5% of PMA and ALS patients are omitted.

Table 4. Number of impaired tests and percentages of patients and controls demonstrating impairments.

<table>
<thead>
<tr>
<th>No. of tests impaired</th>
<th>PMA (%)</th>
<th>ALS (%)</th>
<th>HC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52.2</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>1</td>
<td>17.4</td>
<td>20</td>
<td>12.5</td>
</tr>
<tr>
<td>2</td>
<td>13.3</td>
<td>3.3</td>
<td>8.3</td>
</tr>
<tr>
<td>≥3</td>
<td>17.3</td>
<td>26.6</td>
<td>4.2</td>
</tr>
</tbody>
</table>
DISCUSSION

Cognitive dysfunction in PMA

This study is the first to demonstrate cognitive dysfunction in a relatively large cohort of PMA patients taking into account the potential negative influence of motor impairment and respiratory compromise on the neuropsychological assessment. Group differences between PMA and controls were found for attention/working memory (digit span) and category fluency. Seventeen percent of PMA patients showed cognitive impairment with attention/working memory (letter-number sequencing) and story recall being most frequently abnormal. Some tests showed group effects while they were not the most frequently abnormal tests. This inconsistency may result from a significant proportion of patients that have subclinical levels of impairment (for example in category fluency) yielding group differences, but no individual impairments.

The cognitive impairments in PMA patients, together with similar findings in ALS and PLS patients, suggest that extra-motor cerebral involvement is present in MND regardless of the presence or absence of UMN-signs.\textsuperscript{17,20,21,35} Indeed, when PMA and ALS patients were analyzed together no correlation between the degree of upper motor neuron signs and the presence of cognitive impairment could be demonstrated in this study. One earlier study also examined cognitive functions in PMA with adaptation of tests to motor impairment and exclusion of patients with respiratory weakness. This study did not show cognitive deficits. However, it may have been underpowered with 12 PMA patients undergoing 8 neuropsychological tests.\textsuperscript{23}

In the present study the PMA patients were found to have executive dysfunction with impairments on tests of category fluency and digit span backward. The profile of executive dysfunction is supported by the results of the letter-number sequencing test, a working memory task that was the most frequent abnormal test compared to norm scores in our PMA patients (22%). This is in agreement with impairments of attention and working memory in patients with ALS in our and other studies.\textsuperscript{18,20,50,104,105}

Since executive dysfunction, including fluency deficits, has been demonstrated in patients with depression,\textsuperscript{106} it is worth mentioning that our PMA patients did not
show signs of depression, and no differences in depression or anxiety scores were shown between PMA patients with and without cognitive impairment.

**Cognitive dysfunction in ALS: memory**

It has been suggested that in ALS retrieval is predominantly affected and recognition/encoding is relatively intact. Retrieval requires integrity of the prefrontal cortex for its executive component. Indeed, in ALS both prefrontal dysfunction and free recall problems have been shown. However, our findings in ALS patients indicate that in addition to retrieval (story recall), recognition is impaired, as the Doors B test showed group effects in ALS patients compared to controls. The Doors B test does not rely on active retrieval, but on passive recognition and its results are more specifically related to the process of encoding. Therefore, impairments on the Doors B test in ALS patients suggest that encoding deficits may as well underlie memory impairments in ALS. Whether encoding deficits in ALS are related to hippocampus dysfunction or attention deficits, or both, needs to be further studied.

**Cognitive dysfunction in ALS: visuospatial functions**

In the present study no visuospatial abnormalities were found in ALS (nor in PMA) patients compared to controls. We used more sensitive tests (e.g. space relations) compared to earlier studies that employed solely the judgment of line orientation or the Visual Space and Object Perception (VSOP) battery. Therefore, the findings of the present study demonstrate the “frontotemporal” cognitive profile in non-demented ALS, as memory, language and executive dysfunction was observed, while visuospatial dysfunction is absent.

**Comparison of the cognitive profiles of PMA and ALS**

In both PMA and ALS patients category fluency deficits were found. Also, in both PMA and ALS patients diverging results regarding executive tests were found: impaired fluency (letter and or category fluency) and normal results on the modified Wisconsin Card Sorting Test and Stroop interference tests. This pattern is in agreement with other neuropsychological studies in ALS and it emphasizes the different pathways in the executive system which may be selectively involved in MND. In addition to
executive deficits, in ALS, but not in PMA, the cognitive profile includes recognition and language deficits.\textsuperscript{18, 20} The MMSE was significantly lower in PMA patients but not in ALS patients compared to controls. However, differences between the MMSE scores are negligible and have thus very little clinical significance. In addition, the MMSE has a strong ceiling effect in controls, i.e., cognitively normal people perform (almost) perfectly resulting in small variance of scores in controls.

**Bulbar involvement**

The finding of cognitive impairment in our PMA patients, in whom bulbar symptoms were absent or if they occurred during the course were very mild, corroborates earlier findings that cognitive impairment does occur in MND-patients with isolated limb involvement.\textsuperscript{72} The potentially negative effects of dysarthria on neuropsychological measures are therefore not applicable to the great majority of the PMA patients in this study.\textsuperscript{17} In our ALS patients cognitive impairment was related to bulbar-onset, but not to bulbar involvement.\textsuperscript{41} These results show that in MND-patients bulbar onset predisposes to cognitive impairment, but is not a condition sine qua non.

**Upper motor neuron involvement**

This study shows that MND patients have cognitive impairments that are not per se related to the presence of UMN signs. One must bear in mind that the absence of (bulbar or spinal) UMN-signs does not exclude UMN-pathology in MND: pyramidal tract pathology in the spinal cord may go undetected in PMA patients and is only identified at autopsy.\textsuperscript{95} Indeed, it is interesting to examine whether cognitive deficits predict the development of UMN signs (i.e. ALS). However, this requires a longitudinal study, which is beyond the scope of this paper.

**Strengths and limitations**

Strengths: Firstly, bias due to severe motor impairment, dysarthria and respiratory dysfunction have been minimized in our study-design. Secondly, a wide range of cognitive domains was measured, including three tests assessing different
visuospatial abilities. Thirdly, two analytical procedures have been applied to assess
cognitive functions, i.e., comparison with normative data, and comparison of
neuropsychological performance with a matched control group.
Limitations: Firstly, some normative datasets are of better quality than other datasets,
e.g. correction for education is not possible for every test. Secondly, our criterion for
respiratory failure was based on the vital capacity only (VC<70% of predicted value),
which is a widely used and validated measure. However, this may not have entirely
excluded those patients with incipient respiratory failure. Currently, other methods
are known to have a higher sensitivity to assess respiratory failure in MND (e.g. Sniff
nasal inspiratory pressure, SNIP). Thirdly, patients with MND may complain of fatigue
which may influence neuropsychological scores negatively. We tried to exclude
fatigue as much as possible by appropriate timing and setting of the
neuropsychological examination. However, as we did not quantify fatigue we can not
completely exclude such an influence on our data.
Finally, as we have taken data from a clinic-based cohort, recruitment-bias may be
suspected. However, in the Netherlands the great majority of patients with
(suspected) MND and not only the “special” cases, are referred to specialized clinics
(e.g. Amsterdam and Utrecht) to verify the diagnosis. We estimate that the proportion
of patients that refused to cooperate with the study is about 20-30%.
In conclusion, in this study executive dysfunction and verbal recall deficits are
demonstrated in PMA. In ALS similar but more extensive cognitive deficits are found.
The cognitive impairments in different MND phenotypes may contribute to
understanding the extra-motor involvement and the heterogeneity within the MND
spectrum.
Appendix 1 – Neuropsychological investigations

Premorbid intellectual ability (National Adult Reading Test, Dutch version, DART)\textsuperscript{108}

Global cognitive functioning (MMSE)\textsuperscript{109}

Attention and working memory:

- Wechsler Adult Intelligence Scale-revised (WAIS-R) forward and backward digit span, and the WAIS-R letter-number sequencing.\textsuperscript{110}

Executive functions:

- Modified Wisconsin Card Sorting Test (MWCST)\textsuperscript{111}
- Category fluency (animals and supermarket items)\textsuperscript{112}
- Letter fluency or Controlled Oral Word Association Test\textsuperscript{113}
- Stroop Color-Word Test part C\textsuperscript{114}

Psychomotor speed:

- Stroop Color Word Test Part A and B\textsuperscript{114}

Memory:

- Rey Auditory Verbal Learning Test [8]\textsuperscript{115}
- Rivermead Behavioral Memory Test (RBMT) immediate and delayed story recall\textsuperscript{116}
- Doors Test A and B (visual recognition test)\textsuperscript{117}

Language:

- Boston Naming Test (BNT)\textsuperscript{118}

Visuospatial abilities:

- Judgment of line orientation test (JOLO)\textsuperscript{119}
- Differential Aptitude Test, subtest Space Relations\textsuperscript{120}
- Mental rotation task (Appendix 2).
Appendix 2 - The mental rotation task

Subjects had to judge whether drawings of hands on a computer screen were left or right hands. Images of hands could be presented in two views (back in picture plane, palm in picture plane) and six angular orientations (upright stimuli with fingers pointing upwards had a rotation angle of 0°; five clockwise rotations of upright stimuli, namely 60°, 120°, 180°, 240° and 300°, were used). After a practice session of twelve images two separate trials of 144 images in a random sequence were presented with a number of other neuropsychological tests in between. The judgments were separated in time to avoid an effect of fatigue. The participant had to respond as fast as possible by pressing a button with the index or middle finger of the right hand, when a hand was judged a left or a right hand, respectively. The image disappeared when the button was pressed and was followed by the next image after a fixed interval of 500 milliseconds (ms). A computer program logged reaction times and correct and false responses. Only correct responses were analysed.

To adjust for motor impairment we constructed a simple button press task as a control task: on a screen 50 consecutive pictures of geometric forms (triangle, circle or square) were shown randomly with a variable time in between the forms (a jitter of 600-1800 ms). Participants used the same device as in the mental rotation task and were instructed to respond as quickly as possible after a form appeared. We used two versions of 50 pictures, for both the index and middle finger for which a mean reaction time (RT) was calculated separately, from the automatically logged results. Tasks were programmed using the E-prime software running on a PC.

From the hand rotation data, the mean reaction time (RT) of the sum of responses for each angle was calculated (using SPSS) for both hands and for both views. The mean RT of the control task (i.e. index or middle finger) was distracted from the appropriate (i.e. reactions with either index or middle finger) RTs of the mental rotation task generating a corrected mental rotation time for every angle, for both left and right hands and both views. These mean corrected reaction times were added to calculate a total mean corrected RT for every individual. This was used in the analyses (table 2).

We also analysed the results of percentage correct, right and left hands separately, and different angles, separately which did not show significant differences between the study groups. Finally, we pooled the results of ALS and PMA patients as one group.
(i.e. MND patients). Compared to controls MND patients did not perform worse on the mean RT or any of the additional analyses described above.

A second version of the mental rotation task consisted of one trial of 144 images of normally or mirror-imaged displays of the letter “R” in the same angles as the hands; patients had to judge whether the “R” was normally or mirror imaged. This task had a similar design compared to the hand rotation task and was analysed accordingly (table 2). For this task additional analyses as described above did not show significant differences between PMA and controls or ALS and controls.
Is the Frontal Assessment Battery reliable in patients with amyotrophic lateral sclerosis?

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Chapter 4

ABSTRACT

Objective
The assessment of frontal functions in ALS patients is important because of the overlap with the behavioral variant of frontotemporal dementia (bvFTD). We investigated the applicability and reliability of the Frontal Assessment Battery (FAB) within a cohort of predominantly prevalent ALS patients.

Methods
The FAB was administered to 85 ALS patients and eight ALS-bvFTD patients. Original scores and the percentage of items that could be performed were recorded. Item-adjusted scores of the FAB were calculated. The ALS Functional Rating Scale-Revised version (ALSFRS-R) was used to assess disease severity.

Results
Eighty-seven patients (94%) had ALS symptoms of more than one year. Twenty patients (21.5%) were not able to perform one or more FAB items. The original FAB score correlated with the ALSFRS-R score ($r=0.30$; $p<0.01$), while the item-adjusted FAB score did not. In contrast to the original FAB scores, the item-adjusted FAB score was lower in ALS-bvFTD patients (66.7, range 33.3 – 100) compared to ALS patients without bvFTD (94.4, range 38.9 – 100; $p < 0.01$).

Conclusion
Twenty percent of prevalent ALS patients could not complete the FAB, which limits its use in ALS and emphasizes the importance of disease specific instruments and adjusting for motor impairment in cognitive and behavioral examinations of ALS patients.
INTRODUCTION

The assessment of frontal functions in amyotrophic lateral sclerosis (ALS) is of utmost importance because of the overlap with the behavioral variant of frontotemporal dementia (ALS-bvFTD). Recently, several research groups suggested that the Frontal Assessment Battery (FAB) is a feasible screening instrument for frontal dysfunction in ALS patients with mild disease severity. Five of the six FAB items rely on the ability to speak quickly or to move the (dominant) hand(s) (e.g. fluency, the Luria, fist-edge-palm test, “do not take my hands”). In patients without dysarthria and motor symptoms these items measure frontal lobe dysfunction. However, it is unknown whether these items are applicable and valid in ALS patients with moderate to severe speech and motor impairment. This is of particular interest as bvFTD may develop during the course of ALS and may have a negative impact on the initiation of palliative therapy and survival. We investigated the applicability and reliability of the FAB in a cohort of ALS patients with a diverging severity and duration of the disease.

METHODS

We administered the FAB to 93 ALS patients diagnosed at a tertiary referral center for ALS and we recorded original scores and percentage of items that could be performed. Item-adjusted scores of the FAB were calculated according to the formula: Item adjusted score = original score * 100 / % of items performed. We administered the ALS Functional Rating Scale Revised version (ALSFRS-R) as a measure of disease severity (maximum score of 48 indicates no impairment). The Mann Whitney U test, Fisher exact test and Spearman correlation coefficient were used.

RESULTS

Most of the 93 ALS patients (ALS=85, ALS-FTD=8) were prevalent cases: 87 had symptoms more than 1 year; 67 patients were diagnosed more than 1 year previously. The FAB was administered to 85 ALS and 8 ALS-bvFTD patients (diagnosed according to El Escorial and Neary criteria; table). Twenty patients (21.5%) were unable to perform one or more items of the FAB due to muscle weakness of the (dominant) hand(s) and dysarthria. Five patients missed one item, seven patients missed two
items, seven patients missed four items and one patient missed five items. Nineteen patients could not perform the Luria item and 14 patients could not perform the “Do not take my hands” item. In the total cohort of 93 patients the original FAB score correlated with the ALSFRS-R score (r=0.30; p <0.01), while the item-adjusted FAB score did not correlate with the ALSFRS-R score (-0.05, p=0.61). Compared to the patients with a complete FAB, the 20 patients with an incomplete FAB had a lower ALSFRS-R score (median 23.5 (13-34) vs. 34 (8-47), p <0.001) and a longer, albeit not significantly, disease duration (median 46 months (12-328) vs. 34.5 (0-322), p=0.32). The table shows the characteristics of the ALS and ALS-bvFTD patients. Compared to ALS patients the item-adjusted FAB score was lower in ALS-bvFTD patients, while the original FAB score was not significantly lower in ALS-bvFTD patients.

**DISCUSSION**

Our data show that 20% of predominantly prevalent ALS patients cannot complete the FAB due to motor symptoms. These findings limit the use of the FAB in ALS patients and emphasize the importance of disease specific instruments and adjusting for motor impairment in cognitive and behavioral examinations of ALS patients.

| Table. Demographic and clinical characteristics of ALS patients assessed with the FAB |
|---------------------------------|------------------|------------------|------------------|
|                                | ALS (n=85)       | ALS-bvFTD (n=8)  | p-value |
| Age (y)                        | 61.2 (11.4)      | 62.5 (10.4)      | 0.69    |
| Sex (m/f)                      | 60/25            | 6/2              | 0.57    |
| Limb/bulbar onset              | 74/11            | 3/5              | <0.01   |
| Bulbar involvementa            | 63.5%            | 100%             | 0.05    |
| Disease duration, months (median, range) | 36 (8-328) | 29.5 (0-80) | 0.20    |
| Time since diagnosis, months (median, range) | 24 (1-310) | 12 (4-40) | 0.18    |
| ALSFRS-Rb                      | 31.4 (9.1)       | 31.9 (5.8)       | 0.99    |
| Original FAB score (median, range) | 16 (3-18)   | 12 (6-18)        | 0.10    |
| Item-adjusted FAB scorec       | 94.4 (38.9-100)  | 66.7 (33.3-100)  | <0.01   |

Data are mean (SD) or as stated. BvFTD = behavioral variant frontotemporal dementia; a score <4 on ≥1 of the bulbar items of the ALSFRS-R. bMaximum score is 48 indicating no motor dysfunction. cItem-adjusted FAB score: raw total score *100/% of items performed. FAB = Frontal assessment battery; maximum score is 18, indicating no frontal impairment; 26 patients (28%) scored in the FTD range (below 12).
The verbal fluency index: normative data for cognitive testing in ALS

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ABSTRACT

Objective
Executive dysfunction occurs in 30-50% of amyotrophic lateral sclerosis (ALS) patients and is most frequently assessed with the verbal fluency test. The verbal fluency index (VFI) has been developed to correct for slowness of speech in ALS, but its use as a marker of cognitive impairment is hindered by the absence of valid norm scores. Therefore, we provide normative data for the VFI.

Methods
Dutch volunteers were demographically matched to the Dutch ALS population and completed the verbal fluency index (one-minute and three-minutes spoken letter fluency). Multiple stepwise linear regression was performed to assess the influence of demographic and disease variables.

Results
273 volunteers participated in this study. Educational level was negatively correlated to one-minute and three-minutes VFI performance (r = -0.3 and r = -0.4, p < 0.001, respectively). No correlations for age, gender medication, past medical history and alcohol use were found. A formula for standardized z-scores, corrected for educational level, for the one-minute and three-minutes VFI was calculated.

Conclusion
We provide normative data for the verbal fluency index, which can be used internationally, but validation in other countries is recommended. The findings illustrate the importance of valid disease specific norm scores for motor speed dependent cognitive tests in ALS.
INTRODUCTION
In 30-50% of amyotrophic lateral sclerosis (ALS) patients cognitive changes have been demonstrated, in particular executive dysfunction. Verbal fluency is a sensitive and reliable test of executive functioning and is used as a marker of cognitive performance in ALS. Verbal fluency performance is related to educational level and age. Because verbal fluency is a time-dependent task, it is important to correct for slowing of speech in ALS patients. For this reason, the verbal fluency index (VFI) has been developed, which represents the average thinking time per word. Most frequently, one-minute and three-minutes versions of the spoken version of the VFI (letter fluency) are used. Preliminary English normative VFI data did not include correction for educational level or age and were based on 20 healthy controls who had a slightly higher education level than the ALS patients, possibly overestimating dysfunction in patients. The interpretation of fluency deficits in ALS patients can be further improved by normative VFI data based on a larger sample of controls. This cohort should be carefully matched with ALS patients on demographic variables that may exert an effect on letter fluency performance, i.e. education and age. Our aim was to provide normative data for the one- and three-minute letter fluency index.

METHODS
Study population
Two hundred and ninety-five native Dutch speaking volunteers participated in a population-based epidemiological ALS-study in the Netherlands (PAN) and were selected by general practitioners who look after patients with ALS. The volunteers were matched for age, gender and education to 1009 ALS patients of the PAN study, included between June 2006 and May 2012. No VFI data of ALS patients are presented in this study; the demographic data of the ALS patients were only used to analyze whether the cohort matched with a representative ALS population. This study was approved by the Ethics Committee of the University Medical Centre Utrecht, and procedures were according to the Helsinki Declaration of 1975, revised in 1983.
Demographic variables

The past medical history and use of alcohol and sedative medication were recorded and dichotomized with 0 indicating no supposed effect on VFI performance and 1 indicating a possible effect on VFI performance (e.g. epilepsy in past medical history, use of sedative medication or three or more alcohol units per day). The level of education was classified into seven categories, ranging from primary school to university degree, which closely resembles the International Standard Classification of Education (ISCED, 2011).

Procedures

Research assistants of the Dutch epidemiological study were trained twice by two authors (EB and JR) and administered the VFI to the volunteers during a home visit. Participants were asked to name as many words beginning with the letter “D” in three minutes. The letter “D” was chosen following a strategy comparable to that used for the COWAT fluency test by Benton and Hamsher. This strategy is based on the frequency of words in a language. The letter “D” in Dutch resembles the letters “F” and “S” in English, in terms of difficulty. Names, variations of the same word (e.g. “door” followed by “doors”), same words with a different suffix (e.g. “doorknob” followed by “doorpost”), repetitions and non-existing words were not permitted. The number of words after one and three minutes was recorded. The VFI (letter version) consists of two conditions: in the generation condition participants name as many words beginning with a certain letter in three minutes. In the control condition, participants have to read aloud these produced items as quickly as possible. The fluency index is calculated as follows:

\[ \text{VFI} = \frac{\text{time needed for generation} - \text{time needed for reading}}{\text{total number of items generated}} \]

The VFI reflects the average thinking time needed to generate a word. We used the spoken version of the VFI in this study. To screen for executive dysfunction, the frontal assessment battery (FAB) was administered to all participants (maximum score is 18; scores < 14 indicate frontal/executive dysfunction).
Statistical analysis
The volunteers were matched to 1009 ALS patients for age (independent t-test),
gender (chi-square test) and level of education (Mann-Whitney U test). To examine
the effects of age, gender, education, medication, past medical history and alcohol and
tobacco use on VFI scores in the volunteer group, multiple stepwise linear regression
was used.

RESULTS
Study population
Twenty-two participants with more than 5 errors (perseverative errors, rule-breaks
and non-existing words) were excluded. Data of 273 participants were analysed (165
males, 60.4%). The mean (SD) age was 64.0 years (9.2). The median (interquartile
range) educational level was 4 (3-6) and ranged from ‘primary school’ (n= 13) to
‘university degree’ (n= 18, table).

Table. Levels of education of the volunteers

<table>
<thead>
<tr>
<th>Level of education</th>
<th>Number of volunteers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Primary school</td>
<td>13 (4.8)</td>
</tr>
<tr>
<td>2  Lower secondary education</td>
<td>49 (17.9)</td>
</tr>
<tr>
<td>3  Upper secondary education</td>
<td>67 (24.5)</td>
</tr>
<tr>
<td>4  Post-secondary education</td>
<td>46 (16.8)</td>
</tr>
<tr>
<td>5  First stage of tertiary education</td>
<td>28 (10.3)</td>
</tr>
<tr>
<td>6  College degree</td>
<td>52 (19.0)</td>
</tr>
<tr>
<td>7  University degree</td>
<td>18 (6.6)</td>
</tr>
</tbody>
</table>

Levels of education are categorized according to the International Standard Classification of Education
2011, excluding the levels 0 (less than primary), 8 (doctoral) and 9 (not elsewhere classified).

The volunteers were matched for age (p= 0.1) and gender (p= 0.8) to the ALS patients
in the PAN study: mean age 63.0 (10.9); 603 males (59.8%), 406 females. The
distribution of education levels of the volunteer cohort and the PAN study cohort was
comparable (p= 0.08).
Verbal fluency index

The mean (SD) number of words (raw score) of the one-minute and three-minutes versions was 11.0 (3.9) and 22.8 (7.6), respectively. The median (interquartile range) VFI of the one-minute and three-minutes versions was 4.7 (3.5-6.4) and 7.0 (5.6-9.5), respectively. Educational level was negatively correlated to one-minute and three minutes VFI performances (r= -0.3 and r=-0.4; p <0.001, respectively). There was no effect of age, gender, medication, past medical history and use of alcohol and tobacco on VFI scores. The regression formula for the transformation of raw scores into a standardized z-score for the VFI one-minute version was $Z = \frac{(7.39 - (0.50 \times \text{education}) - \text{VFI})}{2.72}$; and for the three-minutes version this was $Z = \frac{(11.23 - (0.81 \times \text{education}) - \text{VFI})}{3.46}$. For “education” we used the classification ranging from 1 to 7, as shown in table 1.

DISCUSSION

In this study we provide normative data for a spoken fluency test for Dutch ALS patients based on a large dataset. Verbal fluency index (VFI) scores in the present study correlated to the level of education, with better performance in higher educated subjects, which is similar to conventional fluency tests, that are not corrected for motor slowness. Fluency performance on conventional tests increases until 30 – 39 years of age with only a mild decline after the age of 70.60 We did not find age-related differences on VFI performance in our volunteer cohort. The majority of the volunteers were between 40 and 70 years of age, which might explain the absence of an age effect in this cohort.

Data collection for the written version of the VFI is in progress and a preliminary analysis of 34 participants showed an effect of education on VFI, comparable to the spoken version (data not shown). A possible drawback of our study is that the test was administered in the home setting, where subjects may be easily distracted (e.g. by telephone). However, this setting could also be an advantage, as cognitive testing in ALS patients is frequently performed at home to spare them the fatigue of travelling.129

Twenty-two participants were excluded due to a high number of errors on the VFI. The errors consisted mainly of rule-breaks, i.e. ‘door’ followed by ‘doors’. These
participants did not show evidence of frontal lobe dysfunction on the FAB and did not differ from the included participants on demographic variables. Therefore, we assume that for these participants the instructions of the VFI have not been sufficiently clear. An exploratory regression analysis including these 22 participants did not change the regression coefficients. Currently available English norm scores of the VFI for ALS patients are not corrected for education or age. They are based on a cut-off of 2 standard deviations below the mean of the scores of 20 healthy controls, who had a relatively high level of education, compared to the ALS patients. Importantly, the present study is based on 273 subjects with a wide range of age and educational levels, comparable to a Dutch ALS population. Therefore, our normative data and z-score transformation formula can be used to further improve the assessment of letter fluency deficits in ALS patients. According to the consensus criteria for cognitive impairment in ALS, a score below the 5th percentile is considered abnormal, which corresponds to a z-score below -1.64. These normative data might be used internationally as the letter “ D ” in Dutch was chosen following a strategy similar to that used for the COWAT test and the classification of educational levels is comparable to the ISCED 2011 (11,14). We recommend validation of our findings in other countries.
Part II

Behavioral disturbances in motor neuron disease
A systematic review of behavioral changes in motor neuron disease

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Objective
Motor neuron disease (MND) and the behavioral variant of frontotemporal dementia (bvFTD) are thought to be part of a disease spectrum. There is uncertainty about the frequency and characteristics of behavioral changes in MND, and similarly, about a relation between bvFTD and the site of onset of MND. Our aim was to perform a systematic review of the publications on behavioral changes in MND.

Methods
An extensive search for articles on behavioral changes in MND patients was performed. First, cohort studies of MND patients were reviewed to summarize the prevalence of bvFTD and mild behavioral changes. Second, data on bvFTD symptoms (mostly from case-reports) of individual MND-bvFTD patients were used to analyze characteristics and pooled prevalences of bvFTD symptoms. In addition, site of onset, survival and demographic variables of MND-bvFTD patients were analysed.

Results
In cohorts, 8.1% (95% CI 5.6-11.5%) of MND patients had bvFTD. In 170 individual patients with MND-bvFTD, perseveration (40%), apathy (29%) and disinhibition (26%) were the most frequently reported behavioral changes; 43% had memory disturbances and bulbar onset was found in 48%.

Conclusion
Eight percent of MND patients have bvFTD, with perseveration being reported most frequently. MND-bvFTD is often accompanied by memory disturbances and is related to bulbar onset.
INTRODUCTION
Neuropathological and genetic studies have suggested a disease spectrum with motor neuron disease (MND) and frontotemporal lobar degeneration (FTLD) on the extreme ends.\textsuperscript{12,31} This spectrum includes a variety of cognitive disturbances and behavioral symptoms in amyotrophic lateral sclerosis (ALS), the major form of MND. When these behavioral symptoms are severe, criteria for the behavioral variant of frontotemporal dementia (bvFTD) may be fulfilled.\textsuperscript{10}
Neuropsychological studies have shown that cognitive deficits can be observed in 27-45\% of ALS patients including impairments of executive, memory and language functions.\textsuperscript{17,20,40} These findings, and the absence of visuospatial dysfunction,\textsuperscript{140} suggest a “frontotemporal cognitive profile.”\textsuperscript{107} Similar findings have been shown in patients with progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS), the lower and upper motor neuron variants of MND, respectively.\textsuperscript{21,140}
The frequency and characteristics of behavioral symptoms however, which are the hallmark of bvFTD, have not been firmly determined in MND. There is ongoing debate about the prevalence of behavioral changes (both bvFTD and mild behavioral changes) and the association of bvFTD with clinical variables of MND, i.e. bulbar onset and survival.\textsuperscript{15,24,35,126}
Our aim was to systematically review the literature on MND and behavior in order to 1. estimate the prevalence of bvFTD and of mild behavioral changes in MND; 2. calculate prevalence rates of bvFTD symptoms (behavioral, cognitive and psychiatric symptoms) in MND-bvFTD patients, and 3. determine the site of MND onset, survival and age of onset in MND-bvFTD patients.

METHODS
Literature search
A comprehensive literature search was done in October 2011 in PubMed (1954-) Web of Science (1975-) and PsycInfo (1860-) for articles in English, French, German, Italian and Dutch with the search terms in box 1. The nomenclature of the entity now known as bvFTD has changed over time, and therefore patients with the diagnoses: “MND-Pick’s disease, MND-dementia” were included in our search. Full-length articles, reviews and abstracts were considered. Articles were retrieved on MND patients with
bvFTD on the one hand, and patients with dementia and MND symptoms on the other hand. Articles were screened by their title and if judged possibly relevant, the abstract was read. Relevant articles were evaluated in detail. Reference lists were checked for additional articles (figure 1).

**Inclusion and exclusion criteria**

Articles judged to be relevant were divided into cohort studies (part A) and case-studies/series (part B, figure 1).

In part A of the study, the cohort studies were used to examine the prevalence of bvFTD and mild behavioral changes in MND.

For part A of the study we included all prospective studies with an inception cohort if they reported: 1) description of the patient sample; 2) a validated method to assess either FTD or mild behavioral changes and 3) prevalence rates, or data enabling calculation of prevalence rates of the behavioral subtype of frontotemporal dementia/frontotemporal lobar degeneration (FTLD), or mild behavioral changes.

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**Box 1 List of keywords**

**MND related keywords:**
- Amyotrophic Lateral Sclerosis; ALS; Gehrig Disease; Gehrig's Disease; Gehrig's Disease; Lou Gehrig Disease; Lou Gehrig's Disease; MND; Motor Neuron Disease; Motor Neuron Disease; amyotrophe Lateralsklerose; amyotrofischen Lateralsklerose; amyotrophische Lateralsklerose; amyotrophischer Lateralsklerose; sclerose laterale amiotrofica; sclerose laterale amiotrophiique; sclerosis laterale amiotrofica; SLA; Progressive muscular atrophy; Progressive Spinal Muscular Atrophy; PMA; PSMA, atrophie musculaire progressive, lower motor neuron disease, lower motoneuron disease, lower motor neurone disease, Primary Lateral Sclerosis; PLS, upper motor neuron disease, upper motoneuron disease, upper motor neurone disease (the search was repeated with "disease" replaced by “disorder” and “syndrome”).

**FTD related keywords:**
- Behavior; Behavioral changes; Behavior; Behavioral changes; Mild behavioral changes; Dementia; Frontal lobe dementia; Frontotemporal dementia; Frontotemporal Lobar Degeneration; Frontotemporal Lobar Degenerations; Frontotemporal lobe degeneration; FTD; FTLD; Pick Disease; Pick's disease; Picks Disease; Presenile dementia; Demence; Demence presenile; Demence progressive; disturbi mentali; disturbi psichici; les troubles mentaux; maladie de Pick; Pickse Krankheit; Psychiatrische Störungen; Psychiatrischen Störungen; Psychische Störung; Psychischen Symptomen
Legend: Nine out of the 21 included cohort studies calculated the prevalence of bvFTD in MND, of which four also determined the prevalence of mild behavioral changes in MND; four other studies calculated the prevalence of mild behavioral changes in MND and eight studies described behavioral changes without presenting prevalence rates.
For part B of the study, case reports and case series were used to calculate prevalence rates of bvFTD symptoms (behavioral, cognitive and psychiatric symptoms) in MND-bvFTD patients. In addition, within the group of MND-bvFTD patients we compared the site of onset, survival and age of onset between the MND onset and bvFTD onset patients.

For part B, single case studies, case series and reviews including one or more case studies of MND-bvFTD patients with either MND or bvFTD onset were included if they reported:

- bvFTD symptoms in one (single case study) or more (case series) individual patients
- information allowing the extraction of
  - the diagnosis ALS, PMA or PLS
  - one of the following diagnoses: FTD, Pick’s disease, FTLD or ALS-dementia

Studies were excluded for part B of the study if they reported:

- patients with pure language variants of FTLD (i.e. without behavioral changes) or Alzheimer’s disease (i.e. a clinical and pathological diagnosis).
- patients with MND variants (e.g. Mills’ syndrome or Kennedy’s disease)
- less than two behavioral symptoms or only cognitive or only psychiatric symptoms.

**Assessment of studies**

A significant proportion of the included studies in part B was published before the diagnostic El Escorial criteria for ALS and the Neary criteria for a diagnosis of FTD were established.\(^57, 141\) One of the authors (JR) assessed the diagnoses of these patients. This assessment was based on the clinical description in combination with the results of a pathological examination, which was available in 81 cases (48%). Based on descriptions of definite upper motor neuron signs and symptoms (forced yawning, crying and laughing, clonus of masseter reflex, (sub)clonic myotatic reflexes, Hoffmann-Trömner sign, extensor plantar response and spasticity), and when
available, results of a pathological examination, all patients could be classified as either PMA, ALS or PLS. Accordingly, based on clinical descriptions and pathological examination when available, patients could be labeled as FTD (including Pick’s disease).

Data extraction
For part A: prevalence of bvFTD and mild behavioral changes in MND, the following data were extracted from the cohort studies: number of patients; percentage of ALS patients with bulbar onset; description of the patient sample; method used to assess bvFTD or mild behavioral changes; (point) prevalence of bvFTD, or mild behavioral changes; description of the diagnosis, i.e. the definition of bvFTD.

For part B: bvFTD symptoms in MND patients, the following data were extracted from the case studies/case series: gender, age at onset, age at diagnosis, MND diagnosis (ALS, PMA or PLS) duration of disease, whether the patient was first diagnosed as MND or bvFTD, bulbar or limb onset MND, bvFTD symptoms (i.e. behavioral, cognitive and psychiatric symptoms).

Data analysis
Study, demographic and clinical characteristics were summarized with simple descriptive statistics.

Part A: prevalence of bvFTD and mild behavioral changes in MND: Point prevalence rates presented in the cohort studies were pooled, accounting for inter-study variation and analysed using a nonlinear random effects model.

Part B: bvFTD symptoms in MND patients: Differences regarding gender, age, survival and site of onset (of ALS) between patients with ALS-onset and patients with bvFTD-onset were analysed using a two group t-test or Mann-Whitney U test, when appropriate. Data analyses were performed in SPPS version 17.0 and SAS 9.1 (module proc. nlmixed).

Additional data analysis for part B: the descriptions of behavioral, cognitive and psychiatric disturbances respectively, were categorized into bvFTD symptoms (appendix 1). When memory problems were mentioned in the patient description, all of the following descriptions: “disturbances”, “changes”, “impairment”, and “deficits”
were interpreted as “memory disturbance”, in the absence of a formal neuropsychological examination. A small number of studies reported neuropsychological test results; these were not analysed in this study. Percentages of the categorized bvFTD symptoms were calculated from patients in case studies or case series (numerator = number of patients with the disturbance; denominator = total number of patients). Using these percentages pooled prevalence rates accounting for inter-study variation were analysed using a nonlinear random effects model.

RESULTS

Part A
Prevalence of bvFTD in MND patients.
The search retrieved nine studies with prevalence rates of bvFTD in cohorts of MND patients (table 1). ALS patients were studied in eight studies24, 35, 41, 133, 142, 145-147; ALS and PMA patients in one study.144 In four studies selection bias was evident from the patient sample description: only bulbar onset MND patients were included145; or cohorts consisted of subsets of MND patients who underwent further neuropsychological investigation after an initial screening.41, 133, 146 In the remaining 5 studies, which either included consecutive MND patients visiting a clinic, or members of a MND patient-association responding to a postal survey, or a population based cohort, the prevalence of bvFTD according to Neary’s criteria ranged from 5.3% to 12.5% (table 1).24, 35, 142, 144, 147 The pooled prevalence rate of bvFTD in MND taken from these five studies is 8.1% (n= 570; 95% CI 5.6-11.5%).

Prevalence of mild behavioral changes in MND patients
The search retrieved eight studies with prevalence rates of mild (n=7) or moderate (n=1) behavioral changes in cohorts of MND patients without dementia (table 2).24, 133, 142, 144, 148-151 ALS patients were studied in seven studies; ALS and PMA patients in one study.144
Table 1. Prevalence of the behavioral variant FTD in MND: results from cohort studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Bulbar %</th>
<th>Patient sample</th>
<th>Assessment</th>
<th>Prevalence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringholz</td>
<td>279</td>
<td>34</td>
<td>Consecutive patients in two hospitals (USA)</td>
<td>NPE, (family) interviews</td>
<td>5%</td>
<td>bv-FTD</td>
</tr>
<tr>
<td>Murphy</td>
<td>23</td>
<td>27</td>
<td>Volunteer cohort, multidisciplinary clinic (USA)</td>
<td>NPE, NPI, MRI</td>
<td>9%</td>
<td>behavioral variant FTLD</td>
</tr>
<tr>
<td>Lillo</td>
<td>92</td>
<td>22</td>
<td>Respondents to postal survey sent to members of patient association (AUS)</td>
<td>Clinical questionnaire for bvFTD symptoms and CBI-R</td>
<td>11%</td>
<td>(estimated to) fulfill criteria for bvFTD</td>
</tr>
<tr>
<td>Phukan</td>
<td>160</td>
<td>34</td>
<td>Population based (Ireland)</td>
<td>Semi-structured interviews</td>
<td>11%</td>
<td>bv FTD</td>
</tr>
<tr>
<td>Gibbons</td>
<td>16</td>
<td>13</td>
<td>Consecutive patients in MND clinic (UK)</td>
<td>Informant based semi-structured interview</td>
<td>13%</td>
<td>behavioral symptoms in the range seen in FTD</td>
</tr>
<tr>
<td>Portet</td>
<td>23</td>
<td>100</td>
<td>Bulbar ALS patients in a neurology clinic (F)</td>
<td>NPE, clinical exam. during hospital admission</td>
<td>18%</td>
<td>severe behavioral changes consistent</td>
</tr>
<tr>
<td>Woolley</td>
<td>31</td>
<td>34</td>
<td>Subset of patients visiting two ALS clinics (USA)</td>
<td>NPE, FrSBe</td>
<td>19%</td>
<td>FTD</td>
</tr>
<tr>
<td>Lepow</td>
<td>37</td>
<td>n.g.</td>
<td>Subset of patients at and ALS clinic who underwent further testing after screening (USA)</td>
<td>NPE, FrSBe</td>
<td>19%</td>
<td>FTD</td>
</tr>
<tr>
<td>Lomen-Hoerth</td>
<td>44</td>
<td>43</td>
<td>Subset of 100 pts of an ALS clinic who underwent further testing after screening or were referred to memory clinic (USA)</td>
<td>NPE, NPI, CDR</td>
<td>27%</td>
<td>research criteria for for probable or variant of FTLD</td>
</tr>
</tbody>
</table>

n = number. Bulbar % = % of patients with bulbar-onset; n.g. = not given; NPE: neuropsychological examination; NPI = Neuropsychiatric Inventory; CBI-R = Cambridge Behavioral Inventory-Revised; FrSBe = Frontal Systems Behavior Scale; CDR = Clinical Dementia Rating Scale; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration.
Mild to moderate behavioral changes (according to diverging definitions, and examined with instruments which have not been validated for MND patients) were shown in 17-88% of MND patients (table 2). The search retrieved another 6 studies which examined mild behavioral changes in MND patients without presenting prevalence rates. These data are summarized in a supplementary table (appendix 2).

Part B

Clinical characteristics of MND-bvFTD patients.

In this part of the review, data from individual patients from case studies or case series were analysed. From the literature search 20 reports were excluded which reported patients with MND variants, Alzheimer’s disease, less than two behavioral symptoms, or only cognitive symptoms. Ninety-eight articles met the inclusion criteria for part B (figure 1, and appendix 3 for all references).

In these 98 studies 170 patients were described: 135 ALS patients, 21 PMA patients and 3 PLS patients; one patient had progressive bulbar palsy without central motor neuron signs and was included in the PMA group; no information on reflexes or pyramidal tract involvement was available from 10 other patients, and these were included in the ALS group. Of the 170 patients, 142 could also be classified as suffering from bvFTD or Pick’s disease, and 28 as probable bvFTD. In the following sections the Pick’s disease and probable bvFTD cases are included in the “bvFTD” group. Clinical and demographic data are summarized in table 3.

The male to female ratio of the 170 MND-bvFTD patients was 1.3 : 1. BvFTD developed after a median time of 16 months in MND patients (range 2-40; n=21, missing data 42%); MND developed after a median time of 18 months in bvFTD patients (range 2-168; n=60; missing data 35%, difference not significant between MND or bvFTD onset).

Forty-two percent of the MND-bvFTD patients had bulbar-onset MND and 41% had limb onset. Site of onset was not significantly different between patients with MND and bvFTD onset (missing data 3%). When ALS-bvFTD patients were analysed separately, the proportion of bulbar, limb, and simultaneous limb and bulbar onset was 48%, 39% and 10%, respectively (missing data 3%)
Table 2. Prevalence of mild to moderate behavioral impairment in MND patients without dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Bulbar %</th>
<th>Patient sample</th>
<th>Assessment</th>
<th>Prevalence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy(^{142})</td>
<td>23</td>
<td>27</td>
<td>Volunteer cohort, multi-disciplinary clinic (USA)</td>
<td>NPE, NPI, MRI</td>
<td>17%</td>
<td>score of 3 or more on 2 or more behaviors (NPI)</td>
</tr>
<tr>
<td>Woolley(^{133})</td>
<td>31</td>
<td>34</td>
<td>Subset of group of patients visiting visiting two ALS clinics (USA)</td>
<td>NPE, FrSBe</td>
<td>19%</td>
<td>mild behavioral impairment w/wo cognitive impairment</td>
</tr>
<tr>
<td>Lillo(^{143})</td>
<td>92</td>
<td>22</td>
<td>Respondents to postal survey sent to members of pts association (AUS)</td>
<td>Clinical questionnaire for bvFTD symptoms and CBI-R</td>
<td>20%</td>
<td>moderate behavioral changes not fulfilling bvFTD criteria</td>
</tr>
<tr>
<td>Witgert(^{148})</td>
<td>225</td>
<td>24</td>
<td>Consecutive ALS patients from ALS clinic (USA)</td>
<td>FrSBe</td>
<td>24%</td>
<td>&gt;1.5 SD total FrSBe score</td>
</tr>
<tr>
<td>Woolley(^{149})</td>
<td>16</td>
<td>6</td>
<td>Recruited from ALS clinic (USA)</td>
<td>FrSBe</td>
<td>25%</td>
<td>&gt;1.5 SD total FrSBe score</td>
</tr>
<tr>
<td>Chio(^{150})</td>
<td>70</td>
<td>23</td>
<td>Consecutive patients from ALS clinic (It)</td>
<td>FrSBe</td>
<td>49%</td>
<td>&gt;1.5 SD total FrSBe score</td>
</tr>
<tr>
<td>Meier(^{151})</td>
<td>18</td>
<td>n.g.</td>
<td>Recruited from MND clinic (New Zealand)</td>
<td>NPI</td>
<td>50%</td>
<td>score of 3 or more on 2 or more behvaiors (NPI)</td>
</tr>
<tr>
<td>Gibbons(^{144})</td>
<td>16</td>
<td>13</td>
<td>Consecutive patients in MND clinic (UK)</td>
<td>Informant based semi-structured interview</td>
<td>88%</td>
<td>some sort of change in affect/social conduct</td>
</tr>
</tbody>
</table>

n = number; Bulbar % = % of patients with bulbar-onset; w/wo = with or without; n.g. = not given; NPE: neuropsychological examination; NPI = Neuropsychiatric Inventory; CBI-R = Cambridge Behavioral Inventory-Revised; FrSBe = Frontal Systems Behavior Scale; CDR = Clinical Dementia Rating Scale; bvFTD = behavioral variant of frontotemporal dementia.
Table 3. Clinical and demographic data of 170 patients with MND-bvFTD

<table>
<thead>
<tr>
<th></th>
<th>bvFTD onset</th>
<th>MND onset</th>
<th>Simultaneous onset of MND and bvFTD</th>
<th>Unknown onset</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>93</td>
<td>36</td>
<td>32</td>
<td>9</td>
<td>170</td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>21</td>
<td>21</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>15</td>
<td>11</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>53 (16-73)c</td>
<td>64 (25-80)</td>
<td>53 (32-66)</td>
<td>43 (38-70)</td>
<td>54 (16-80)</td>
</tr>
<tr>
<td>Missing</td>
<td>19</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Survival, months</td>
<td>36 (9-156)c</td>
<td>29 (12-108)</td>
<td>23 (12-99)</td>
<td>36 (15-84)</td>
<td>33 (9-156)</td>
</tr>
<tr>
<td>Missing</td>
<td>38</td>
<td>12</td>
<td>17</td>
<td>4</td>
<td>71</td>
</tr>
</tbody>
</table>

Onset MND:
- limb: 34 16 16 4 70
- bulbar: 41 16 13 1 71
- limb and bulbar: 10 2 3 1 16
- Missing: 8 2 0 3 13

Values are totals (%), or median (range). aALS (n=145), PMA (n=22), PLS (n=3) bDuration between the first symptom as reported by the patient or a relative, and death. p<0.01 compared to patients with MND onset.

BvFTD symptoms: characteristics, relative frequencies and pooled prevalences.

From the descriptions of 170 MND-bvFTD patients 59 different bvFTD symptoms were listed (appendix 1). The number of bvFTD symptoms reported per patient, and their frequencies, are shown in table 4. In total 960 bvFTD symptoms were described in 170 patients (mean 5.6 bvFTD symptoms per patient). Pooled prevalence rates showed that perseveration was the most frequently described behavioral disturbance (40%). Apathy and disinhibition showed pooled prevalence rates of 29 and 26%, respectively (figure 2). Three cognitive symptoms were listed: memory disturbances, attention deficits and disorientation. Memory disturbances, ranging from mild to severe showed a pooled prevalence of 43%. Memory disturbance was the first bvFTD symptom in 20% of the patients. Of the psychiatric symptoms, delusions, paranoia and hallucinations showed a pooled prevalence rate of 9, 8 and 12%, respectively.
Table 4. Number of bvFTD symptoms reported per patient

<table>
<thead>
<tr>
<th>Number of bvFTD symptoms</th>
<th>number of patients</th>
<th>cumulative percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>23</td>
<td>13.5</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>30.0</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>43.5</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>59.4</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>68.8</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>75.9</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>82.9</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>88.8</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>93.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Most frequently described bvFTD symptoms in MND patients

DISCUSSION

This systematic review shows that 8% of MND patients have bvFTD and that perseveration, apathy and disinhibition are the most frequently described behavioral symptoms of patients with MND-bvFTD. We also found that bvFTD occurs relatively more often in bulbar-onset MND.
A noticeable finding is the high frequency of memory disturbance, compared to behavioral symptoms in MND-bvFTD patients.

**Prevalence of FTD**

The prevalence of bvFTD in MND in this review varied between 5 and 27% which is related to diverging definitions (i.e. research criteria for probable FTD vs. Neary criteria) and different patient samples (e.g. a subset of patients investigated after an initial screening test vs. population-based samples). The study with the largest cohort including 279 ALS patients shortly after diagnosis had been established, showed a lower prevalence of bvFTD (5%) compared to the population or “patient-association based” studies (11%), which encompassed MND patients with a longer disease duration.\(^{24, 35, 147}\) This higher prevalence of bvFTD in the latter studies may reflect the development of bvFTD in the course of MND.

**Clinical variables – MND or bvFTD: which disease comes first?**

There has been debate in the literature on whether the occurrence of bvFTD precedes that of MND in nearly all patients with MND-bvFTD,\(^{152}\) or whether bvFTD develops in the course of MND. Taking into consideration the differences in disease duration between FTD (6-8 years) and MND (3 years), and presuming that the chance of developing one disease when the other is present, is equal, then FTD patients have at least twice as much time to develop MND, compared to MND patients to develop FTD.\(^{153, 154}\)

In agreement with this assumption, in 161 MND-bvFTD patients in this systematic review 55% presented with bvFTD, 21% with ALS and in 19% there was a simultaneous onset. In comparison, a recent study in 31 behavioral predominant MND-FTD patients showed 68% patients presenting with bvFTD, 10% with MND and 22% with a simultaneous onset.\(^{155}\) Differences in disease onsets in MND-bvFTD cohorts may be related to the site where patients are recruited (i.e. dementia clinic vs. MND clinic).
Clinical variables – bulbar-onset ALS  There have been conflicting data about a relationship between FTD and bulbar-onset MND/ALS. Depending on whether a cohort with prevalent or incident MND/ALS patients (without dementia) is studied, 19-30% of MND/ALS patients have bulbar onset. In this systematic review we found bulbar onset in 42% of MND-bvFTD (48% of ALS-bvFTD patients), which is within the range found by two other studies (39-61%) in patients with MND-bvFTD. This supports and association of bulbar-onset and extramotor cortex involvement in MND.

Clinical variables – survival
In this study, MND-bvFTD patients with MND onset had a shorter survival compared to MND-bvFTD patients with bvFTD onset (table 3). Compared to the survival of bvFTD patients without MND, the development of MND in bvFTD patients reduces survival by at least 50%. The survival of all MND-bvFTD patients in this review with complete data is 13 months shorter compared to findings of a retrospective study, which may be related to the higher proportion of MND onset patients (22% vs. 10%) in our study. When only bvFTD onset MND-bvFTD patients were analysed the survival in the present study (36 months) was similar, respectively 7 months longer compared to two smaller studies in MND-bvFTD patients. The difference may be ascribed to a higher proportion of bulbar onset ALS patients in one of the latter studies. Thus, our review corroborates earlier findings that the occurrence of MND in bvFTD leads to a shorter survival. Interestingly, the survival of MND patients who developed bvFTD is similar to a population-based prospective survey in MND patients with a comparable age at onset and a lower proportion bulbar onset MND. Thus, our data do not support the observations made by others that bvFTD leads to a shorter survival in MND, although missing data in 33% made this finding less reliable.

A negative effect of bvFTD on survival in MND has been shown by others to be related to a higher noncompliance with non-invasive ventilation and feeding tube insertion, and to a higher proportion of bulbar onset MND in MND-bvFTD.
Therefore the impact of FTD on the survival of MND patients, irrespective of these confounders, needs to be studied further.\textsuperscript{126}

**Cognitive variable – memory disturbance**

This review shows that 43\% of MND-bvFTD patients had early or severe memory disturbances, ranking memory as the most frequent bvFTD symptoms in MND-bvFTD. Although early or severe memory problems are traditionally considered to be rare in bvFTD, initial memory complaints have been reported in 16-60\% of bvFTD patients, and in one study memory problems were the fourth most frequent of 12 bvFTD symptoms.\textsuperscript{154,157,158} In 20\% of the MND-bvFTD patients in the present study, memory disturbance was among the first symptoms, which is in agreement with a recent study in 18 MND-FTD patients.\textsuperscript{154} Of note, in our and other studies, memory disturbances were based on history taking, which may have overestimated the frequency, because other cognitive deficits may have been misinterpreted as memory disturbances.

**Mild behavioral symptoms in MND**

The presence of mild behavioral changes in MND would support the concept of a continuum between MND and bvFTD. In 13 of the 14 retrieved studies concerning mild behavioral changes, these were assessed with the Frontal Systems Behavior Scale, Neuropsychiatric Inventory or Cambridge Behavioral Inventory. These instruments, widely used in patients with dementia, have not been validated in MND patients and are not adapted for motor impairment, which probably results in overestimation of “motor-free” mild behavioral changes in MND. In addition, in only 3 studies a control group was examined.\textsuperscript{159,160} A prospective controlled study with a clear description of the inception cohort with a valid scale is needed to assess the presence of mild behavioral changes in MND. The behavioral characteristics of MND in this review may help to develop such a scale.
Strengths and limitations

In addition to its strengths (large number of patients, systematic analysis) this review has some limitations. The methodological quality of case reports and case series is poor. We found, however, that most patient descriptions were sufficient to extract useful information, which is underlined by the description of at least 4 bvFTD symptoms in nearly three quarters of the patients (table 3).

The pooled prevalences of the bvFTD symptoms from the random effect analysis should be interpreted with caution. In single case studies or case series, authors may tend to describe symptoms which are prominent, interesting and in line with the diagnosis.

In conclusion, bvFTD is present in 8% of MND patients and perseveration, apathy and disinhibition are frequently described in MND-bvFTD. Memory disturbances are another important symptom for the clinician who evaluates a patient with MND, as it may be heralding the onset of bvFTD.
### Appendix 1. Pooled prevalences of bvFTD symptoms in 170 MND-bvFTD patients

<table>
<thead>
<tr>
<th>bvFTD symptom</th>
<th>prevalence rate</th>
<th>bvFTD symptom</th>
<th>prevalence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>memory complaints</td>
<td>42.9</td>
<td>anxious</td>
<td>5.3</td>
</tr>
<tr>
<td>perseveration</td>
<td>40.0</td>
<td>loss of initiative</td>
<td>4.7</td>
</tr>
<tr>
<td>attention deficit</td>
<td>29.8</td>
<td>wasting money</td>
<td>4.7</td>
</tr>
<tr>
<td>apathy</td>
<td>28.8</td>
<td>poverty of speech</td>
<td>4.7</td>
</tr>
<tr>
<td>disinhibition</td>
<td>25.9</td>
<td>loss of emotions</td>
<td>4.7</td>
</tr>
<tr>
<td>loss of disease insight</td>
<td>24.7</td>
<td>obsession with food</td>
<td>4.1</td>
</tr>
<tr>
<td>indifference</td>
<td>24.1</td>
<td>spontaneous</td>
<td>4.1</td>
</tr>
<tr>
<td>loss of interest</td>
<td>19.4</td>
<td>loss of will</td>
<td>4.1</td>
</tr>
<tr>
<td>aggression</td>
<td>18.2</td>
<td>suspicious</td>
<td>3.6</td>
</tr>
<tr>
<td>loss of hygiene</td>
<td>17.1</td>
<td>selfishness</td>
<td>3.5</td>
</tr>
<tr>
<td>disorientation</td>
<td>16.5</td>
<td>imitation</td>
<td>3.5</td>
</tr>
<tr>
<td>irritability</td>
<td>16.5</td>
<td>alcohol addiction</td>
<td>2.9</td>
</tr>
<tr>
<td>labile</td>
<td>13.5</td>
<td>going away</td>
<td>2.9</td>
</tr>
<tr>
<td>mental rigidity</td>
<td>12.9</td>
<td>stubborn</td>
<td>2.9</td>
</tr>
<tr>
<td>restlessness</td>
<td>12.9</td>
<td>uncritically</td>
<td>2.4</td>
</tr>
<tr>
<td>hallucinations</td>
<td>11.8</td>
<td>insomnia</td>
<td>2.4</td>
</tr>
<tr>
<td>withdrawal behavior</td>
<td>11.2</td>
<td>counteracting</td>
<td>2.4</td>
</tr>
<tr>
<td>wandering</td>
<td>10.6</td>
<td>desperate</td>
<td>2.4</td>
</tr>
<tr>
<td>hoarding</td>
<td>10.6</td>
<td>antisocial</td>
<td>1.8</td>
</tr>
<tr>
<td>loss of judgment</td>
<td>10.6</td>
<td>obsession with money</td>
<td>1.8</td>
</tr>
<tr>
<td>loss of decorum</td>
<td>10.0</td>
<td>inactive</td>
<td>1.8</td>
</tr>
<tr>
<td>impulsive</td>
<td>10.0</td>
<td>superficial</td>
<td>1.8</td>
</tr>
<tr>
<td>loss of empathy</td>
<td>9.4</td>
<td>loss of emotions</td>
<td>1.2</td>
</tr>
<tr>
<td>delusion</td>
<td>9.4</td>
<td>kleptomania</td>
<td>1.2</td>
</tr>
<tr>
<td>childish</td>
<td>8.8</td>
<td>narcissism</td>
<td>1.2</td>
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<tr>
<td>euphoria</td>
<td>8.2</td>
<td>attentiveness</td>
<td>1.2</td>
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<tr>
<td>paranoia</td>
<td>7.6</td>
<td>sad</td>
<td>1.2</td>
</tr>
<tr>
<td>obsessive</td>
<td>7.1</td>
<td>changes of activity level</td>
<td>0.6</td>
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<tr>
<td>sexually disinhibited</td>
<td>7.1</td>
<td>extravagance</td>
<td>0.6</td>
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<tr>
<td>excessive social behavior</td>
<td>6.5</td>
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</table>

From case studies/series, percentages of bvFTD symptoms were calculated (numerator = no. of patients with the disturbance; denominator = total no. of patients). Pooled prevalence rates accounting for inter-study variation were analyzed using a nonlinear random effects model.
Appendix 2. The assessment of mild behavioral symptoms in MND patients

Fourteen studies examined mild behavioral changes in MND patients. The Frontal Systems Behavior Scale (FrSBe) was used in 10 studies (table)\textsuperscript{25, 148-150, 159-163} The Neuropsychiatric Inventory, Cambridge Behavioural Inventory-Revised, a clinical questionnaire or semi-structured interview were used in four other studies which are not discussed here (10-13).

Frontal Systems Behavior Scale data of MND patients without dementia

<table>
<thead>
<tr>
<th>author</th>
<th>(n) patients</th>
<th>bulbar %</th>
<th>control group</th>
<th>FrSBe total score (T-score)</th>
<th>Apathy</th>
<th>Disinhibition</th>
<th>Dysexecutive</th>
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<tbody>
<tr>
<td>Woolley\textsuperscript{161}</td>
<td>17</td>
<td>n.g.\textsuperscript{a}</td>
<td>no</td>
<td>56</td>
<td>59</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Wicks\textsuperscript{159}</td>
<td>41</td>
<td>12</td>
<td>n.g.\textsuperscript{c}</td>
<td>55</td>
<td>58</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Wicks\textsuperscript{159}</td>
<td>16</td>
<td>6</td>
<td>no</td>
<td>57</td>
<td>60</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Woolley\textsuperscript{149}</td>
<td>70</td>
<td>23</td>
<td>n.g.\textsuperscript{c}</td>
<td>67</td>
<td>67</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Chio\textsuperscript{150}</td>
<td>225</td>
<td>24</td>
<td>no</td>
<td>55</td>
<td>59</td>
<td>52</td>
<td>53</td>
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<tr>
<td>Witgert\textsuperscript{148}</td>
<td>24</td>
<td>n.g.</td>
<td>no</td>
<td>54</td>
<td>62</td>
<td>49</td>
<td>50</td>
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<tr>
<td>Tsujiimoto\textsuperscript{163}</td>
<td>45</td>
<td>38</td>
<td>n.g.\textsuperscript{c}</td>
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<td>54</td>
<td>46</td>
<td>46</td>
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<tr>
<td>Grossman\textsuperscript{25}</td>
<td>17</td>
<td>n.g.</td>
<td>n.g.\textsuperscript{c}</td>
<td>56</td>
<td>57</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>Girardi\textsuperscript{160}</td>
<td>2</td>
<td>14</td>
<td>7\textsuperscript{d}</td>
<td>67</td>
<td>n.g.</td>
<td>n.g.</td>
<td>n.g.</td>
</tr>
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</table>

\textsuperscript{a}mean bulbar score ALSFRS-R = 9. \textsuperscript{b}two cohorts were described in one paper. From all studies “Post-Illness” scores rated by a carer were taken, except from Girardi et al. who reported self rated scores (no difference was found between carer-rated and self-rated scores in that study); n.g. = not given; \textsuperscript{c}p<0.05; \textsuperscript{d}bulbar symptoms.

The FrSBe is a behavioral scale with three subscales (apathy, disinhibition and executive dysfunction). Half of the 14 items measuring apathy are directly related to motor disabilities (limb or bulbar palsy) and the two other subscales (disinhibition and executive dysfunction) also contain some items related to motor disabilities.

In all studies the apathy subscale showed higher scores compared to the other subscales (see table below). In two of the three controlled studies a significantly higher score for apathy was shown compared to the control group.
### Appendix 3. Case studies and case series included in part B

<table>
<thead>
<tr>
<th>Author</th>
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<td>Amyotrophic lateral sclerosis with psychosis</td>
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<td>Benajiba, L.</td>
<td>TARDBP mutations in motoneuron disease with frontotemporal lobar degeneration</td>
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<td>Su due casi di sclerosi laterale amiotrofica ad inizio pseudobulbar e preceduta da decadimento psichico</td>
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</table>
The ALS-FTD-Q: a new screening tool for behavioral disturbances in ALS

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Ben Schmand
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Leonard H van den Berg
Yolande A Pijnenburg
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Chapter 7

ABSTRACT

Objective
The assessment of behavioral disturbances in amyotrophic lateral sclerosis (ALS) is important, because of the overlap with the behavioral variant of frontotemporal dementia (ALS-bvFTD). Motor symptoms and dysarthria are not taken into account in currently used behavioral questionnaires. We examined the clinimetric properties of a new behavioral questionnaire for ALS patients (ALS-FTD-Q).

Methods
In addition to other clinimetric properties, we examined the reliability, clinical validity and construct validity of the ALS-FTD-Q, using data from patients with ALS (n=103), ALS-bvFTD (10), bvFTD (25), muscle disease controls (39) and control subjects (31). Construct validity of the ALS-FTD-Q was assessed using the Frontal Systems Behavior scale (FrSBe), Frontal Behavior Inventory (FBI), Hospital Anxiety and Depression Scale, ALS Functional Rating Scale-Revised, Frontal Assessment Battery, Mini Mental State Examination and Fluency. In addition, the point prevalence of behavioral disturbances according to the ALS-FTD-Q was compared to those obtained with the FrSBe and FBI.

Results
The internal consistency of the ALS-FTD-Q was good (Cronbach's $\alpha = 0.92$). The ALS-FTD-Q showed construct validity as it correlated highly with other behavioral measures ($r=0.80$ and 0.79), moderately with measures of frontal functions and global cognitive functioning ($r=0.37$; $r=0.32$), and poorly with anxiety/depression and motor impairment ($r=0.18$, for both). The ALS-FTD-Q discriminated between patients with (ALS-)bvFTD, ALS and controls. The point prevalence for severe behavioral disturbances in ALS patients measured with the ALS-FTD-Q was lower compared to the FrSBe and FBI.

Conclusion
The ALS-FTD-Q is a feasible and clinimetrically validated instrument for the screening of behavioral disturbances in ALS.
INTRODUCTION

The frontotemporal brain regions are affected in a proportion of patients with amyotrophic lateral sclerosis (ALS). Clinically, this may lead to the behavioral variant of frontotemporal dementia (bvFTD, in 5-10% of ALS patients), mild frontotemporal cognitive deficits (in 32-45% of ALS patients) or mild behavioral disturbances in ALS patients. These non-motor changes in ALS patients - and especially bvFTD - may negatively influence survival and hinder compliance with therapeutic interventions and relations with caregivers.

The gold standard for behavioral disturbances is a detailed family interview. When this is not feasible (e.g. in a busy clinic), a neuropsychiatric screening instrument is an alternative. Importantly, the scoring of items should not be influenced by muscle weakness, dysarthria and pseudobulbar affect, as these may overestimate behavioral disturbances in ALS patients.

The neuropsychiatric instruments currently available for assessing behavior have not been validated in patients with ALS and contain several items which rely on the ability to speak, eat and move without problems. To overcome these issues, we investigated the clinimetric properties of a new screening tool, the ALS-FTD-Questionnaire, for the detection of bvFTD and mild behavioral disturbances in ALS.

METHODS

Subjects

Five groups of patients were recruited from tertiary referral centers for ALS and tertiary referral centers for dementia, all in the Netherlands.

- 103 patients with ALS (possible, probable or definite ALS according to the El Escorial criteria)
- 10 patients with ALS-bvFTD who had been diagnosed with ALS-bvFTD by the treating clinician prior to this study, according to the El Escorial and Neary criteria.
- 25 patients with bvFTD according to the Neary criteria without ALS who had been diagnosed prior to the study.
- 39 patients with muscle diseases (‘muscle controls’): inclusion body myositis (IBM, n=10), limb girdle dystrophy 2A (LGMD 2A, n=8), oculopharyngeal
muscular dystrophy (OPMD, n=6), Miyoshi myopathy (n=9) and ALS-mimics (n=6)

- 31 subjects who were evaluated at the out-patient neurology clinic for diverging complaints (e.g. sensory complaints, tremor, headache). These subjects had no medical history of muscle disease, central nervous system disorder or psychiatric disorder ('other controls').

The patients with ALS-bvFTD and bvFTD served as positive controls (n=35); the patients with muscle diseases and the other controls served as negative controls (n=70). Only patients with a proxy (see below) were included. Three out of 185 ALS patients (1.6%) who were contacted did not participate because of the absence of a proxy. Patients and controls were excluded if they did not speak Dutch fluently or if they had a (history of a) psychiatric disorder or a neurological disease with CNS involvement.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The local ethics committees of the participating hospitals approved the study. Written informed consent was obtained from all subjects.

**ALS-FTD-Q**

The ALS-FTD-Questionnaire (ALS-FTD-Q) is an observer-report scale aimed at the proxy of an ALS patient (see appendix 1 for the questionnaire). A proxy can be a partner, parent, sibling, adult child or other caregiver who is able to assess the patient's behavior.

Items for the ALS-FTD-Q were taken from a systematic review of neurobehavioral symptoms (i.e. behavioral, cognitive and psychiatric disturbances) in 170 motor neuron disease patients with bvFTD (chapter 6) and the item selection was mainly based on the pooled prevalence rates of neurobehavioral symptoms in the review. The phrasing of the items was adjusted for motor and speech dysfunction. Face-validity of the ALS-FTD-Q is described in appendix 2. The ALS-FTD-Q has 25 items, including 3 cognitive items (e.g. memory) The items have a four-point rating scale with a maximum score of 100. A higher score indicates more behavioral disturbances. The
time required to complete the questionnaire was estimated to be between 5 and 10 minutes.

**Procedure**

Most ALS patients were visited at home (n=97, including 9 ALS-bvFTD patients). The proxy was requested to fill in the ALS-FTD-Q and two other behavioral scales (for instruments, see below) in a separate room while the patient was administered a short battery of tests that assessed cognitive and affective functions and functional motor status. Proxies of 16 consecutive ALS patients (including 1 ALS-bvFTD patient) filled in the ALS-FTD-Q during an out-patient clinic visit, separate from the home visit study. Proxies of the other patients and controls were administered the ALS-FTD-Q at the out-patient clinics during a regular visit, in a room separated from the patient.

**Instruments used in the home-visit study**

The proxy assessed the behavior of the patient with the ALS-FTD-Q and:

- Frontal Systems Behavior Scale (FrSBe), a 36-item behavior scale with carer ratings of pre- and post-morbid behavior in the domains apathy, dysexecutive functioning and disinhibition\(^{26}\)
- Frontal Behavioral Inventory (FBI), a 24-item scale measuring frontal lobe-mediated behavior\(^{167}\)

The patient was administered:

- Mini Mental State Examination (MMSE)\(^{109}\)
- Frontal Assessment Battery (FAB), a 6-item instrument measuring frontal lobe functions e.g. conceptualization, perseveration\(^{125}\)
- Letter (D, A, T) and category (animals and occupations) fluency, measures of executive function with correction for speech/motor dysfunction by calculating a mean thinking time per word in seconds (fluency index)\(^{18,101}\). Written or spoken versions were used depending on disability.
- Hospital Anxiety and Depression scale (HADS), a 14-item scale\(^{99}\)
- ALS Functional Rating Scale Revised (ALSFRS-R), a 12-item questionnaire for motor dysfunction in ALS\(^{68}\)
Patients in whom impaired manual dexterity precluded performance of the “writing a sentence” item of the MMSE were allowed to say the sentence, provided their speech was intelligible. For this, and other items that require manual dexterity, e.g. “intersecting pentagons” of the MMSE and the “go-no go”, “fist, edge, palm” and “do not take my hands” items of the FAB, a note was made when one of these tasks could not be performed. Both the raw scores and percentage of items that could be performed were noted. Extrapolated scores of the MMSE and FAB were used for analyses, according to the formula: \( \text{Extrapolated score} = \frac{\text{raw total score} \times 100}{\% \text{ of items performed}} \).

Disease onset was defined as the month when the first sign of muscle weakness (ALS) or the behavioral changes (bvFTD) were noted. Bulbar involvement was defined as a score \( \leq 11 \) (maximum = 12) on the 3 bulbar items of the ALSFRS-R.

**Clinimetric evaluation of ALS-FTD-Q**

The following clinimetric properties of the ALS-FTD-Q were studied: reliability (both internal consistency and test-retest reliability), construct validity, clinical validity and the presence of a floor and ceiling effect. In addition, in ALS patients without bvFTD the point prevalences of abnormal behavior according to the ALS-FTD-Q, FrSBe and FBI were compared.

Internal consistency refers to the statistical coherence of the scale items and can be measured by the Cronbach \( \alpha \) coefficient which is based on the weighted average correlation of items within a scale. Internal consistency is considered to be good if \( \alpha \geq 0.80 \). We calculated item-total correlations, which represent the correlation of a single item with the sum of all other scale items. Correlations \( \geq 0.30 \) were considered to be sufficient. Test-retest reliability was investigated in a pilot study on the proxies of 17 ALS patients including 4 ALS-bvFTD patients, see appendix 2.

Construct validity was assessed in the group of 97 ALS patients (including 9 ALS-bvFTD patients) who underwent multiple tests at home. We measured the extent to which the ALS-FTD-Q correlates with measures that address the same concept (i.e. ‘frontal’ behavior) and measures that address different concepts. We assumed that in order for the ALS-FTD-Q to be valid, the ALS-FTD-Q scores had to show high
correlations with the other frontal behavior scale scores (FrSBe, FBI), moderate correlations with frontal lobe functions (FAB, fluency) and global cognitive functions (MMSE), and low correlations with affective functions (HADS) and motor functions (ALSFRS-R).

A scale demonstrates clinical validity if it discriminates between groups of patients with known differences in clinical status (i.e. ALS without bvFTD vs. bvFTD with or without ALS). Floor and ceiling effects of the ALS-FTD-Q were analyzed (percentage of patients with a minimum and maximum score).

Point prevalences of abnormal behavior assessed with the ALS-FTD-Q, FrSBe and FBI were compared in the ALS patients without a prior diagnosis of bvFTD. We aimed to assess point prevalences of both mildly and severely abnormal behavior, because a spectrum of behavioral disturbances has been suggested in earlier studies. Point prevalences of abnormal behavior assessed with the ALS-FTD-Q were compared between incident patients (assessed within one year from the diagnosis) and prevalent patients.

The following cut-offs were used:

**ALS-FTD-Q**: A cut-off indicating mild disturbances (below which behavior is normal) was based on the score of the 95th percentile of the 70 negative controls (patients with muscle diseases and other controls). A cut-off indicating severe disturbances (in the bvFTD range) was based on the lowest ALS-FTD-Q score in the group of 35 positive controls (bvFTD and ALS-bvFTD patients).

**FrSBe**: A cut-off indicating mild disturbances was based on the manual (T-score > 65; = > 1.5 SD above the mean). A cut-off indicating severe disturbances of the FrSBe has, to our knowledge, not been published. This cut-off was set at the lowest score of ALS-bvFTD patients who were assessed using the FrSBe in the present study. We expected the FrSBe cut-offs for mild and severe disturbances to be different based on a mean FrSBe T-score of 92 (SD 18.5) in 34 BvFTD patients. The latter implies a mean T-score > 4 SD above the mean for severe disturbances, compared to the T-score of > 1.5 SD above the mean for mild disturbances.
FBI: A cut-off indicating mild behavioral changes has to our knowledge not been published and could not be constructed from available studies. A cut-off indicating severe disturbances was based on the literature.\textsuperscript{167}

**Statistical analysis**

Internal consistency of the ALS-FTD-Q scores was expressed in the Cronbach’s $\alpha$ coefficient. Item-total correlations and test-retest correlation were expressed in Pearson correlation coefficient ($r$) and intraclass correlation coefficient, respectively. Associations between the ALS-FTD-Q scores and the other measures were expressed as Spearman rank correlation coefficients ($r_s$). Differences between ALS-FTD-Q scores and patient characteristics in relation to the various subgroups were analyzed using the Mann-Whitney U test, Kruskal Wallis test or Chi-Square test. Statistical significance level was set at $p = 0.05$. Analyses were performed in PASW Statistics (SPSS), version 18.

**RESULTS**

We included 113 ALS patients (80 male = 70.8%), 10 of whom were diagnosed with ALS-bvFTD prior to the study. The mean age at examination was 61.3 years (SD 11.7) and the median disease duration was 2.8 years (34 months, range 4-328 months; table 1). Ninety-three patients (82.3%) had limb-onset ALS. Bulbar involvement was present in 72 patients (63.7%). Gender and age were not different between any of the groups.

**Clinimetrics**

The ALS-FTD-Q scores showed substantial internal consistency: Cronbach’s alpha = 0.92, and 23 of the 25 items showed an item-total score correlation ranging between 0.31 and 0.78. Two items (hypersexuality and euphoria) had an item-total score correlation of 0.20 and 0.26. The test-retest intraclass correlation of the ALS-FTD-Q total score was 0.89 ($n=17$; mean time between two assessments 65 days (SD 26.7, see appendix 2 for additional data on the test-retest group).
Table 1. Demographic and clinical characteristics of the ALS patients and positive and negative controls assessed with the ALS-FTD-Q

<table>
<thead>
<tr>
<th></th>
<th>Positive controls</th>
<th>Negative controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALS</td>
<td>ALS-bvFTD</td>
</tr>
<tr>
<td></td>
<td>(n=103)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.4 (11.9)</td>
<td>60.2 (10.4)</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>73/30</td>
<td>7/3</td>
</tr>
<tr>
<td>Bulb/limb</td>
<td>89/14</td>
<td>4/6</td>
</tr>
<tr>
<td>Bulb. involv.*</td>
<td>60.2%</td>
<td>100%</td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>33.5</td>
<td>35.5</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>31.5 (9.2)</td>
<td>32.9 (6.1)</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (range) or numbers. BvFTD = behavioral variant frontotemporal dementia; Bulb/limb = bulbar or limb onset; involv. = involvement. *Bulbar involvement was defined as a score below four on one of the bulbar items of the ALSFRS-R. mo = months. The maximum score of the ALSFRS-R (ALS Functional Rating Score Revised) = 48 and indicates no motor dysfunction.

Construct validity was shown by high correlations between the ALS-FTD-Q and the FrSBe and FBI, moderate correlations with the FAB, Fluency and MMSE, and low correlations with the HADS and ALSFRS-R (table 2 and figure 1). There was a floor effect (16 of the 208 patients, 7.7%, had a minimum score of 0); no ceiling effect was observed. With regard to clinical validity, the median ALS-FTD-Q score of ALS patients without bvFTD (9, range 0-46) was lower compared to both ALS-bvFTD patients (42, range 30-56) and bvFTD patients (50, range 29-68), and higher compared to the muscle disease control group (6, range 0-24) and the other controls (5, range 0-20; figure 2).

**Point prevalence of behavioral disturbances in ALS patients without a prior diagnosis of bvFTD**

Based on our scoring algorithm (Method section), the ALS-FTD-Q cut-off indicating mild disturbances was set at ≥ 22; the cut-off indicating severe disturbances (in the bvFTD range) was set at ≥ 29. In patients without a prior diagnosis of bvFTD who had complete data for the 3 behavioral scales (n=86), mild and severe behavioral disturbances were shown 11 (10.7%) and 7 patients (6.8%), respectively.
Table 2. Test scores and correlations of the ALS-FTD-Q with other measures of behavioral, cognitive, affective and motor functions in ALS patients.

<table>
<thead>
<tr>
<th>Test score with ALS-FTD-Q</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FrSBe</td>
<td>97</td>
</tr>
<tr>
<td>FBI</td>
<td>95</td>
</tr>
<tr>
<td>FAB</td>
<td>92</td>
</tr>
<tr>
<td>Fluency</td>
<td>92</td>
</tr>
<tr>
<td>MMSE</td>
<td>97</td>
</tr>
<tr>
<td>HADS</td>
<td>85</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>97</td>
</tr>
</tbody>
</table>

Score values are median and ranges; correlation values are expressed in Spearman correlation coefficient. *Negative as higher scores on the FAB, MMSE and ALSFRS-R indicate better performance. Fluency = letter fluency index (correlation coefficient for category fluency index = 0.30). For abbreviations, see text.

In comparison, according to the FrSBe and FBI 16 patients (18.6%) had mild behavioral changes and 12 patients (14%) had severe behavioral changes. Of the 103 patients who were assessed with the ALS-FTD-Q, 27 (26.2%) were assessed within 1 year of the diagnosis (patients with incident disease), of whom 4 (14.8%) scored in the mild range and 1 in the severe range on the ALS-FTD-Q. The proportion of those with mild behavioral disturbances of the patients with incident disease was not significantly different from patients with prevalent disease ($\chi^2$ test: not analyzed for severe behavioral disturbances).

DISCUSSION

This study shows the clinimetric properties of a new screening instrument for behavioral disturbances, which was constructed to avoid bias due to motor and speech impairment in patients with ALS. The ALS-FTD-Q showed substantial internal consistency and retest reliability, and both construct and clinical validity. Construct validity was shown by high correlations of the ALS-FTD-Q with two other frontal behavioral scales (same construct), intermediate correlations with frontal cognitive functions (related construct) and low correlations with anxiety/depression and motor function (not related constructs).
The intermediate correlation between fluency and the ALS-FTD-Q in our study is comparable to findings by others and shows that the questionnaire measures a construct (frontal mediated behavior) which is related to fluency, supporting the construct validity of the ALS-FTD-Q. In addition, clinical validity was shown as the ALS-FTD-Q discriminated between patients with a known difference in the presence of frontal behavioral disturbances (bvFTD (with or without ALS) and ALS, and also between ALS and controls). These good clinimetric properties and the easy way to administer the ALS-FTD-Q make it a feasible screening instrument in clinical practice as well as for research.
projects. The ALS-FTD-Q mainly identifies behavioral disturbances and is not designed to screen for cognitive impairment. To our knowledge, three screening instruments for non-motor involvement in ALS patients have been investigated, which focus on frontal cognitive functions (e.g. fluency).\textsuperscript{133, 169, 170} One screen contains 15 questions about behavior,\textsuperscript{133} two other screens included the FBI.\textsuperscript{169, 170} Compared to (the behavioral part of) these screening instruments the ALS-FTD-Q has four advantages: a rationale for the selection of behavioral items, the phrasing of the items being adjusted for motor and speech dysfunction, the proof of good clinimetric properties, and a comparison of test scores with negative and positive control groups. Although we phrased our items to exclude negative effects of dysarthria and motor impairment, we felt that a negative control group including patients with several types of muscle disease was needed more urgently than a healthy control group.

\textsuperscript{a}p < 0.0001; \textsuperscript{b}p < 0.05, Mann-Whitney U Test. ALS = amyotrophic lateral sclerosis; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire; bvFTD = behavioral variant of frontotemporal dementia.
The point prevalence of severe behavioral disturbances in our ALS patients without a prior diagnosis of bvFTD is lower with the ALS-FTD-Q compared to the FrSBe and FBI and the prevalence of mild behavioral disturbances was also lower according to the ALS-FTD-Q compared to the FrSBe (not investigated with FBI). Our data may suggest that the FrSBe and FBI could overestimate behavioral disturbances in ALS patients (because of bias due to motor symptoms and dysarthria). The alternative explanation, i.e. a low sensitivity of the ALS-FTD-Q, is less likely for three reasons. First, we carefully selected items based on a systematic review to capture the full range of behavioral changes known to occur in ALS, including delusions, such as paranoia, hallucinations, apathy and eating disturbances, which were recently found to be prominent in bvFTD-ALS patients. Second, our cut-off included all the patients with a prior diagnosis of bvFTD and ALS-bvFTD, which implies a high sensitivity of the ALS-FTD-Q. Third, the point-prevalence of 7% severe behavioral disturbances in ALS patients (without a prior diagnosis of bvFTD) in our cohort, is in agreement with a pooled prevalence of 8% bvFTD in 570 ALS patients in a systematic review of population based or out-patient clinic based studies using family interviews or clinical questionnaires (accepted for publication).

The estimation of mild behavioral changes with the ALS-FTD-Q (11%) is lower compared to other studies (17-50%). We argue against a low sensitivity of the ALS-FTD-Q for mild behavioral disturbances for two reasons. Compared to earlier studies, our cohort had the lowest prevalence of mild behavioral changes assessed with the FrSBe. Thus, we studied a population with a relatively low prevalence of behavioral changes. Secondly, earlier studies used instruments which have not been validated for the assessment of behavioral changes in ALS and contain items which have not been corrected for motor impairment. In particular, apathy has been shown to be present in up to 50% of ALS patients. However, apathy was studied with the 14-item FrSBe apathy subscale of which seven items are directly related to speaking and moving, which may have led to overestimation of motor-related mild behavioral changes, e.g. apathy.

The mild and severe behavioral changes in ALS in the present study have to be interpreted in relation to the cut-offs, which have to be further validated, and in relation to the study population. Our study population was largely a prevalence cohort.
with patients with a relatively long disease duration and bulbar-onset in 18% (compared to 30% in incidence cohorts). The design of this study with more prevalent than incident patients, was chosen in order to examine our questionnaire in patients with different disease durations, as previous studies described the development of bvFTD in the course of ALS.

In terms of further validation of the ALS-FTD-Q, the high test-retest correlation should be replicated and the responsiveness (detection of changes over time) of the ALSFTD-Q should be explored in depth in a large sample of incident patients. When sufficient data are collected a factor analysis may generate insight in subscales and a subset of items that would suffice, which would make the scale even more usable. The ALS-FTD-Q is a unique and novel instrument to be used in the clinic for the screening of behavioral disturbances in ALS patients. It is a user-friendly tool with validated clinimetric characteristics.
Appendix 1

Amyotrophic Lateral Sclerosis - Frontotemporal Dementia - Questionnaire (ALS-FTD-Q)

The behaviour of your partner, family member or friend will be evaluated in the following questionnaire. Wherever, "him" or "his" is stated, it can be replaced by "her". Completing the questionnaire should take approximately 10 minutes and ideally should be done in a room separated from the patient. To answer a question, check the box with the most appropriate answer. The questionnaire consists of two parts; A and B.

Date . . - . . . . Filled out by (e.g. partner, sibling, child) ...........................................................
Name of the patient ............................................................................................................................
Date of birth of the patient . . - . . . . Gender of the patient M / F
Highest level of education completed by the patient .................................................................

Part A The following 13 statements compare the present behaviour of your partner to his behaviour three years ago.

<table>
<thead>
<tr>
<th>Possible answers are the following:</th>
<th>Completely disagree</th>
<th>Largely disagree</th>
<th>Largely agree</th>
<th>Completely agree</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Your partner is less interested in his surroundings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Your partner pays less attention to his personal hygiene</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Your partner puts himself first more often</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Your partner becomes irritated or angry more easily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Your partner's ability to concentrate has decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Your partner's behaviour is more restless</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Your partner displays more withdrawn behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Your partner seems to undertake more aimless activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Your partner has more problems with memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Your partner contacts strangers more frequently</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Your partner has an increased urge for sex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(if not applicable; leave unanswered)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 7

Some ALS patients experience compulsive laughter or crying: laughing or crying without a logical reason. The following two statements DO NOT describe this phenomenon; they describe changes in your partner's emotions in general.

12. Your partner is emotionally less stable
13. Your partner is more often extremely cheerful

Part B The following 12 statements are about the behaviour of your partner during the past month. Please note: some statements describe normal behaviour, while others describe abnormal behaviour. Therefore, please read the statement carefully prior to answering.

Possible answers are the following:
- Never
- Sometimes
- Often
- Always

14. Your partner is suspicious
15. Your partner repeatedly uses the same gestures or sentences
16. Your partner is shameless
17. Your partner is aware of his whereabouts
18. Your partner displays offensive behaviour
19. Your partner is able to assess situations well
20. Your partner hoards food or is preoccupied by food
21. Your partner understands what his disease is about
22. Your partner sees or hears things that are not there
23. Your partner displays childish behaviour
24. Your partner knows which part of the day it is
25. Your partner imitates you or others
Scoring of the ALS-FTD-Q

Items 1-13:

<table>
<thead>
<tr>
<th>Value</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Items 14, 15, 16, 18, 20, 22, 23 and 25:

<table>
<thead>
<tr>
<th>Value</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Items 17, 19, 21 and 24:

<table>
<thead>
<tr>
<th>Value</th>
<th>Never</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**ALS-FTD-Q score:**

Item scores are summed to calculate the ALS-FTD-Q score.

**Cut-off values:**

mild behavioral disturbances ≥ 22; severe behavioral disturbances (in the bvFTD range) ≥ 29.

These are tentative cut-off values, pending future validation.
Appendix 2: Face-validity and clinical and demographic characteristics of the test-retest group

Face-validity was examined in a pilot study on 17 ALS patients and their proxies, using a semi-structured interview. The interviewee was asked whether the scale was user-friendly, comprehensible and not too lengthy, if all behavioral problems were covered and if items or their phrasing were felt to be too intimate or offensive. According to these interviews no items were missed or inappropriate.

Test-retest reliability was investigated in the same group of 17 ALS patients including 4 ALS-bvFTD patients. The group consisted of 11 males and 6 females; 14 had limb-onset ALS and three had bulbar-onset ALS. The mean age was 61.7 years (SD 12.1) and the median disease duration was 36 months (range 14-179). The mean ALSFRS-R score was 27.8 (SD 10.4). The mean time between the two assessments was 65 days (SD 26.7). The median ALS-FTD-Q score for these patients at t=0 and t=1 was 8 (range 0-56) and 10 (range 1-68), respectively. The test-retest intraclass correlation of the ALS-FTD-Q total score was 0.89.
Part III

Functional and structural imaging correlates of cognitive impairment in motor neuron disease
Prefrontal involvement related to cognitive impairment in progressive muscular atrophy

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Neurology 2014;83:818-25
ABSTRACT

Objective
To examine brain activation patterns during verbal fluency performance in patients with progressive muscular atrophy (PMA) and amyotrophic lateral sclerosis (ALS).

Methods
Functional MRI (fMRI) was used to examine the blood oxygenation level dependent (BOLD) response during letter and category fluency performance in 18 PMA patients, 21 ALS patients and 17 healthy control subjects, matched for age and education. fMRI results are reported at \( p < .05 \), Family Wise Error (FWE) corrected for multiple comparisons. We analyzed effects of performance, age related white matter changes (ARWMC) and regional brain volumes; all participants underwent neuropsychological investigation.

Results
Disease duration of patients with PMA (mean 26.0 months, SD 13.6) and ALS (22.2; SD 11.4) were comparable. PMA and ALS patients had mild to moderate disease severity and showed impaired letter fluency compared to controls. Between group analysis showed a main effect of group in the left inferior frontal gyrus (IFG, Brodmann area 45) during letter fluency which was unaffected by performance, ARWMC and IFG volume: PMA patients showed lower activation than controls but higher than that of ALS patients (ALS<PMA<HC; \( p_{FWE} = 0.035 \), Z-score 4.11; size = 11 voxels). A more caudal region in the IFG showed lower activation in PMA patients than controls during letter fluency performance (post-hoc test; \( p_{FWE} = 0.026 \)). No activation differences were observed during the category fluency task.

Conclusion
Prefrontal activation abnormalities are related to an important clinical measure of executive dysfunction, in motor neuron disease patients with and without upper motor neuron signs.
INTRODUCTION

Motor neuron disease (MND) encompasses amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy (PMA; only lower motor neuron clinical features). 30-50% of ALS patients have cognitive impairments, which are correlated to impaired decision-making (e.g. feeding tube insertion and non-invasive ventilation) and decreased survival. One of the most consistently reported cognitive abnormalities is letter fluency impairment, which is used as a clinical screening measure and has been related to reduced activation in prefrontal and temporal brain regions on functional MRI (fMRI) and PET. These functional imaging findings have been corroborated by studies relating abnormal regional brain metabolites and grey matter densities to fluency impairment in ALS.

In PMA, non-motor cerebral involvement is disputed: no abnormalities have been shown on cognitive testing, regional cerebral blood flow imaging or magnetic resonance spectroscopy of the prefrontal cortex (PFC) in PMA patients. However, we previously found fluency deficits in PMA patients and reduced fractional anisotropy in the white matter of the PFC in another cohort of PMA patients, suggesting non-motor cerebral involvement, although neuropsychological assessment was not performed in the latter study.

The presence of non-motor cerebral involvement in PMA would add to clinical, genetic and pathological findings, which support the view that a proportion of PMA patients should be regarded as ALS. The latter is important for future revisions of diagnostic criteria of MND (should PMA with cognitive impairments be regarded as ALS?) and eligibility for therapeutic trials.

The aim of this study was to examine whether non-motor cerebral involvement in PMA could be established using fMRI. We hypothesized that PMA patients show non-motor cerebral involvement in frontal and temporal brain regions previously associated with fluency performance in ALS.

METHODS

Participants

Patients were recruited from tertiary referral centers for MND in Amsterdam (Academic Medical Center) and Utrecht (University Medical Center). Spouses and
friends participated as healthy controls (HC), matched for education and age. The patients with ALS could be classified as probable or definite ALS (revised El Escorial criteria).\(^{56, 140}\) PMA patients fulfilled the criteria as earlier described:\(^{3, 140}\) (1) diagnosed within 5 years, (2) clinical and electrophysiological evidence of lower motor neuron involvement in two or more regions (bulbar, cervical, thoracic and lumbosacral), (3) no conduction blocks on extensive nerve conduction studies, and (4) no clinical upper motor neuron signs (UMN) and symptoms.\(^{3, 140}\) We excluded patients and controls if they had pre-existent frontotemporal dementia or another dementia according to consensus criteria (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association 1994 and Lund-Manchester criteria\(^ {10}\)), a history of another neurological disorder associated with cognitive impairment, a vital capacity lower than 70% of the predicted value and severe dysarthria.\(^ {140}\) Patients had to be able to push a button with the index finger of the right hand without difficulty, had to be free of psycho-active medication and had to speak Dutch fluently.\(^ {140}\)

Before this study, one comparable fMRI study in ALS had been performed precluding a valid power analysis. Moreover for fMRI, generally accepted methods for power calculation are not yet available. Methodological studies with simulated and real data have shown that group sizes of 12-20 participants are sufficient for detecting small to medium effects.\(^ {174, 175}\)

**Standard protocol approvals, and patient consents**

This study was approved by the medical ethical committees of the hospitals. Written informed consent was obtained from all participants.

**Clinical assessment**

We used the revised ALS rating scale (ALSFRS-R) to assess the functional status of the patients.\(^ {68}\) Further assessments included site of onset (bulbar or limb); bulbar involvement (a score < 4 on one or more of the bulbar items of the ALSFRS-R); UMN score (sum-score of myotatic and pathological UMN reflexes and pseudobulbar affect; range 0-48; based on Ellis et al. and described earlier).\(^ {98, 140}\) disease duration (months between first sign of muscle weakness and the MRI scan) and the years of formal education.
Neuropsychological assessment

Patients and controls underwent a comprehensive neuropsychological examination in an out-patient clinic near the patient’s home, including rest periods if needed. The tests were administered in a fixed order and covered premorbid intellectual ability, global cognitive impairment, executive functions, memory, language, attention and working memory, psychomotor speed and visuospatial functions as described earlier (tests and adjustments for motor and speech impairment are described in appendix 1 and the method section of chapter 3. We used two fluency tests: letter fluency (Controlled Oral Word Association Test, using the letters K, O and M) and category fluency (animals and supermarket items). We rated anxiety and depression using the Hospital Anxiety and Depression Scale (HADS).99,140

Statistical analysis of neuropsychological test results

Group differences of neuropsychological measures (PMA vs. ALS and controls) were analyzed using ANOVA, chi-square/Fisher’s exact test, or Student’s t-test, where appropriate. Two sided p-values <0.05 were considered significant. Data were analyzed with SPSS, IBM, version 21.

MR-imaging

Patients and controls underwent an MRI scan within four weeks of the neuropsychological examination, i.e. not on the same day to prevent fatigue effects. Images were acquired on a Philips Intera 3T MR scanner with a SENSE-6 channel head coil for radio frequency transmission and reception.

fMRI task

The letter and category fluency tasks used here have shown robust left prefrontal activation in healthy controls with a mean age of 60 years (SD 8.2) in a previous study.29 Three letter fluency blocks and three category fluency blocks, of 30 seconds each, alternated with seven blocks of a baseline task (counting backwards) of 15 sec each. During the fluency blocks, participants had to press a button for every covertly generated word (without pronouncing the word, to reduce movement artifacts and not to burden patients with bulbar involvement) either starting with the letter or
belonging to the category. Participants were informed about the task before entering the scanner and examples of each of both tasks, not used in the scanner or in the neuropsychological investigation, were given. Patients were instructed not to produce names and consecutive words starting with the same prefix and to keep their eyes open during the experimental and baseline conditions. During the baseline task, participants pressed a button for every number covertly counted backwards. Performance was measured as the total number of button presses registered through two magnet-compatible button boxes. To reduce possible retest effects, we used parallel versions of the fluency tests with the letters D, A, and T and categories: “vegetables/fruit,” “tools,” and “occupations.”

**Structural MRI acquisition and analysis** (appendix 2).

For each subject, a three-dimensional gradient-echo T1-weighted image and a T2-weighted structural image were acquired. We used T1-weighted scans for a preprocessing step of the fMRI analysis and to calculate mean volumes of structures containing significant activation effects – scaled for total grey matter volume. T2-weighted images were used to rate white matter lesions according to the Age Related White Matter Changes scale (ARWMC).

**fMRI acquisition and analysis**

For each subject 250 echo planar imaging (EPI) volumes sensitive to the blood oxygenation-level dependent (BOLD) effect were obtained, entailing a T2-weighted gradient echo sequence (repetition time 2300 ms, echo time 30.0 ms, flip angle 80°) using axial whole-brain acquisition, with an interleaved slice acquisition order. The EPI volumes were acquired at 40 slices (3 mm thickness, no gap); matrix size 96x96 voxels; in-plane resolution 2.29x2.29 mm.

fMRI data were pre-processed and analyzed (appendix 2) using Statistical Parametric Mapping software (SPM8) implemented in Matlab version 7.8.0 (The MathWorks Inc., USA).

Following the summary statistics approach, contrast images were calculated per subject on a voxel-by-voxel basis and entered into second-level analyses for between-group (PMA, ALS, HC) comparisons (ANCOVA) with performance as covariate (set to
interact with factor ‘group’ to allow further investigation of performance effects within groups). The main effect of the fMRI task is reported at a threshold of $p < 0.05$ whole-brain corrected for family-wise error (FWE).

Age and education were added to the model to account for variance related to these factors. To investigate an effect of white matter changes and regional volume, in addition, we added the ARWMC scores and mean volumes of the structures containing significant activation effects as covariates.

For the between-group comparisons we restricted the area for correction to include the left inferior frontal gyrus, left middle frontal gyrus (dorsolateral PFC), left middle temporal gyrus and bilateral anterior cingulate cortex as regions of interest, based on our hypothesis and their known involvement in letter fluency processing in ALS. We constructed a composite mask with the aid of the Anatomical Automatic Labeling implemented in the WFU-pick atlas using the labels: Frontal_Inf_Tri_L, Frontal_Inf_Oper_L, Frontal_Mid_L, Temporal_Mid_L, Cingulum_Ant_L, Cingulum_Ant_R. Main effects of group (F-test) and post-hoc t-tests are reported at $p<0.05$, FWE-corrected for the extent of this composite mask.

A similar approach for category fluency analyses is described in appendix 2.

**RESULTS**

MRI scans of 18 PMA patients, 21 ALS patients and 17 HC were analyzed. Thirty-six participants (64.2%) underwent the neuropsychological investigation first; the other 20 participants underwent MRI scanning first. The order of the investigations (neuropsychological investigation and MRI) did not differ between PMA, ALS and HC ($p = 0.35$). Three left-handed participants were included. UMN score, site of onset and bulbar involvement differed between ALS and PMA patients; none of the demographic and other clinical characteristics differed significantly between the groups (table 1).

**Neuropsychological test performance**

The PMA, ALS and HC groups showed significant differences on two tests: letter fluency (table 2) and digit backward raw score, which is a measure of attention and working memory (see appendix 1 for neuropsychological test results).
Table 1. Demographic and clinical characteristics of PMA and ALS patients and control subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PMA (n=18)</th>
<th>ALS (n=21)</th>
<th>HC (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>13/5</td>
<td>15/6</td>
<td>10/7</td>
<td>0.481</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.4 (9.7)</td>
<td>60.3 (10.2)</td>
<td>59.0 (10.8)</td>
<td>0.904</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>16/2</td>
<td>21/0</td>
<td>16/1</td>
<td>0.301</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>100.8 (16.9)</td>
<td>104.4 (16.4)</td>
<td>106.2 (16.8)</td>
<td>0.656</td>
</tr>
<tr>
<td>Education (y)</td>
<td>14.4 (3.1)</td>
<td>14.1 (2.6)</td>
<td>13.9 (2.1)</td>
<td>0.843</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>4.3 (2.5)</td>
<td>3.9 (3.0)</td>
<td>4.7 (3.2)</td>
<td>0.571</td>
</tr>
<tr>
<td>HADS depression</td>
<td>3.9 (2.6)</td>
<td>4.1 (3.6)</td>
<td>3.5 (4.1)</td>
<td>0.840</td>
</tr>
<tr>
<td>HADS total</td>
<td>8.2 (4.8)</td>
<td>8.2 (6.8)</td>
<td>8.0 (6.2)</td>
<td>0.994</td>
</tr>
<tr>
<td>Disease duration (mo.)</td>
<td>26.0 (13.6)</td>
<td>22.2 (11.4)</td>
<td>-</td>
<td>0.353</td>
</tr>
<tr>
<td>Bulbar onset, No. (%)</td>
<td>0 (0)</td>
<td>5 (23.8)</td>
<td>-</td>
<td>0.050*</td>
</tr>
<tr>
<td>Bulbar region affected, No. (%)</td>
<td>4 (22.2)</td>
<td>12 (57.1)</td>
<td>-</td>
<td>0.037*</td>
</tr>
<tr>
<td>Familial/sporadic</td>
<td>1/17</td>
<td>4/17</td>
<td>-</td>
<td>0.355</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>41.5 (3.7)</td>
<td>40.0 (4.9)</td>
<td>-</td>
<td>0.298</td>
</tr>
<tr>
<td>UMN score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.0 (6.8)</td>
<td>33.3 (7.1)</td>
<td>-</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>ARWMC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.5 (1.4)</td>
<td>2.3 (2.3)</td>
<td>1.2 (1.3)</td>
<td>0.137</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless stated otherwise. *p-values <0.05. HADS = Hospital Anxiety and Depression Scale; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. <sup>b</sup>Bulbar region affected = score below 4 on one of the bulbar items of the ALSFRS-R; <sup>c</sup>Upper motor neuron score (max = 48; normal score is 16). <sup>c</sup>Age Related White Matter Changes scale (max =30; indicates severe white matter changes).

**Performance in the scanner: letter and category fluency**

The mean number of words generated on the letter fluency task in the scanner differed among the PMA, ALS and HC groups ($F =$ 3.7; p<0.05); PMA patients generated on average 38.2 (SD 12.5) words, ALS patients generated 31.1 (10.8) words and HC generated 40.6 (11.3) words (p<0.05 for ALS vs. HC). Performance during the control condition (counting backwards) did not differ significantly between groups.

The mean number of words generated on the *category fluency* task in the scanner was higher than that of the letter fluency task: PMA patients generated 44.2 (14.1) words; ALS patients generated 38.8 (10.2) words and HC generated 44.3 (11.0) words.

This result indicates that the participants complied with the task instructions, as similar differences between letter and category fluency performance were found
during neuropsychological testing outside the scanner, and have been reported in the literature.\textsuperscript{60} Note that the neuropsychological examination and fMRI tasks differed in time durations with respect to fluency, hampering a direct comparison.

Table 2. Letter and category fluency test results in patients and control subjects

<table>
<thead>
<tr>
<th>Fluency</th>
<th>PMA (n=18)</th>
<th>ALS (n=21)</th>
<th>HC (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter score</td>
<td>35.5 (11.4)	extsuperscript{a}</td>
<td>35.3 (11.9)	extsuperscript{b}</td>
<td>43.7 (9.9)</td>
<td>0.048*</td>
</tr>
<tr>
<td>perseverations</td>
<td>1 (0-4)</td>
<td>0 (0-10)</td>
<td>0 (0-3)</td>
<td>0.771</td>
</tr>
<tr>
<td>motor speed corr.</td>
<td>4.4 (2.0)</td>
<td>4.3 (1.8)</td>
<td>3.3 (0.8)</td>
<td>0.070</td>
</tr>
<tr>
<td>Category score</td>
<td>44.7 (13.5)</td>
<td>43.3 (11.9)</td>
<td>51.5 (10.8)</td>
<td>0.104</td>
</tr>
<tr>
<td>perseverations</td>
<td>0 (0-4)</td>
<td>0 (0-4)</td>
<td>0 (0-2)</td>
<td>0.305</td>
</tr>
<tr>
<td>motor speed corr.</td>
<td>2.1 (1.4)</td>
<td>1.9 (0.8)</td>
<td>1.5 (0.5)</td>
<td>0.132</td>
</tr>
</tbody>
</table>

Data represent neuropsychological test results. Values are mean (SD) or median (range); score = number of words in three (letter) or two (category) trials of one minute. Results of other neuropsychological tests are in appendix 1. \textsuperscript{*}p-value <0.05 (ANOVA); \textsuperscript{a}PMA vs. HC: p = 0.033; \textsuperscript{b}ALS vs. HC p = 0.027 (Student’s t-test). Motor speed corr. = motor speed corrected; described on page 45/46. PMA = progressive muscular atrophy, ALS = amyotrophic lateral sclerosis, HC = Healthy controls.

**Cerebral activation related to letter fluency performance: blood oxygenation level dependent activation**

Whole-brain analysis of functional activation data across all participants showed letter fluency-related activation of left sided brain regions including inferior frontal, dorsal lateral prefrontal, anterior cingulate, and posterior temporal and bilateral occipital cortices (figure 1). The category fluency fMRI task showed robust left frontal and left (para)hippocampal activation (p < 0.05 whole brain corrected for family-wise error), also as described before.\textsuperscript{29}

**Between group comparison of letter fluency related cerebral activation**

Between group comparison of activation changes with performance as a covariate showed a significant difference of letter fluency BOLD activation between PMA, ALS and HC in the left inferior frontal gyrus (IFG, Brodmann area (BA) 45) (figure 2 and table 3).
The main effect of the fMRI task (all subjects) is reported at a threshold of $p < 0.05$ whole brain corrected for family-wise error. Regions (L = left, R = right) of activation include (Brodmann areas, BA): L middle frontal gyrus, BA 9 and 46; L inferior frontal gyrus BA 45 and 47; R occipital lobe, lingual gyrus; BA 18, L cerebellum, posterior lobe; R occipital lobe BA 17, L superior frontal gyrus BA 6 and 8; L middle temporal gyrus BA 22; L cingulate gyrus BA 24. The Talairach coordinates of the most medial part of the left frontal region are $x=33$, $y=30$, $z=0$, which corresponds the inferior frontal gyrus, Brodmann area 47.

The BOLD activation in BA 45 of PMA patients was lower compared to that of controls and higher compared to that of ALS patients ($p = 0.035$, Z-score 4.11, voxel size = 11). Another cluster in the IFG (BA 9) showed a trend (Z-score 3.92; $p=0.069$; voxel size 8) with lower activation in both PMA and ALS patients compared to HC (table 3). Repeated analysis without performance as a covariate revealed similar results for the cluster in the left IFG (BA 45; Z-score 4.24; $p = 0.022$; voxel size = 14). Repeated analysis with age and education as covariates (BA 45; Z-score 4.72; $p =0.003$; voxel
and adding the ARWMC and volume of the IFG (BA 45; Z-score 4.53; p=0.008; voxel size 15) did not change the results. Excluding five familial cases (BA 45; Z-score 4.12; p=0.036; voxel size = 8) or three left-handed participants (BA 45; Z-score 4.03; p = 0.048; voxel size = 11) revealed similar results (appendix 2).

**Between group comparison of category fluency BOLD activation**

Between group comparisons did not show significant activation changes during category fluency. Two small clusters in the left middle frontal gyrus (Talairach coordinates: x= -24, y=21, z=57; BA 6; Z= 3.40; voxel size =3) and left parahippocampal gyrus (x=-33, y=-33, z=-12; BA 36; Z=3.58; voxel size =3) did not survive FWE.

**Structural MRI – Regional brain volume and age related white matter scores.**

No differences were shown for mean volumes of the IFG scaled for total grey matter volumes, between patients with PMA, ALS and HC ($F = 2.3; p = 0.112$). The ARWMC score did not show significant differences between PMA, ALS and HC (table 1).

Table 3. Comparison of letter fluency fMRI activation between groups

<table>
<thead>
<tr>
<th>Contrast</th>
<th>k</th>
<th>side</th>
<th>BA gyrus</th>
<th>MNI coordinates</th>
<th>$F$</th>
<th>$Z$</th>
<th>$p_{(FWE)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of diagnosis:</td>
<td>11</td>
<td>L</td>
<td>45 Inf Fr G</td>
<td>-48 36 6</td>
<td>13.52</td>
<td>4.11</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>PMA, ALS, HC</td>
<td>8</td>
<td>L</td>
<td>9 Inf Fr G</td>
<td>-36 6 27</td>
<td>12.30</td>
<td>3.92</td>
<td>0.069</td>
</tr>
<tr>
<td>PMA&lt;HC</td>
<td>2</td>
<td>L</td>
<td>32 Ant Cing</td>
<td>-6 36 18</td>
<td>8.52</td>
<td>3.22</td>
<td>0.484</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>L</td>
<td>9 Inf Fr G</td>
<td>-33 6 27</td>
<td>4.54</td>
<td>4.14</td>
<td><strong>0.026</strong></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>L</td>
<td>32 Ant Cing</td>
<td>-6 36 18</td>
<td>4.11</td>
<td>3.80</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>L</td>
<td>45 Inf Fr G</td>
<td>-51 36 3</td>
<td>3.89</td>
<td>3.62</td>
<td>0.143</td>
</tr>
<tr>
<td>ALS&lt;HC</td>
<td>24</td>
<td>L</td>
<td>45 Inf Fr G</td>
<td>-48 36 6</td>
<td>5.19</td>
<td>4.63</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>L</td>
<td>9 Inf Fr G</td>
<td>-36 6 27</td>
<td>3.97</td>
<td>3.69</td>
<td>0.118</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>L</td>
<td>6 Mid Fr G</td>
<td>-33 6 51</td>
<td>3.63</td>
<td>3.40</td>
<td>0.259</td>
</tr>
</tbody>
</table>

Main effects of group and post-hoc t-tests are reported at $p<0.05$, family wise error-corrected for the extent of the composite mask with performance as covariate. Abbreviations: $K =$ number of voxels. L = left. Inf Fr G = Inferior frontal gyrus, Ant Cing = anterior cingulate cortex, Mid Fr G = middle frontal gyrus. PMA: progressive muscular atrophy, ALS: amyotrophic lateral sclerosis, HC: Healthy controls.
Figure 2. Between-group comparison of letter fluency-related cerebral activation – region of interest analysis

Contrast estimates at the left inferior frontal gyrus (Talairach coordinates: x=-48, y=36, z=6, Brodmann area 45; p = 0.035, Z-score 4.11; size = 11 voxels) for PMA and ALS patients and healthy controls. Main effects of group are reported at p<0.05, family-wise error corrected for the extent of the composite mask with performance as covariate. PMA: progressive muscular atrophy; ALS: amyotrophic lateral sclerosis.
DISCUSSION

This study revealed cerebral activation abnormalities in motor neuron disease (MND) patients with and without clinical signs of upper motor neuron (UMN) involvement. A letter fluency task showed lower activation in the inferior frontal gyrus (IFG) of PMA and ALS patients which was most pronounced in ALS patients. These results demonstrate that fMRI is a feasible and sensitive measure to detect non-motor cerebral changes related to cognitive dysfunction in MND.\textsuperscript{20,178,179}

Our finding of lower regional cerebral activation in PMA complements reduced fractional anisotropy in the prefrontal white matter on diffusion tensor imaging in 10 other PMA patients in our earlier study.\textsuperscript{28} A cerebral blood flow study (PET) during a joystick movement paradigm in PMA patients did not show changes in the prefrontal cortex (PFC), which may have been related to the task used and a relatively small sample (n=5).\textsuperscript{27} Magnetic resonance spectroscopy showed a correlation between a reduced N-acetyl acetate/creatinine-phosphocreatinine ratio in the PFC and letter fluency performance in ALS patients, but not in PMA patients. Also in this study, a small sample size (n=5 PMA patients) precluded firm conclusions.\textsuperscript{131}

The neuropsychological assessment in the present study showed letter fluency impairment in PMA patients, which is the most consistent cognitive abnormality in ALS and has likewise been described in limb-onset ALS patients and PMA patients.\textsuperscript{72,107,130,131} The neuropsychological assessment further showed that the cognitive profile of ALS patients was largely in agreement with that reported in the literature including deficits on letter and category fluency, naming and memory.\textsuperscript{20,107,129,140} The present study thus demonstrates that non-motor cerebral activation abnormalities (impaired recruitment of the left IFG) are linked to impairment on an important clinical measure of executive dysfunction in PMA patients comparable to findings in ALS patients.\textsuperscript{20,173}

Cortical atrophy of the PFC, including the (IFG), is a consistent imaging finding in ALS, in particular in ALS-FTD patients.\textsuperscript{8,20,180} The IFG contains Brodann area (BA) 45 and showed lower activation in MND patients in the present study, which is in agreement with fMRI findings in ALS patients without dementia by others.\textsuperscript{20} BA 45 is designated as Broca's area together with BA 44, and has been implicated in word retrieval.\textsuperscript{181} A post mortem study has shown pronounced pathological changes
in BA 45 and 44 in MND patients with aphasia or dementia. Together with evidence of language and semantic memory impairment in MND patients without dementia, this supports the notion that the left IFG is vulnerable to the pathological process underlying the MND-FTD spectrum. Together with clinical, pathological and imaging evidence of corticospinal tract changes in PMA, the impaired prefrontal activation as shown in the present study argues against the view of PMA and ALS being separate diseases. Therefore, the current diagnostic criteria for MND, which are based on the presence of UMN signs and actually exclude PMA, may need to be reconsidered.

Several methodological issues of the present study warrant consideration. First, dysarthria may result in overestimation of fluency impairment. Three features argue against such a bias: 1) none of our PMA patients had bulbar onset, 2) four PMA patients had only slight bulbar involvement which did not affect fluency testing (an exploratory analysis showed that their demographically corrected fluency scores were normal; percentile range: 21 to 70); 3) we used a covert fluency fMRI task, minimizing orofacial movements in the scanner.

Second, due to careful matching of PMA patients with ALS patients and healthy control subjects, and the results of the analyses of covariance, we think it is unlikely that the impaired prefrontal activation is related to depression, anxiety, age, education or white matter changes.

Further, impaired IFG activation in the present study is unlikely to result from non-compliance because 1) the use of fluency performance as a covariate did not substantially alter the results, 2) performance of the control condition (counting backwards) in the scanner did not differ between groups and 3) differences between performance on letter and category fluency tasks (higher scores for category) in the scanner are compatible with that in the neuropsychological investigation outside the scanner in our study, and similar differences have been reported in our earlier work and the literature.

Some potential limitations of this study should be noted. First, patients samples are relatively small sample and we obtained some trend-significant results on neuropsychological and fMRI analyses, suggesting that more power is needed to establish the non-motor cerebral involvement of PMA in more detail. Second,
although disease duration of PMA patients was limited to five years, the remaining heterogeneity within the PMA cohort may have obscured fMRI changes. Our results indicate impaired prefrontal activation related to fluency deficits in MND patients regardless of UMN signs. Future studies should examine PMA patients at an early disease stage to assess whether non-motor changes have an impact on treatment issues, patient-caregiver interaction and survival duration, similar to ALS. In addition, studies on non-motor changes in MND should include measures of UMN severity in addition to the ALSFRS-R (which is mostly a LMN measure) to further confirm the hypothesis that a proportion of PMA patients may be viewed as ALS minus detectable UMN signs.
## Appendix 1. Neuropsychological test results: raw scores and p-values

<table>
<thead>
<tr>
<th>Test</th>
<th>PMA (n=18)</th>
<th>ALS (n=21)</th>
<th>HC (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMSE</strong></td>
<td>28.1 (1.6)</td>
<td>28.4 (1.6)</td>
<td>29.0 (1.0)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Attention/working memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits forward raw score</td>
<td>7.5 (2.2)</td>
<td>8.1 (2.4)</td>
<td>8.6 (2.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Digits backward raw score</td>
<td>4.1 (1.8)a</td>
<td>5.6 (1.9)</td>
<td>5.8 (1.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Number letter sequencing span</td>
<td>9.4 (2.8)</td>
<td>9.3 (1.8)</td>
<td>10.4 (1.5)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop C time (s)b</td>
<td>108.7</td>
<td>107</td>
<td>102.4</td>
<td>0.90</td>
</tr>
<tr>
<td>(SD)</td>
<td>(38.3)</td>
<td>(47.5)</td>
<td>(34.5)</td>
<td></td>
</tr>
<tr>
<td>Stroop (interference) time (s)</td>
<td>44.8</td>
<td>53.1</td>
<td>45.8</td>
<td>0.67</td>
</tr>
<tr>
<td>WCST categories</td>
<td>5.5 (1.1)</td>
<td>5.8 (0.5)</td>
<td>5.7 (0.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>1.9 (2.3)</td>
<td>2.1 (2.6)</td>
<td>1.9 (3.3)</td>
<td>0.97</td>
</tr>
<tr>
<td>non. pers. errors</td>
<td>5.0 (4.6)</td>
<td>4.1 (3.1)</td>
<td>2.7 (2.5)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter time/item (s)</td>
<td>4.4 (2.0)a</td>
<td>4.3 (1.8)a</td>
<td>3.3 (0.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>raw score</td>
<td>35.5 (11.4)a</td>
<td>35.3 (11.9)a</td>
<td>43.7 (9.9)</td>
<td>0.048</td>
</tr>
<tr>
<td>Category time/item (s)</td>
<td>2.1 (1.4)</td>
<td>1.9 (0.8)</td>
<td>1.5 (0.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>raw score</td>
<td>44.7 (13.5)</td>
<td>43.3 (11.9)a</td>
<td>51.5 (10.8)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doors A</td>
<td>10.3 (2.3)</td>
<td>9.8 (1.5)</td>
<td>9.9 (1.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Doors B</td>
<td>6.2 (2.0)a</td>
<td>6.1 (2.6)a</td>
<td>7.7 (2.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>15 words test direct recall</td>
<td>40.0 (12.2)</td>
<td>44.0 (10.0)</td>
<td>44.9 (6.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>delayed recall</td>
<td>7.7 (4.0)</td>
<td>9.4 (3.0)</td>
<td>9.0 (2.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>recognition</td>
<td>13.6 (1.3)a</td>
<td>14.1 (1.1)</td>
<td>14.5 (0.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>RBMT immediate recall</td>
<td>17.2 (5.6)</td>
<td>16.4 (5.6)</td>
<td>16.9 (4.3)</td>
<td>0.88</td>
</tr>
<tr>
<td>delayed recall</td>
<td>13.1 (5.3)</td>
<td>13.0 (5.2)</td>
<td>13.1 (4.0)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston naming test</td>
<td>54.3 (5.9)</td>
<td>53.7 (5.5)a</td>
<td>56.6 (1.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Visuospatial functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JOLO</td>
<td>26.2 (4.4)</td>
<td>24.8 (4.5)</td>
<td>26.1 (4.0)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Values are mean (SD). P-values of <0.05 are considered significant (ANOVA), shown in bold. a Significant p-values of PMA vs HC or ALS vs HC; shown here irrespective of the ANOVA results to provide insight in the cognitive profiles of PMA and ALS patients. MMSE: Mini-mental state examination; WCST: Modified Wisconsin Card Sorting Test; Fluency motor speed corr. = motor speed corrected. RBMT: Rivermead Behavioral Memory Test; JOLO: judgment of line orientation.
Appendix 2. MRI analysis

Subjects
Scans were available from a subset of participants who were reported earlier. Apart from participants who underwent neuropsychological examination without a scan, or gave consent for a structural scan only, one PMA patient who showed (movement) artifacts was excluded.

fMRI data pre-processing and analysis
Before pre-processing, manual origin setting was performed to the anterior commissure on the EPI volumes. Temporal and spatial correction of the data included slice timing correction, spatial realignment to the first image, co-registration between the anatomical and mean EPI images, spatial normalization to the standard Montreal Neurological Institute (MNI), resampling into a 3x3x3 mm grid, and spatial smoothing using a Gaussian kernel (8 mm full-width at half-maximum). To remove low-frequency temporal noise, a high-pass filter was applied, with a cut-off of 128 s, to the fMRI time-series. A canonical hemodynamic response function, with the temporal derivative and the dispersion derivative, was used in a general linear model and parameter estimates were generated for each voxel, for each condition. A post-hoc analysis of individual activation patterns of the three left-handed participants showed predominantly left sided frontotemporal activation.

Category fluency
For the analysis of group effects on category fluency fMRI data, the approach was similar to that described for letter fluency, except for the regions of interest. For the between-group comparisons we restricted the area for correction to include the left inferior frontal gyrus, left middle frontal gyrus (dorsolateral prefrontal cortex), bilateral anterior cingulate and the whole temporal lobe as regions of interest, based on earlier reports. We constructed a composite mask with the aid of the Anatomical Automatic Labeling implemented in WFU-pick atlas using the labels: Frontal_Inf_Tri_L, Frontal_Inf_Oper_L, Frontal_Mid_L, Cingulum_Ant_L, Cingulum_Ant_R, Hippocampus_L and ParaHippocampal_L Temporal_Sup_L Temporal_Pole_Sup_L, Temporal_Mid_L, Temporal_Pole_Mid_L and Temporal_Inf_L.
Main effects of group (F-test) and post-hoc t-tests are reported at p<0.05, FWE-corrected for the extent of this composite mask.

**Structural MRI acquisition and analysis**
For each subject, a three-dimensional gradient-echo T1-weighted image (repetition time 9 msec, echo time 3.5 msec; matrix 256x256; voxel size: 1x1x1 mm; 170 slices) and a T2-weighted structural image (repetition time 3752 ms, echo time 80 ms, voxel size 0.45x0.45 mm; 45 slices) were acquired. T1-scans were used for normalization into MNI space (preprocessing; see above). In addition, individual modulated grey matter images were derived from the T1 scans to calculate mean volumes of structures containing significant activation effects, based on the Anatomical Automatic Labeling templates, scaled for total grey matter volumes.\textsuperscript{177} For the optimized voxel-based morphometry procedure, we used the same methods as in a previous study.\textsuperscript{184}

**Age Related White Matter Changes scale**
An experienced neuroradiologist (CBM) who was blind for the diagnosis, rated white matter lesions on T2-weighted images, according to the Age Related White Matter Changes scale (ARWMC) which is a 4-point scale (0-3) comprising five brain regions (frontal, parieto-occipital, temporal, infratentorial and the basal ganglia).\textsuperscript{185}
Prose memory impairment is related to hippocampus volume in amyotrophic lateral sclerosis

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ABSTRACT

Objective
Thirty percent of ALS patients have non-motor symptoms, including executive and memory deficits. The in vivo anatomical basis of memory deficits in ALS has not been elucidated. In this observational study we investigated brain atrophy in relation to memory function in ALS patients and controls.

Methods
Twenty-six ALS patients without dementia and 21 healthy volunteers matched for gender, age and education level underwent comprehensive neuropsychological evaluation and T1 and T2-weighted 3T MRI scanning of the brain. Grey and white matter brain volumes were analysed using voxel based morphometry and age related white matter changes were assessed. The most frequently abnormal memory test (<2 SD below normative data corrected for age, gender and education) was correlated with regional brain volume variations by multiple regression analyses with age, gender and total grey matter volumes as covariates.

Results
Immediate and Delayed Story Recall scores were abnormal in 23% of ALS patients and correlated to bilateral hippocampus grey matter volume ($r = 0.52$ for both memory tests; $p < .05$; corrected for age, gender and total grey matter volume). This correlation was not found in healthy controls with similar age, education, anxiety and depression levels and white matter changes.

Conclusion
Prose memory impairment is a frequent finding in this cohort and is associated with hippocampus volume in ALS patients without dementia. These findings complement previous hippocampus changes in imaging studies in ALS and suggest involvement of the hippocampus in cognitive dysfunction of ALS.
INTRODUCTION

Approximately 30% percent of ALS patients have cognitive impairments, and another 8-15% have severe behavioral changes consistent with the behavioral subtype of frontotemporal dementia (ALS-FTD). These non-motor changes are likely to be associated with lower survival, higher caregiver burden and may hinder decision making regarding feeding tube insertion and non-invasive ventilation. In ALS patients without frank dementia reduced cerebral blood flow and atrophy of the (dorsolateral) prefrontal cortex has been related to executive dysfunction. Other brain areas are also likely to be involved, as the cognitive profile of ALS is broader than executive deficits, and includes, besides language and social cognition changes, memory deficits, conceivably due to involvement of the medial temporal lobe. The dentate gyrus of the hippocampus is typically abnormal in post mortem studies of ALS-FTD patients (and to a lesser extent in ALS without FTD) showing neuronal loss and pathological inclusions. In contrast, most structural and functional imaging studies did not reveal hippocampal abnormalities in ALS patients with or without FTD. Diffusion tensor imaging and volumetric MRI studies that did show hippocampal changes in ALS(-FTD) patients, could not relate these to cognitive functioning as neuropsychological testing had not been performed, with one recent exception. Thus, the relation between hippocampal changes and memory dysfunction in ALS is incompletely understood.

In the present study, we addressed this issue by investigating ALS patients and healthy controls, using three memory tests as part of a comprehensive neuropsychological investigation and whole-brain MRI with voxel-based morphometry. We examined whether memory impairments in ALS patients, if present, are associated with gray matter reductions in the medial temporal lobe.

METHODS

Participants

Patients were recruited from tertiary referral centers for motor neuron disease in Amsterdam (Academic Medical Center) and Utrecht (University Medical Center). Spouses and friends participated as healthy controls (HC), matched for age and education. The medical ethical committees of the hospitals approved the study. We
obtained written informed consent from all participants. All patients with ALS included in the study could be classified as probable or definite according to the revised El Escorial criteria, as described before. Patients and controls were excluded if they had pre-existent dementia, including frontotemporal dementia, according to consensus criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM), American Psychiatric Association, 1994 and Lund-Manchester Criteria), a history of another neurological disorder associated with cognitive impairment, a vital capacity lower than 70% of the predicted value (to prevent bias of respiratory compromise on cognitive measures), severe dysarthria or anarthria, as described before. Patients had to speak Dutch fluently and they had to be free of psychoactive medication (benzodiazepines, antidepressants, antipsychotics). ALS patients with mild cognitive impairment (ALSci) or mild behavioral changes (ALSbi) were not excluded.

**Clinical assessment**

We used the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) to evaluate the functional status of the patients and we assessed site of onset (bulbar or limb), degree of bulbar involvement (defined as a score below 4 on 1 or more of the bulbar items of the ALSFRS-R), disease duration (defined as the number months between the first symptom and the neuropsychological assessment) and years of formal education.

**Neuropsychological assessment**

Patients and controls underwent a comprehensive neuropsychological examination in an out-patient clinic near the patient's home. Tests were administered in a fixed order with rest periods if needed, as described in chapter 3 (methods and appendix 1). Three memory tests were used: Rivermead Behavioral Memory Test (RBMT; immediate and delayed recall of two stories, an objective measure of episodic memory in everyday situations); Doors Test A and B, a visual recognition test with two levels of difficulty, and the Rey Auditory Verbal Learning Test, a verbal memory test with immediate and delayed recall. The test-protocol further covered premorbid intellectual ability, global cognitive performance, executive functions, attention and
working memory, psychomotor speed, language and visuospatial functions (tests and adjustments for motor and speech impairment are described in chapter 3: methods and appendix 1). We used the Hospital Anxiety and Depression Scale (HADS) to rate symptoms of depression or anxiety.

Neuropsychological data analysis

Cognitive deficits were examined using standard scores, similar to methods commonly applied in clinical practice. Either scaled scores (mean 10; SD 3) or T-scores (mean 50; SD 10) were derived from normative data available in test manuals and other sources (described in appendix 1 of chapter 3). A test score was considered abnormal if it was at least two standard deviations (SD) below the mean score of the normative sample, after correction for age, gender and, if possible, education. This cut off is based on consensus criteria for cognitive dysfunction in ALS. Controls with cognitive impairment (defined as two or more abnormal tests, were excluded from further analyses). The comparisons with normative data were made to assess individual cognitive performances and to correlate the performance on the most frequently abnormal memory test with the MRI data. Second, raw neuropsychological test scores were compared between ALS and controls to establish the cognitive profile of the ALS patients.

Demographic, clinical and neuropsychological data were analysed with SPSS, IBM, version 21.

MRI-data acquisition

Imaging data were acquired using a Philips Intera 3T MR-system at the Department of Radiology of the AMC equipped with a SENSE-6 channel head coil. For each subject, anatomical images were obtained using a sagittal 3D gradient-echo T1-weighted sequence (TR=9 msec, TE=3.5 msec; matrix 256x256; voxel size: 1x1x1mm; 170 slices, duration: 4.5 min) and using a T2-weighted sequence (repetition time 3752 ms, echo time 80 ms, voxel size 0.45x0.45 mm; 45 slices).
Chapter 9

**MRI-data analysis:**

A neuroradiologist (CBM) who was blind for the diagnosis rated T2-weighted scans to quantify white matter lesions according to the Age Related White Matter Changes scale (ARWMC) on a 4-point scale (0-3) in five brain regions in the right and left hemisphere separately (frontal, parieto-occipital, temporal, infratentorial and the basal ganglia, leading to a sum-score of 30). These ARWMC-scores were analysed (ALS vs. HC) to exclude marked differences in lesions due to brain infarctions. Voxel Based Morphometry (VBM) following the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) approach was performed using Statistical Parametric Mapping software (SPM5) implemented in Matlab 7.1.0 (MathWorks, Natick, Massachusetts). For a detailed description of DARTEL we refer to previous reports. DARTEL has shown to generate reliable measures of regional brain volume, especially with regard to the hippocampus.

VBM-DARTEL preprocessing, after extensive quality evaluation of the data, included the following steps: 1) Manual reorientation of the images to the anterior commissure. 2) Segmentation of the anatomical images into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using the standard segmentation option implemented in SPM5. The CSF segments were not used for further analyses. 3) Applying the DARTEL approach for registration, normalization and modulation. Next, images were normalized to MNI space. 4) Smoothing of the GM and WM images using an 8mm, full width at half-maximum, Gaussian kernel to increase signal-to-noise ratio. In the resulting images, each voxel represents an absolute amount of brain volume, equivalent to the brain volume per unit prior to normalization. Subsequently, data were analysed in the context of the General Linear Model.

We planned the following comparisons: a 2-sample ANCOVA was performed to compare regional brain volume differences between ALS patients and control subjects, with age, gender and GM totals added as covariates.

**Correlation of MRI and neuropsychological data.**

For each group separately, multiple regression analyses were performed with gray matter (GM) volume maps as a dependent factor and the continuous neuropsychological normative scores (corrected for age, gender and education) of the
most frequently abnormal memory test as main regressor. Age, gender and GM totals were added to the model as covariates. The analyses were repeated with white matter (WM) volume as dependent factor. In order to achieve maximal sensitivity, to optimize voxel residual smoothness estimation and to exclude false positives in non-GM tissue, voxel-wise comparisons were masked using a comparison-specific explicit optimal threshold GM mask created using the Masking toolbox. Based on previous reports in ALS and our hypothesis, we set the following a priori regions of interest (ROI) for the multiple regression analyses: dorsolateral and medial prefrontal cortex, motor cortex, hippocampus and adjacent parahippocampal gyrus. To further protect against type I error, effects had to meet $p<0.05$ familywise error corrected for the spatial extent of the volume of interest, to be considered significant. For this small volume correction, we used the Automated Anatomical Labeling atlas implemented in the Wake Forest University Pick Atlas toolbox. To account for the number of a priori ROIs, we corrected the $p$-value for the number of regions ($n=5$). A standard Bonferroni correction ($p<0.01$) would be too rigorous as the dependent variables are measured within the same individuals. We took this interdependency of the ROIs into account and calculated the mean correlation of the volumes of the ROIs using the Automated Anatomical Labeling atlas; right and left regions were taken together. The mean correlation of these volumes across all participants was $r=0.80$. Using the Simple Interactive Statistical Analysis Bonferroni tool at http://www.quantitativeskills.com/sisa/calculations/bonfer.htm (alpha = 0.05, number of tests = 5, correlation = 0.8) the adjusted Bonferroni's correction resulted in an alpha ($p$-value) of 0.036. For non-regions of interest, a voxel level threshold of $p<0.05$ whole brain familywise error corrected was set a priori.

**RESULTS**

MRI imaging and neuropsychological examinations of 26 ALS patients of whom three were familial, and 21 healthy controls (HC) were analysed. Age, gender distribution, years of education, DART-IQ estimate, HADS and Age Related White Matter Changes (ARWMC) scores did not differ significantly between patients and HC (table 1).
Neither did ARWMC subscores of the left and right frontal and temporal lobes differ between ALS patients and HC.

Table 1. Demographic and clinical characteristics of ALS patients and healthy controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALS (n=26)</th>
<th>HC (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>14/12</td>
<td>12/9</td>
<td>0.821</td>
</tr>
<tr>
<td>Age (y)</td>
<td>60.7 (12.5)</td>
<td>60.7 (11.2)</td>
<td>0.995</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>102.2 (15.9)</td>
<td>108.7 (19.0)</td>
<td>0.206</td>
</tr>
<tr>
<td>Education, years (median, range)</td>
<td>13 (10-19)</td>
<td>13 (12-19)</td>
<td>0.973</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>4.4 (2.8)</td>
<td>4.7 (3.1)</td>
<td>0.705</td>
</tr>
<tr>
<td>HADS depression</td>
<td>4.2 (3.5)</td>
<td>3.3 (3.5)</td>
<td>0.363</td>
</tr>
<tr>
<td>HADS total</td>
<td>8.6 (5.9)</td>
<td>8.0 (6.2)</td>
<td>0.730</td>
</tr>
<tr>
<td>Disease duration (mo)</td>
<td>23.3 (11.3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bulbar onset, No. (%)</td>
<td>8 (31%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bulbar region affected a, No. (%)</td>
<td>13 (50%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>41.5 (3.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>White matter changes b</td>
<td>1 (0-7)</td>
<td>1 (0-4)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless stated otherwise. HC: Healthy controls. HADS: Hospital Anxiety and Depression Scale, maximum score (anxiety and depression) is 21 and indicates severe symptoms. Mo = months. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (max. = 48; indicates no handicap). a Bulbar region affected was defined as a score below 4 on one of the bulbar items of the ALSFRS-R. b Age Related White Matter Changes scale (maximum score = 30 indicating severe changes).

Neuropsychological performance

Individual performance - Immediate prose recall was abnormal in six ALS patients (23%) and in one (5%) of the controls (p=0.08). Delayed story recall was abnormal in six ALS patients (23%) and in none of the controls (p= 0.018). Word recall (15 word test) and visual memory scores (Doors B) were abnormal in three and two ALS patients, respectively (not significantly different compared to controls who all scored normal). Out of the executive tests, only letter number sequencing was abnormal in 5 ALS patients (19%) and none of the HC (p=0.034). The proportion of ALS patients with abnormal scores on other tests did not differ compared to controls.
VBM comparisons between ALS and controls

No significant difference in total grey and white matter volumes of the ALS patients compared to controls was observed. Although regions in the right and left frontal lobe showed grey matter volume reduction in ALS patients compared to controls at $p<0.001$, uncorrected, these effects did not survive correction for multiple comparisons (appendix 2). Hippocampal volumes did not differ between patients with bulbar or spinal involvement at the time of examination ($p=0.96$).

Group comparisons - Compared to controls, as a group, ALS patients showed impaired performance on letter-number sequencing (span), letter fluency, Boston naming test, and color naming of the Stroop test (appendix 1).

Table 2: Regression of delayed story recall on regional grey matter volumes in ALS patients

<table>
<thead>
<tr>
<th>R/L</th>
<th>region</th>
<th>k</th>
<th>MNI coordinate</th>
<th>z-value</th>
<th>$P_{\text{FWE(AAL)}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>hippocampus</td>
<td>680</td>
<td>-27 -24 -21</td>
<td>4.40</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-27 -12 -14</td>
<td>3.60</td>
<td>.020</td>
</tr>
<tr>
<td>R</td>
<td>hippocampus</td>
<td>98</td>
<td>23 -29 -8</td>
<td>3.72</td>
<td>.014</td>
</tr>
</tbody>
</table>

The two clusters were $p<0.05$ (figure 1) $P_{\text{FWE(AAL)}}=$ familywise error (FWE) voxel corrected for the spatial extent of the volume of interest using the Automated Anatomical Labeling (AAL) atlas. $P$-values are below the adjusted Bonferroni correction ($p=0.036$, which is calculated for five regions with a mean correlation of 0.8; see methods). The other regions of interest (dorsolateral and medial prefrontal cortex, precentral gyri and parahippocampal gyrus) did not reach statistical significance in the regression model. $k=$cluster size, R/L=right/left hemisphere.

Correlations of cognitive measures with VBM-data

In ALS patients, performances on the delayed and immediate story recall test were significantly correlated to bilateral hippocampal grey matter volume ($r = 0.52$ for both tests; delayed recall; left: $Z=4.40$, $p<.05$, SVC corrected; right: $Z=3.72$, $p<.05$, SVC corrected, table 2, figures 2 and 3). The results remained significant following the adjusted Bonferroni correction. The correlation coefficient was unchanged when three familiar ALS patients were excluded ($r=0.53$). These associations were not found in controls. No significant correlations between the story recall tests and white matter volume were found in patients or controls.
A correlation is shown ($r = 0.52; p < 0.05$) within the ALS group, between hippocampal volume corrected for age, gender and total grey matter volume, and the t-scores of the delayed prose recall test (Rivermead Behavioral Memory Test).

**DISCUSSION**

In the present study, hippocampal gray matter volume correlated to prose memory performance in a group of 26 ALS patients without dementia. This association was not present in a control group well matched for age, gender distribution, level of education, anxiety, depression and cerebral white matter changes. A relation between hippocampus volume and cognitive performance in ALS adds to previously reported neuropathological and imaging abnormalities of the hippocampus in particular in ALS patients with FTD. The pathological changes of characteristic inclusions and neuronal degeneration in the dentate gyrus have been associated with memory.
Figure 1. Effects of a regression analysis of delayed story recall scores on regional grey matter volumes in the ALS patients

The left hippocampus is shown in panel A. In panel B, which is slightly more posterior and cranial compared to panel A, the left and right hippocampus are shown. Both panels are displayed at $p<0.05$ family-wise error voxel corrected for the spatial extent of the volume of interest.
performance in ALS patients with and without dementia.\(^{37} \text{188}\) Imaging studies have shown cerebral blood flow changes and reduced white matter volume or white matter integrity of the hippocampus in ALS- FTD more than in ALS patients.\(^{28, 33, 34, 194}\) The latter studies did not include neuropsychological investigations, hampering a relation between hippocampus changes and memory performance.\(^{28, 33, 34}\)

Together with these pathological and imaging findings, the association between memory performance and hippocampus volume observed in the present study implicates the medial temporal lobe in the cognitive dysfunction of ALS, which is not restricted to ALS-FTD.

The cognitive profile of the ALS patients in this study is largely in agreement with the profile as described by us and others including letter fluency, language and attention/working memory deficits, although other executive deficits were less prominent in this study.\(^{8, 20, 35, 46, 107, 129}\) A large cohort study recently identified a subgroup of ALS patients with non-executive cognitive impairment with prominent prose recall deficits.\(^{129}\) Our cohort may resemble these patients to some extent, as the most frequently abnormal test (compared to normative data) in the present study was prose recall.\(^{35, 48, 129, 187}\) Of note the performance of our ALS patients, as a group, on the prose recall test did not differ compared to healthy controls. This may be related to some ALS patients with relatively high scores on the prose recall test and to a relatively small sample size (the latter also may have obscured a VBM group effect), reflected by the large confidence intervals.\(^{195}\)

We explored the possibility of a relation between memory performance and depression, anxiety and cerebral white matter changes. However, none of the memory tests correlated significantly with either the total score or sub-scores of the Hospital Anxiety and Depression Scale (HADS, data not shown). These HADS scores were below the thresholds of clinically relevant depression or anxiety; the latter is in agreement with previous studies in ALS.\(^{20, 129}\) The age related white matter change score (ARWMC) did not differ between ALS and controls and did not correlate with performance on the prose memory tests (results not shown).

In addition to strengths of this study (reduction of bias due to motor impairment, combination of neuropsychological tests and MRI data, analysis of lesions of brain infarctions, a matched control group, and normative scores to calculate individual
performances) several potential limitations need to be addressed. Firstly, some normative datasets of neuropsychological tests are of better quality than others, e.g. correction for education is not possible for every test, but could be performed for the prose recall test. Secondly, our criterion for respiratory failure was based on the vital capacity (<70% of predicted value), a widely used and validated measure in ALS, which may not have fully captured those patients with incipient respiratory failure. Other methods with a higher sensitivity to assess respiratory failure in ALS are known (e.g. nasal inspiratory pressure). However, any effects on our results are probably negligible as prose recall has a non-significant relation to respiratory function in ALS.

This study shows an association between hippocampus grey matter volume and memory performance in ALS patients without dementia, which corroborates recent findings of other authors. The results indicate that MR-imaging in combination with neuropsychological evaluation is a feasible method for detecting grey matter correlations of cognitive impairment in ALS patients. The findings suggest a role for the hippocampus in cognitive dysfunction of ALS patients without FTD.
Appendix 1. Neuropsychological test results: raw scores and p-values

<table>
<thead>
<tr>
<th>Test</th>
<th>ALS (n=26)</th>
<th>HC (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMSE</strong></td>
<td>28.6 (1.3)</td>
<td>28.9 (1.1)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Attention/working memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits forward raw score</td>
<td>7.6 (2.4)</td>
<td>8.3 (2.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Digits backward raw score</td>
<td>5.2 (1.7)</td>
<td>5.7 (1.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Number letter sequencing</td>
<td>9.3 (2.8)</td>
<td>10.6 (1.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>span</td>
<td>5.0 (1.1)</td>
<td>5.6 (0.7)</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Executive functions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop color word</td>
<td>121.6 (57.1)</td>
<td>100.4 (25.7)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroop &quot;interference score&quot;</td>
<td>1.8 (0.5)</td>
<td>1.9 (0.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>WCST categories</td>
<td>5.4 (1.1)</td>
<td>5.6 (0.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>perseverative errors</td>
<td>2.8 (4.2)</td>
<td>2.0 (2.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>non. pers. errors</td>
<td>5.2 (7.3)</td>
<td>3.7 (3.8)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter time/item (s)</td>
<td>4.2 (1.8)</td>
<td>3.3 (0.8)</td>
<td>0.041</td>
</tr>
<tr>
<td>raw score</td>
<td>35.2 (11.7)</td>
<td>43.2 (9.8)</td>
<td>0.018</td>
</tr>
<tr>
<td>Category time/item (s)</td>
<td>1.9 (0.8)</td>
<td>1.5 (0.5)</td>
<td>0.061</td>
</tr>
<tr>
<td>raw score</td>
<td>42.3 (12.8)</td>
<td>50.8 (10.5)</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doors A</td>
<td>9.8 (1.6)</td>
<td>9.8 (1.6)</td>
<td>0.92</td>
</tr>
<tr>
<td>Doors B</td>
<td>6.3 (2.5)</td>
<td>7.2 (2.5)</td>
<td>0.19</td>
</tr>
<tr>
<td>15 words test direct recall</td>
<td>44.1 (10.5)</td>
<td>43.6 (7.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>delayed recall</td>
<td>9.4 (3.3)</td>
<td>8.7 (2.7)</td>
<td>0.32</td>
</tr>
<tr>
<td>recognition</td>
<td>14.0 (1.6)</td>
<td>14.3 (1.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>RBMT immediate recall</td>
<td>15.5 (6.7)</td>
<td>16.3 (4.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>delayed recall</td>
<td>12.4 (6.1)</td>
<td>13.0 (4.0)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston naming test</td>
<td>54.0 (5.4)</td>
<td>56.8 (1.7)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Visuospatial functions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JOLLO</td>
<td>25.0 (4.1)</td>
<td>26.0 (4.3)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are mean (SD). P-values of <0.05 are considered significant (ANOVA), shown in bold. MMSE: Mini-mental state examination; WCST: Modified Wisconsin Card Sorting Test. RBMT: Rivermead Behavioral Memory Test; JOLLO: judgment of line orientation.
Appendix 2. Grey matter volume in ALS patients compared to controls: group comparisons

<table>
<thead>
<tr>
<th>R/L</th>
<th>BA</th>
<th>region</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z</th>
<th>( P_{\text{FWE}(\text{AAL})} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>6</td>
<td>precentral g.</td>
<td>10</td>
<td>44</td>
<td>-4</td>
<td>43</td>
<td>3.43</td>
<td>0.08</td>
</tr>
<tr>
<td>R</td>
<td>6</td>
<td>superior frontal g.</td>
<td>22</td>
<td>12</td>
<td>32</td>
<td>60</td>
<td>3.33</td>
<td>0.07</td>
</tr>
<tr>
<td>R</td>
<td>9</td>
<td>middle frontal g.</td>
<td>9</td>
<td>30</td>
<td>24</td>
<td>42</td>
<td>3.30</td>
<td>0.16</td>
</tr>
<tr>
<td>R</td>
<td>8</td>
<td>superior frontal g.</td>
<td>16</td>
<td>12</td>
<td>41</td>
<td>48</td>
<td>3.25</td>
<td>0.08</td>
</tr>
<tr>
<td>R</td>
<td>10</td>
<td>middle frontal g.</td>
<td>3</td>
<td>40</td>
<td>49</td>
<td>1</td>
<td>3.19</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Regions showing decreased grey matter volume in ALS as compared to healthy controls (HC). The volume differences in these regions did not survive correction for multiple comparisons, i.e. were not significant. \( P_{\text{FWE}(\text{AAL})} \) = familywise error voxel corrected for the spatial extent of the volume of interest using the Automated Anatomical Labeling (AAL) atlas. R/L = right/left hemisphere, BA = Brodmann Area, k = cluster size, g. = gyrus.
General discussion and directions for future research
GENERAL DISCUSSION

Progressive muscular atrophy (PMA) and amyotrophic lateral sclerosis (ALS) are collectively referred to as motor neuron disease (MND). Depending on the clinical involvement of the lower or upper motor neurons, a diagnosis of PMA (lower motor neurons) or ALS (lower and upper motor neurons) will be reached. Although motor impairment is the characteristic feature of MND, cognitive impairment and behavioral disturbances are increasingly recognized in MND patients. So-called extramotor involvement may have significant impact on decision making on and compliance with therapeutic interventions, and hence on survival (chapter 1).\(^{172}\)

Assessment of these non-motor symptoms should lead to more accurate phenotyping, which is essential for the detection of susceptibility genes and environmental factors which may cause MND or increase the risk of developing the disease. Based on the clinical overlap between PMA and ALS, and the presence of cognitive impairment in a proportion of ALS patients, our primary aim was to examine the presence of cognitive impairment in PMA and compare findings with those in ALS patients.\(^3\)

Second, we aimed at investigating the presence of behavioral changes in MND, based on the reported overlap between ALS and frontotemporal dementia.\(^{16}\)

Third, we investigated whether imaging studies could establish structural and functional brain abnormalities beyond the motor cortex in MND patients. MND with isolated upper motor neuron involvement (i.e., primary lateral sclerosis) was beyond the scope of this thesis.
The main findings of our study are the following:

1. The cognitive profile of ALS extends beyond executive dysfunction; it also includes memory changes which were found to be related to hippocampal volume loss. Visuoperceptive dysfunction was not found.

2. Cognitive changes also occur in PMA and are related to prefrontal brain changes, similar to ALS.

3. Frontal lobe mediated executive dysfunction and behavioral changes in ALS are overestimated when general scales without a correction for motor and speech impairment are used.

4. Behavioral changes fulfilling the criteria for the behavioral variant of FTD occur in 8% of ALS patients. Additionally, ~10% of ALS patients have less severe behavioral changes.

The above findings, including their relevance and the implications for clinical practice are discussed below. Further, recommendations for future research are given.

1. THE COGNITIVE PROFILE OF ALS

Meta-analysis of the cognitive profile of ALS

We initiated a meta-analysis of neuropsychological studies in ALS patients to gain insight in the cognitive profile and to direct neuropsychological examinations in our patients.

Prior to our meta-analysis cognitive impairment in ALS patients was considered to be characterized by executive dysfunction, in particular fluency deficits. Previous studies yielded inconsistent findings regarding other executive functions and other cognitive domains (language, memory), possibly due to small sample sizes which did not allow for detection of subtle cognitive changes.

We hypothesized that pooling of neuropsychological data from multiple controlled studies in ALS patients would clarify whether the cognitive profile included other executive deficits than fluency deficits, and memory, language and visuoperceptive impairment in ALS patients.

Out of 48 neuropsychological studies, 16 were eligible for inclusion in the meta-analysis, encompassing 554 ALS patients without dementia (chapter 2). A large,
statistically significant effect size was found for global cognition as measured by the MMSE (Cohen’s d = 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). In the domains psychomotor speed and executive functioning, bias due to motor impairment could not be ruled out. The effect sizes of the other cognitive domains were not significant.

Indeed, pooling of neuropsychological data increased our insight in the cognitive profile of ALS, which entails more than executive (or frontal) impairment and also includes deficits of verbal and visual memory, working memory and language (object naming). Over the last years others have investigated these non-frontal cognitive deficits of ALS patients in more detail. Both language impairment and memory changes were shown to be present in a substantial proportion of ALS patients.

Together these findings have resulted in the notion that the cognitive profile of ALS is “more than frontal”. For clinical practice this implies that a cognitive screening instrument for ALS should contain a language and memory task in addition to a fluency task.

Memory deficits and MR imaging correlates in ALS
Following our meta-analysis, the issue remained unsolved whether memory impairments in ALS patients are mediated by frontal lobe involvement (reduced retrieval of information) or medial temporal lobe dysfunction (impaired encoding of information). Although the meta-analysis was not designed to discern between these two, we will discuss some of our results. We analysed effect sizes of both immediate verbal memory and delayed verbal memory. In general, medial temporal lobe involvement results in delayed memory deficits. Conversely, immediate memory deficits may be explained by executive problems due to pathology in the frontal cortex.

The effect sizes of immediate and delayed verbal memory were equal (0.5) but the confidence interval of delayed verbal memory did not reflect a significant finding (-0.02 to 0.97) as opposed to that of immediate verbal memory (CI 0.16-0.86).

Consequently, we could only suggest, but not firmly conclude, that memory changes in
ALS are mediated by medial temporal lobe dysfunction. A recent update of the meta-analysis by our group (46 studies; 1325 patients and 1176 healthy controls; manuscript in preparation) showed a statistical significant effect size of the delayed verbal memory domain (effect size 0.47; confidence interval (0.27-0.68)), which suggests that the medial temporal lobe plays a role in the cognitive impairment of ALS.

We and others recently provided more evidence of involvement of the medial temporal lobe (in particular the hippocampus) in ALS patients without dementia. We correlated the most frequently abnormal memory test (i.e. prose recall) with brain volumes obtained by voxel based morphometry (VBM) in 26 ALS patients (chapter 9). We found a moderate correlation (r=0.52) between the volume of the hippocampus and the score of the delayed prose recall test. The scores of the delayed and immediate prose recall tests showed a strong correlation, and hippocampus volumes also correlated with immediate prose recall. The correlation between prose recall and hippocampus volume was absent in a control group matched for age, education level, anxiety and depression scores and white matter lesion scores. Although this may be merely a correlational finding, the finding of hippocampal involvement is in line with reported post mortem abnormalities (pathological inclusions and neuronal loss), frequently encountered in the dentate gyrus of the hippocampus in ALS-FTD patients and to a lesser extent in ALS patients without FTD. The absence of a group effect in our study may be related to individual ALS patients with relatively high scores, and the relatively small sample size. Recently, a larger study (n=58) also showed verbal memory impairment (on a group level) and hippocampal volume loss (manually segmented) compared to controls. Contrary to the majority of MRI studies in ALS, not showing hippocampal changes, a few MRI studies did, but these studies could not relate this to cognitive dysfunction (i.e. memory impairment), as neuropsychological assessment had not been performed. We conclude from chapter 9 that VBM in combination with neuropsychological testing provides relevant imaging correlates of cognitive dysfunction in ALS and we suggest that verbal memory tests should be included in the neuropsychological evaluations (even within screening measures) of ALS patients.
Visuospatial dysfunction: absent in ALS

We found that impairment in the visuoperceptive domain had been examined less frequently in ALS compared to the other cognitive domains, and with tests with a large ceiling effect. The effect size of the visuoperceptive domain in our meta-analysis (described above) was not significant, and showed a large confidence interval, and therefore no conclusions could be drawn for this domain (chapter 2). Therefore we studied the visuoperceptive domain in ALS patients in depth, using three tests with different grades of difficulty, including a mental rotation task (chapter 3). We hypothesized that reduced feedback into cerebral networks responsible for the integration of visuospatial information, due to a reduction of movements (in the surrounding space) as a result of motor weakness, could lead to impairment of visuoperceptive functions in ALS. In particular, we expected to find deficits of mental rotation of hands, as measured by judgment of hand laterality. The latter was based on findings of impaired mental rotation including judgment of hand laterality in patients with other disorders of movement, e.g. focal hand dystonia or Parkinson’s disease.

However, in ALS patients, no impairment on any of three visuospatial tests including judgment of hand laterality was shown (chapter 3). The absence of impairment on judgment of hand laterality (mental rotation) may have been related to the relatively preserved hand function of our patients: they had to be able to push a button with their right hand. An effect of the severity of hand dysfunction on mental rotation in ALS patients is suggested by a study showing impaired judgment of hand laterality in ALS patients, who could not move their hands and responded by eye-movements. In the latter study images of hands and the letter “F” very similar to the stimuli in our study were used.

The absence of visuoperceptive deficits in ALS are in agreement with an update of our meta-analysis on the cognitive profile of ALS (46 studies including 1325 patients and 1176 healthy controls; manuscript in preparation) in which visuoperceptive functioning is the only cognitive domain, among 13 domains, without a significant effect size. Taken together, visuoperceptive functions are normal in ALS patients with mild to moderate motor disability. Mental rotation of body parts may be affected in severely disabled MND patients, probably related to a loss of hand movements. If
moderate to severe visuoperceptive deficits are found in an ALS patient, another neurodegenerative disorder than FTD, e.g. a concomitant Alzheimer dementia should be suspected (~2% of ALS patients).

2. COGNITIVE IMPAIRMENT AND PREFRONTAL CHANGES IN PMA

Cognitive impairment

The main aim of the study described in chapter 3 was to investigate the presence of cognitive deficits in PMA patients and compare findings with those in ALS patients. In a cross-sectional neuropsychological study 17% of PMA patients were found to have cognitive impairments (in particular on letter-number sequencing, immediate and delayed story recall), in part similar to those found in ALS patients. Twenty-seven percent of ALS patients showed impairments on the same tests as PMA patients, and on a visual memory test (chapter 3). The proportions (17% and 27%) are based on demographically corrected cut-off scores (below 2 SD of the mean) as described in consensus criteria for the frontotemporal syndrome of MND. The chance that our method (neuropsychological assessment and use of cut-off scores) led to overestimation of cognitive deficits is small, as the proportion of ALS patients with cognitive impairment (~30%) in our study is in accordance with that found in three large cohort studies.

At group level PMA patients showed subtle changes of attention/working memory, fluency and global cognitive functioning (MMSE), while in ALS patients compared to the control group, cognitive changes were more extensive, including language problems (naming). The MMSE showed changes in PMA and not in ALS patients, but differences were very small and are unlikely to have clinical significance. No differences were shown for any of the three visuoperceptive tests in ALS patients, nor, as expected, in PMA patients.

We could demonstrate that cognitive changes in the executive and memory domains occur in PMA patients suggesting that the presence of non-motor symptoms in motor neuron disease is not restricted to patients with upper motor neuron involvement. These findings will be discussed below, together with findings from an fMRI study.
Prefrontal changes in PMA

Before we conducted the study reported in chapter 3, the existence of non-motor cerebral involvement in PMA had been disputed, although the evidence for absence of non-motor involvement in PMA was weak. One negative study on cognitive testing did not allow for definite conclusions because it was underpowered. Another study showed verbal memory changes and attention deficits in PMA but may have been biased due to a lower level of premorbid intellectual functioning in PMA patients compared to controls.\textsuperscript{22, 23}

Two imaging studies in PMA patients (cerebral blood flow and magnetic resonance spectroscopy, respectively) did not show changes in the prefrontal or temporal regions, as opposed to ALS patients, but again, these studies lacked statistical power (5 PMA patients in each study) which precluded firm conclusions on the absence of non-motor cerebral involvement in PMA.\textsuperscript{27, 131}

Previously, our group performed brain imaging on 12 PMA patients showing reduced fractional anisotropy in the white matter of the prefrontal cortex.\textsuperscript{28} This study, to the best of our knowledge, was the first to suggest prefrontal involvement in PMA, although a relation with cognitive dysfunction could not be established as cognitive testing had not been performed.\textsuperscript{28} Therefore, and to further delineate the involvement of non-motor cerebral regions in MND, we undertook a study (chapter 8) in which we examined brain activation patterns during verbal fluency performance in a subset of patients with PMA (n=18) and ALS (n=21) described in chapter 3.\textsuperscript{209} We hypothesized that PMA patients show non-motor cerebral involvement in frontal and temporal brain regions previously associated with fluency performance in ALS.\textsuperscript{20} We chose an fMRI fluency task because we aimed at examining disturbed blood oxygen level dependent response in brain tissue directly related to cognitive functioning. Furthermore we had learned from previous studies in ALS patients that fluency deficits, in particular letter fluency, were most consistently found, with corresponding fMRI changes in frontotemporal regions.\textsuperscript{20}

Between group analysis (PMA, ALS and healthy controls) showed a main effect of group in the left inferior frontal gyrus (IFG, Brodmann area 45, 11 voxels) during letter fluency which was unaffected by performance in the scanner, age-related white matter scores and IFG volume; PMA patients showed lower activation than controls.
but higher than ALS patients. Activation changes during category fluency tests (left middle frontal gyrus and parahippocampal gyrus) did not survive corrections for multiple testing.

The fMRI findings in PMA described in chapter 8 are in agreement with previous findings in ALS patients during a fMRI letter fluency task. Moreover, the fMRI changes were found in brain regions that showed pathological neuronal inclusions in ALS, but also in PMA patients, in particular, prefrontal brain areas.20, 210, 211

These fMRI findings, together with the DTI results from a previous study by our group provided further evidence for functional and structural involvement of the prefrontal cortex in PMA patients, which resembles the changes found in ALS patients, albeit they were more pronounced.28

In conclusion, prior to our studies, the “motor” overlap between PMA and ALS had been derived from clinical, pathological and genetic data. The disease course in a proportion of PMA patients resembles that of ALS, upper motor neuron involvement is found, post mortem in PMA, and PMA and ALS patients share gene mutations (viz. SOD1 and C9ORF72).3, 6, 95, 212 Our studies corroborate that PMA and ALS are not separate disease entities but belong to a disease spectrum, with PMA on the one end, PLS on the other end and ALS in the middle.213 We also added another piece to the puzzle (i.e., the “non-motor piece”) and showed that there is an overlap between both ALS and PMA and frontotemporal lobar degeneration disorders (figure 1).186, 214

As such, our studies contribute to the insight that the current diagnostic criteria for ALS (El Escorial criteria) need to be amended, to include better definition of well-defined established phenotypes i.e. PMA.215

The recognition of cognitive disorders in MND and the suggested association with a poor survival (further discussed below) should lead to robust tests to enable stratification of those patients with cognitive deficits in future clinical trials.126, 215

In addition, the recognition of these subtypes may contribute to unraveling their pathogenesis, in particular of familial cases, by improved phenotype-genotype correlations.
Figure 1. Spectrum of motor neuron disease and frontotemporal dysfunction

3. ASSESSMENT OF FRONTAL LOBE DYSFUNCTION AND BEHAVIORAL CHANGES IN ALS PATIENTS.

Despite the findings of memory and language changes in PMA and ALS patients, the assessment of frontal lobe functions (e.g. executive functions) remains a fundamental component of a neuropsychological examination or bed-side screening in ALS patients. This is because fluency deficits comprise the most consistent cognitive abnormality in ALS, and because executive dysfunction (as opposed to “non-executive cognitive dysfunction”) was found to be independently associated with a poor prognosis in ALS patients in one cohort study.

In addition to the assessment of cognitive/executive deficits, which have been studied systematically since 1986, there is increasing awareness of the importance of behavioral assessment in ALS. The latter is related to case reports, genetic and pathological studies that suggest an overlap between ALS and frontotemporal dementia, of which the most prevalent subtype is characterized by behavioral changes (discussed in more detail below).

Several authors have explored the value of a single test, a screening measure or
existing questionnaires in order to examine executive deficits and behavioral changes, respectively, in ALS.\textsuperscript{41, 55} In the following section, we discuss the advantages and disadvantages of commonly used measures of executive dysfunction (n=2) and behavioral disturbances in ALS (n=2, and a new instrument).

**Executive dysfunction - Verbal Fluency Index**

The performance of MND patients on cognitive tests, in particular timed tests (and many executive tests are timed tests), could be influenced by motor and speech problems. Although most neuropsychological studies in ALS have recognized this and have excluded patients who were not able to perform certain tests due to motor weakness, moderate motor impairment may still lead to overestimation of subtle cognitive deficits on timed tests. To overcome this for the fluency test the verbal fluency index (VFI) was developed, which corrects the verbal fluency tests (both letter and category fluency) for motor or speech problems.\textsuperscript{18} The VFI reflects the average time taken to think of each word. The words generated during the test (either spoken or written) are copied by the patient, and the time it takes to copy the words allows for the calculation of a mean thinking time per word (VFI). Comparison of scores on the “uncorrected” verbal fluency test and the VFI demonstrated that correction for slower writing and, in particular slower speaking due to ALS, prevents overestimation of cognitive deficits.\textsuperscript{18} The VFI is one of the most popular cognitive tests in MND and has been around since 2000, but reliable normative data are as yet not published. Based on data from 273 healthy control subjects (matched for gender, age and education with 1009 ALS patients) we calculated Dutch norm scores for both the 1 and 3-minute version of the VFI (chapter 5). The healthy controls and patients were recruited by the *Prospectieve ALS studie Nederland (PAN)* in collaboration with the department of neurology of the University Medical Centre Utrecht. The publication of normative data enables the assessment of individual performance, which is important for the use of the VFI in clinical practice.\textsuperscript{216} As of yet, no comparable normative scores of the VFI are available in other countries. In Ireland and Italy, prospective ALS studies similar to the PAN have been initiated, which may facilitate the development of normative score for the VFI in these countries.
Executive dysfunction - Frontal Assessment Battery

Another instrument for the assessment of frontal lobe mediated cognitive changes is the Frontal Assessment Battery (FAB).\textsuperscript{125} The FAB has been validated in patients with various degrees of frontal lobe dysfunction, but with less prominent motor impairment compared to ALS, such as multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy and frontotemporal dementia. This tool has never been validated in ALS/MND patients, to the best of our knowledge.\textsuperscript{125} The FAB, however, is a widely used measure in the clinic and has been used to investigate frontal lobe dysfunction in ALS.\textsuperscript{122} In chapter 4 we aimed to investigate the reliability of the FAB in ALS patients. We used data from 93 ALS patients of whom most patients (94\%) were diagnosed more than 1 year ago (i.e. prevalent patients) and of whom 10 patients had concomitant bvFTD (this cohort is described in detail in chapter 7). Twenty patients (22\%) could not perform one or more items of the FAB due to motor and or speech impairments. For example, 19 patients could not perform the fist-edge-palm test (Luria item). The original FAB score correlated with the ALSFRS-R (a 12-item disability measure which contains 7 motor items) and the item-adjusted FAB score did not. The latter may suggest that the FAB measures motor impairment to some extent. We concluded that the FAB may be reliable in early stages of ALS with minimal motor or speech impairment, but for prospective studies or studies in populations with moderate to severe motor impairment, other instruments with less confounding factors, i.e., motor and speech impairment should be used.\textsuperscript{217-219}

Our studies in chapter 4 and 5 may encourage other research groups, with similar datasets, to investigate whether standard frontal lobe tests can be used in their populations. If not, other authors should generate disease specific normative data for important neuropsychological tests in order to improve cognitive testing in MND. These findings have the following clinical implications: the assessment of frontal lobe dysfunction in ALS should be carried out with tests that account for motor and speech impairment, and for which normative data are available.\textsuperscript{132} Screening measures that have not been validated in ALS and contain items which rely on motor function should be avoided, in particular in longitudinal studies.\textsuperscript{139}
Behavioral disturbances - Neuropsychiatric Inventory

In our study on cognitive impairment in PMA, described in chapter 3, we included a measure for behavioral disturbances, the Neuropsychiatric Inventory (NPI), which at that time was thought to be the most appropriate. It covers a wide range of behavioral and psychiatric changes known to occur in neurodegenerative disorders, it provides the possibility to grade the behavioral changes, and a proxy rating is included.\textsuperscript{166} During the study we noticed that the scoring on a substantial number of items of the NPI was influenced by motor impairment, e.g. the apathy items, or items measuring perseveration. For these items the investigator had to choose which part of the answer provided by the proxy was related to motor impairment due to ALS, and which part was not.

Although others have used the NPI in ALS patients in this manner and showed behavioral changes in half of ALS patients (without dementia), we felt that these ad hoc adaptations for motor impairment and dysarthria during the interview would be less consistent and would hinder a useful comparison between patients and between different studies.\textsuperscript{151}

Behavioral disturbances - Frontal Systems Behavioral Examination.

The Frontal Systems Behavioral examination (FrSBe) which has been validated in patients with traumatic brain injury, has similar disadvantages. In the domain “Apathy” 7 out of the 14 items rely on intact motor and speech functions. Behavioral changes, and in particular apathy, were found in 24-49\% of ALS patients using the FrSBe. \textsuperscript{148, 150, 151}

Behavioral disturbances – ALS-Frontotemporal Dementia-Questionnaire

To overcome these disadvantages, we examined the clinimetric properties of a newly designed screening instrument for behavioral changes in ALS, the ALS-Frontotemporal dementia Questionnaire (ALS-FTD-Q), which is described in chapter 7.

Based on the pooled prevalence of the solitary bvFTD symptoms derived from a systematic review on bvFTD in motor neuron disease (described below), we constructed a 25-item proxy questionnaire. The ALS-FTD-Q is to be used as a
screening instrument for behavioral disturbances and bvFTD in ALS. We carefully tried to avoid phrasings that would lead to confounding of motor or speech impairment on the scoring.\textsuperscript{127}

The ALSFTD-Q showed substantial internal consistency and retest reliability, and both construct and clinical validity (chapter 7). The point prevalence of mild (11%) and severe behavioral disturbances (8%) was lower when assessed with the ALS-FTD-Q compared with the FrSBe (for both mild and severe disturbances) and compared with the Frontal Behavioral Inventory (for severe disturbances). In a cross-sectional cohort study on 113 ALS patients, the ALS-FTD-Q confirmed the prevalence of bvFTD from the systematic review (7.8% with ALS-FTD-Q versus 8% in the systematic review).\textsuperscript{121, 127}

We concluded that a proxy-based questionnaire is a feasible screening instrument in ALS and helps to prevent overestimation of behavioral disturbances compared to existing instruments in ALS.

It should be noted that we have developed a screening instrument, and not a test that allows a definite conclusion on the presence or absence of clinically relevant behavioral changes in ALS. When clinically relevant behavioral changes are suspected following the administration of the ALS-FTD-Q, we suggest that a formal family interview should be performed to corroborate this.

4. THE BEHAVIORAL VARIANT OF FTD IN MOTOR NEURON DISEASE.

Long before authors started to study cognitive impairment in cohorts of ALS patients (1986), other authors (e.g. Braunmuhl, 1932) have highlighted the overlap between ALS and Pick’s disease, the former denominator for FTD.\textsuperscript{11, 220} The most prevalent subtype of FTD is the behavioral variant (bvFTD). BvFTD is characterized by impaired social conduct, impulsivity, apathy or perseveration, eating disturbances, loss of empathy and impaired disease insight.\textsuperscript{221} The language subtypes of FTD, i.e. progressive aphasia and semantic dementia, are less frequently associated with MND and will not be discussed here.\textsuperscript{75}

As we and others had shown cognitive abnormalities in PMA and PLS, we assumed that bvFTD may well occur in these MND subtypes.\textsuperscript{21, 209} In order to get insight in the behavioral profile of MND and to obtain a database of items for the ALS-FTD-Q, we
performed a systematic review of behavioral changes in patients with MND (PMA, ALS and PLS) with bvFTD. In the systematic review, we examined 1) the prevalence of bvFTD in MND, 2) the pooled prevalence of solitary bvFTD symptoms in MND, and 3) associations of bvFTD with site of onset of MND and with survival. These issues, except no. 2, will be discussed in separate paragraphs below. Issue no. 2, i.e. the pooled prevalence of solitary bvFTD symptoms, will not be discussed in detail here, as comparable studies in bvFTD have not been performed. Here we comment that the three symptoms with the highest prevalence in our review show overlap with symptoms in the diagnostic criteria for bvFTD, i.e., perseveration, apathy and disinhibition. The other two behavioral symptoms of the diagnostic criteria, i.e. hyperorality/dietary changes and loss of empathy showed a lower prevalence in our systematic review (e.g. 63% vs 16% for loss of empathy). We systematically reviewed the literature before the identification of the hexanucleotide repeat expansion on chromosome 9 (C9ORF72), which is associated with both ALS and FTD. For a description of the clinical characteristics of this mutation, we refer to other reports.

Prevalence of bvFTD in MND

A minority of the MND-bvFTD patients in our systematic review (total n=170) had no clinical involvement of the central motor neuron, i.e. the PMA subtype of MND (n=21, 12.4%). Three patients had PLS. When we compare the proportion of PMA patients in our systematic review (which included patients with concomitant bvFTD only), with a single centre consecutive cohort of 962 patients with either PMA or ALS (a cohort that has been published without information on the presence of bvFTD), our proportion of 12% of PMA patients is in agreement with that found in the single centre cohort, which comprised 9.5% PMA patients.

Although large prospective studies are needed to confirm this, from these two studies it can be inferred that, when a patient has both MND and bvFTD, the frequency of MND being of the PMA type, is not very different compared to that found in MND without bvFTD (i.e. around 10%).

We used data of five studies to calculate the prevalence of bvFTD in ALS (n= 570 MND patients of whom all patients had ALS). The pooled prevalence rate accounting for...
inter-study variation showed that 8% had bvFTD according to neuropsychological examinations and/or family interviews. The latter is considered the gold standard.\textsuperscript{221} Interestingly, this percentage is in agreement with the prevalence that we would later find in a subsequent study when we examined the properties of the ALS-FTD-Q in a cross-sectional cohort study on 113 ALS patients (7.8%).\textsuperscript{121, 127}

**Association between site of onset of MND and bvFTD**

We found a relatively high proportion of bulbar onset ALS (48%) in our systematic review on behavioral changes in MND, compared to 30% bulbar onset in population based ALS cohorts.\textsuperscript{129, 134} The relatively high proportion of bulbar onset in ALS-bvFTD is in line with two other cohort studies that showed bulbar onset in 39% and 60% of ALS-FTD patients, respectively.\textsuperscript{155, 225} These findings corroborate the association between bulbar onset, or prominent bulbar involvement during the disease course, and bvFTD, which had already been recognized in historical case reports.\textsuperscript{152} There is no robust explanation for this association. However, it is an interesting finding in light of one of the most widely supported views on the pathogenesis of ALS. This postulates a focal onset of ALS with combined UMN and LMN involvement at one region and subsequent spreading to contiguous anatomic regions (separately at the UMN and LMN levels, along their independent anatomy) over time through transneuronal signaling or axonal transport mechanisms.\textsuperscript{226}

The cerebrum, including frontotemporal regions, can be viewed as an anatomical region rostral to the bulbar region. The underlying neuronal degeneration would then have to spread via direct brainstem-prefrontal connections, or via the basal ganglia, which have been shown to be abnormal in ALS patients.\textsuperscript{194} The larger proportion of patients with bulbar onset in combination with bvFTD, supports this contiguous spread hypothesis.\textsuperscript{152}

One could argue, however, that other findings in this thesis (chapters 3, 6 and 8) contradict the abovementioned hypothesis of a spreading disease process. The prefrontal involvement in PMA patients, of whom a considerable proportion had no bulbar involvement, and descriptions of non-bulbar PMA with bvFTD in our systematic review. Apparently, anatomic regions (i.e. the bulbar region) may be
bypassed, at least at the level of clinical detection, by the (spreading?) disease process. An alternative explanation is that there is disease activity at the bulbar region, in PMA patients with prefrontal changes or bvFTD, but too subtle to be picked up by clinicians. This is supported by diffusion tensor imaging changes in the pons, in a group of 12 limb onset ALS patients (of whom only one patient had bulbar symptoms). The phenomenon of subclinical disease activity has been reported in PMA previously. UMN involvement (macrophage permeation in the corticospinal tracts) has been demonstrated in the spinal cord on post mortem examination of patients who did not show UMN signs on clinical examination. In conclusion, whereas the association of bulbar onset ALS with bvFTD favors the concept of a spreading disease process of MND, the subtle cognitive impairment and prefrontal involvement of PMA is a little more difficult to reconcile with this hypothesis. Together, these findings call for large prospective cohort studies addressing clinicopathological correlations, including, neuropsychological, imaging and post-mortem examination of brains (and spinal cords) in patients across the whole spectrum of MND-bvFTD.

**Association between bvFTD and survival of MND patients**

Not surprisingly, MND has a negative effect on survival when it develops in bvFTD patients; it reduces survival by at least 50%. Whether the occurrence of bvFTD has a negative influence on survival in MND has not been elucidated yet. Our systematic review on behavioral changes in MND showed a median survival of 29 months in MND patients who developed FTD, which is comparable to survival in prospective population based cohort studies of ALS patients (n=30 months). However, the relatively low number of patients (n=24) and missing data in 33% in our systematic review made this figure less reliable. In a prospective study on 81 ALS patients, a negative effect of FTD (n=28) on survival in a univariate analysis was not statistically significant in a multivariate analysis including bulbar onset and age. Another prospective study (n=139) showed that FTD (n=20, 14%) did show a correlation with survival in a multivariate analysis (median survival time 11 months shorter in ALS-bvFTD patients).
The question then arises whether cognitive and behavioral changes, which do not (yet) fulfill the criteria for FTD, are associated with survival in ALS.

A relation between cognitive dysfunction (without FTD) with survival has been found in a prospective cohort study (n=50), but could not be confirmed in another (case control and retrospective cohort) study (n=40).\textsuperscript{54, 228}

Behavioral changes were found to have a negative effect on survival and the use of NIV in a group of 128 patients, of whom 32% had behavioral dysfunction. However the questionnaire used (FrSBe) in the latter study has not been validated in ALS and tends to overestimate behavioral changes.\textsuperscript{127, 172} Another study showed a negative effect of cognitive and behavioral changes on the use of NIV.\textsuperscript{15} However, in this study bulbar patients (for whom, due to progressive disease NIV is increasingly less applicable due to physical constraints) were overrepresented in the cognitive and behavioral group. These findings and methodological considerations hamper firm conclusions on the association between cognitive and behavioral changes, which do not (yet) fulfill the criteria for FTD, and survival in ALS.

We recently analysed survival data of ALS patients (n=110) from two cohorts described in this thesis. In these cohorts patients have been examined with a disease specific behavioral scale and cognitive measures that take dysarthria and motor impairment into account (chapters 3 and 7). These data show a reduced survival in ALS patients with cognitive impairment (4.3 years) or behavioral changes (3.8 years), or both (3.4 years), compared to survival in ALS patients without cognitive or behavioral changes (5.6 years). An analysis of initiation of NIV (n=43, 39%) revealed that the association of cognitive and behavioral changes with poor survival, is related to reduced efficacy of NIV (manuscript in preparation).

**Methodological considerations**

Strengths of our studies described in chapters 3, 7-10 are the adaptations to correct for speech and motor impairment, careful matching of PMA and ALS patients with regard to age, disease duration, disease severity, education and premorbid intelligence. Another strength is the combination of neuropsychological testing and imaging techniques.

A weakness is the relatively small sample size in particular of PMA patients, which
just failed to meet the required power.

We aimed to minimize the effects of respiratory failure on measures of cognitive dysfunction by exclusion of patients with a predicted value of the vital capacity below 70%. Respiratory failure due to neuromuscular diseases often starts in the supine position, due to weakness of the diaphragm. An association of nocturnal hypoventilation and cognitive deficits in ALS has been suggested by other authors who showed mild improvement on verbal memory and visual memory tests, but not on a measure of verbal fluency, following non-invasive ventilation. Of note, out of the tests used by these authors, a parallel version was available for the verbal memory (list learning) test only. Consequently, practice effects can not be ruled out for the visual memory tests in this study. The association between nocturnal hypoventilation and cognitive and behavioral changes in ALS requires further investigation.

We tried to further minimize effects of nocturnal hypoventilation by the timing of the neuropsychological evaluations, which never took place before 11.00 hours a.m.. However, our cut-off below 70% of the predicted vital capacity (VC) may not have excluded all patients with incipient respiratory failure, as VC is not the most sensitive measure for respiratory failure in all MND patients.

**Future perspectives: implications for genetic and pharmaceutical studies**

Genetic and pathological studies have provided significant insights in the pathogenesis of MND and FTD during the past few years (i.e. TDP-43 inclusions, C9ORF72 mutation). The description of a new phenotype within the MND-FTD spectrum in this thesis (PMA in combination with cognitive deficits) hopefully leads to the discovery of new causative genes, or more likely, susceptibility genes and environmental influences, as only 5-10% of MND patients are familial cases.

In addition, the search for causative genes in C9-negative patients (~ 70% of ALS-FTD patients) and our understanding of the phenotypic variability within families with the C9ORF72 and SOD1 mutations, will be facilitated by accurate descriptions of phenotypes within the MND-FTD spectrum, in particular with regard to non-motor symptoms.
Accordingly, the question whether a patient has PMA or ALS becomes equally important as the question whether an MND patient has concomitant cognitive and/or behavioral dysfunction. The latter should be assessed with valid tools that cover the complete profile of cognitive and behavioral changes and do not overestimate these non-motor symptoms.

Our studies contribute to the insight that the current diagnostic criteria for ALS (El Escorial criteria) need to be amended, to include better definition of well-defined established phenotypes i.e. PMA. The recognition of cognitive disorders in MND and their association with a poor survival should lead to robust tests to enable stratification of those patients with cognitive deficits in future clinical trials.

**Initiatives and suggestions for future research**

We have initiated the following research projects.

1. Longitudinal screening of cognitive and behavioral impairment in PMA, ALS and PLS whose follow-up takes place at the Department of Rehabilitation Medicine in het AMC (n=100). We included the sniff nasal inspiratory pressure (SNIP), in addition to the vital capacity, as a measure of lung function. The SNIP has been shown to be superior to the VC in advanced disease. Expected findings: First, we expect to find that cognitive and behavioral changes deteriorate over time. Second, we expect to find that bulbar involvement more often develops in patients with cognitive or behavioral changes, compared to those without. Third, we expect that cognitive and behavioral changes occur more often in patients with respiratory impairment (see below – suggestions for future research). Collaboration: with the department of Rehabilitation Medicine of the AMC (H. Grupstra, MD) and the Department of Psychology of the UvA (prof Schmand).

2. MRI studies (e.g. DTI, resting state fMRI) and electrophysiological modalities (magneto-encephalography) along with detailed cognitive and behavioral testing in 180 ALS patients in the earliest phases of the disease and a robust follow-up with neuropsychological investigations. Expected findings: functional networks based on MRI and electrophysiology
parameters are abnormal before cognitive or behavioral changes can be detected. These findings will further improve phenotyping and the insight in the temporal involvement of the central nervous system in MND.

Collaboration: with the department of Neuropsychology UvA (Prof Schmand) and with the Alzheimer Centre of the Free University Medical Centre, Amsterdam (Profs Scheltens and Stam and Dr Pijnenburg).

3. The patients of the cohort of project 2 will be included in a prospective follow-up study on the use of NIV, feeding tube placement and survival to further examine the association between non-motor symptoms and these life prolonging therapies. The C9ORF72 status and bulbar involvement will be assessed, being established modifiers of survival.

Expected findings: Cognitive and behavioral changes negatively influence survival, in part due to reduced compliance with non-invasive ventilation and feeding tube placement, irrespective of bulbar involvement and C9ORF72 status.

Collaboration: with the Centres for Home Mechanical Ventilation in the Netherlands and the departments of Neurology of the University Medical Centre, Utrecht (Profs van den Berg and Veldink) and multiple departments of Rehabilitation Medicine in the Netherlands.

4. International/cross-cultural validation and examination of the clinical validity of the ALS-FTD-Q. The Dutch ALS-FTD-Q normative scores may not be applicable to people from other countries due to transcultural differences in behavior.

Expected findings: Normative data for the ALS-FTD-Q from Japan and Italy, descriptive data on the ALS-FTD-Q from France, USA, Australia.

Collaboration: departments of Neurology of the Erasmus Medical Centre Rotterdam (Prof van Swieten), L’universita di Torino, Italy (prof. Chio), Tottori University Yonago, Japan (prof Nakashima and Dr Watanabe), Mason Medical Centre, Seattle, USA (Dr Winnett, Virginia), Groupe Hospitalier Pitié-Salpêtrière, Paris, France (Dr Lacomblez) and the School of Medical Sciences University of New South Wales, Australia (Dr Mioshi).
Suggestions for future research

1. Considering the rarity of PMA, we suggest that an international collaborative study group investigates/replicates our findings of cognitive impairment in PMA with a comprehensive neuropsychological investigation and examination of behavioral changes with a family interview and the ALS-FTD-Q.

2. We suggest an investigation on the association between cognitive and behavioral changes and respiratory impairment in MND, and the effect of NIV on these non-motor symptoms. Neuropsychological tests should be used that have parallel versions (or a negligible practice effect) and which cover the executive, memory and language domains.

3. We suggest a large clinicopathological correlation study in patients across the MND-FTD spectrum to assess: a) to what extent pathological changes in the prefrontal and temporal lobes correspond to nonmotor symptoms and morphological substrate on MRI, b) to study subclinical disease activity in the brain and spinal cord in light of the hypothesis on focal onset of the disease and contiguous spreading.
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SUMMARY

In this thesis we investigated non-motor symptoms and their imaging correlates in motor neuron disease (MND). Cognitive impairment and behavioral disturbances are increasingly recognized in MND and may have impact on therapeutic interventions, survival and relationships with caregivers.\textsuperscript{130} There is a clinical, genetic and pathological overlap between ALS and FTD (chapter 1).\textsuperscript{229, 230}

Accurate phenotyping is essential for correct interpretation of new mutations, susceptibility genes and pathological mechanisms, hopefully leading to a cure for this devastating disorder.\textsuperscript{16}

The focus in this thesis was on cognitive impairment in progressive muscular atrophy (PMA) and on behavioral disturbances in amyotrophic lateral sclerosis (ALS). Another objective was to investigate whether magnetic resonance imaging (MRI) could provide useful imaging correlates of cognitive dysfunction in both disorders.

Part I: Cognitive impairment in MND presence, profile and assessment.

Chapter 2 is a meta-analysis of neuropsychological studies in ALS (16 studies encompassing 554 ALS patients without dementia), which showed that pooling of neuropsychological data remarkably increased our insight in the cognitive profile of ALS. The cognitive profile entails more than just executive (or frontal) impairment and includes deficits of verbal and visual memory, working memory and language (object naming). This finding has now been corroborated by others, and this insight has led to the development of cognitive screens that contain more than a fluency task.\textsuperscript{132}

Based on the clinical and pathological overlap between PMA and ALS and restricted diffusion imaging findings beyond the motor cortex in PMA, we hypothesized that a proportion of PMA patients would have cognitive deficits, comparable to ALS.\textsuperscript{28}

In chapter 3 we report a cross-sectional neuropsychological study in a cohort of 23 PMA and 30 ALS patients and showed that 17\% of PMA patients have cognitive impairments (letter-number sequencing, immediate and delayed story recall), in part similar to those found in ALS (of whom 27\% showed impairments).\textsuperscript{140} These proportions are based on population norms and we used cutoffs based on consensus
criteria for the frontotemporal syndrome of MND. On a group level PMA patients showed subtle changes of attention/working memory, fluency and the MMSE. Strengths of this study are the use of adaptations to correct for speech and motor impairment and careful matching between PMA and ALS patients. A drawback is the relatively small sample size, which is related to the rarity of the disorder. Future study should therefore be carried out to replicate (or refute) our findings.

In chapters 4 and 5 we describe two small studies on valid and reliable assessment of frontal lobe functions in MND. The Frontal Assessment Battery (FAB) is a widely used measure in the clinic and has been used by other researchers to detect frontal lobe dysfunction in ALS.\textsuperscript{123, 218, 219} In chapter 4 we used data from the cohort described in chapter 7 and showed that the FAB is less reliable in ALS patients, in particular when the disease duration is more than one year.\textsuperscript{217} Due to motor dependent tasks of the FAB 22\% of a cohort of 94 ALS and ALS-bvFTD patients could not perform one or more items of the FAB. The original FAB score correlated with a motor score (ALSFRS-R), while an item-adjusted FAB score did not. We concluded that the FAB may be reliable in early stages of ALS with minimal impairment, but for prospective studies or studies in populations with moderate to severe motor impairment, other instruments with no or minimal bias due to motor and speech impairment should be used.

In chapter 5 we calculated norm scores for the verbal fluency index (VFI) based on data from 273 healthy control subjects (matched for 1009 ALS patients) recruited through the \textit{Prospectieve ALS studie Nederland (PAN)} initiated by the University Medical Centre, Utrecht.\textsuperscript{134} Although the VFI is one of the most popular cognitive tests in MND and has been available since 2000, reliable norm scores have not been published in any language.\textsuperscript{18} We present norm scores for both the 1 and 3-minute version of the Dutch VFI to facilitate reliable cognitive testing in MND in the Netherlands. The studies in chapters 4 and 5 might encourage other international research groups, who have collected similar datasets, to investigate whether standard frontal lobe tests can be used in their populations and generate disease specific norm-scores, in order to improve the cognitive testing in MND.
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Part II: Behavioral disturbances in MND: presence, profile and assessment.

Chapter 6 is a systematic review on 1) the prevalence of the behavioral variant of FTD (bvFTD) in MND, 2) pooled prevalences of solitary bvFTD symptoms in MND and 3) associations of bvFTD with site of onset of MND and survival. In nine studies comprising 705 MND patients 8% had bvFTD according to neuropsychological examinations and/or family interviews (gold standard). Mild to moderate behavioral changes (according to diverging definitions, and examined with instruments which have not been validated for MND patients) were shown in 17-88% of MND patients. Pooled prevalence rates from individual cases showed that perseveration was the most frequent behavioral disturbance (40%) followed by apathy and disinhibition (29% and 26%). Memory disturbances, ranging from mild to severe, showed a pooled prevalence of 43%. Of note, memory disturbance was the first bvFTD symptom in 20% of the patients. The memory disturbances in our systematic review were often noted by the examiner/author based on clinical observations (no neuropsychological examination had been performed).

In this systematic review, bulbar onset was more frequent in the ALS-bvFTD patients compared to population based cohorts, which favors an association between site of onset and non-motor features in ALS-bvFTD patients.

Behavioral questionnaires that have been used in previous studies in MND patients do not take motor symptoms and dysarthria into account. Based on the pooled prevalence of the solitary bvFTD symptoms from chapter 6, we therefore constructed a 25-item proxy based questionnaire (ALSFTD-Q) to be used as a screening instrument for behavioral disturbances and bvFTD in ALS.

In chapter 7, we present the ALSFTD-Q, which showed substantial internal consistency and retest reliability, and both construct and clinical validity. Importantly, the point prevalence of mild and severe behavioral disturbances was lower when assessed with the ALS-FTD-Q compared to the Frontal Systems Behavior Scale (FrSBe, for both mild and severe disturbances) and compared to the Frontal Behavioral Inventory (FBI, for severe disturbances). In chapter 7, we further showed in a cross-sectional cohort study in 113 ALS patients, that the ALS-FTD-Q yielded a similar prevalence of bvFTD (7.8%) as compared to that found in the systematic review (8%). Furthermore we showed that moderate behavioral disturbances occur
in a minority of ALS patients (11%). We concluded that a proxy-based questionnaire is a feasible instrument in ALS and helps to avoid overestimation of behavioral disturbances compared to existing instruments in ALS.

**Part III: Functional and structural imaging correlates of cognitive impairment in MND**

We investigated whether functional MRI and voxel based morphometry (VBM) are feasible and sensitive measures to detect cerebral changes related to cognitive dysfunction in MND.

In chapter 8 we examined brain activation patterns during verbal fluency performance in a cohort of 39 patients with PMA and ALS of which a proportion has been described in chapter 3. We hypothesized that PMA patients show non-motor cerebral involvement in frontal and temporal brain regions previously associated with fluency performance in ALS. Between group analysis showed a main effect of group in the left inferior frontal gyrus (IFG, Brodmann area 45, 11 voxels) during letter fluency which was unaffected by performance, age related white matter scores and IFG volume: PMA patients showed lower activation than controls but higher than that of ALS patients. These fMRI findings provide evidence for involvement of the prefrontal cortex in PMA, similarly, but to a lesser extent compared to ALS patients. The imaging findings in PMA are in agreement with the localization of pathological inclusions in ALS and PMA.

Following our meta-analysis (chapter 2) the issue remained unsolved whether memory impairments in MND patients reflect frontal lobe involvement and/or medial temporal lobe dysfunction. Our meta-analysis favored frontal lobe mediated memory dysfunction, although additional temporal lobe involvement could not be ruled out. Yet, another finding in this thesis (chapter 9) supports hippocampal involvement in ALS.

**Chapter 9** is a voxel based morphometry (structural MRI) study in ALS patients and controls, which showed that a moderate correlation exists between the volume of the hippocampus and the score on (both immediate and delayed versions of) a prose recall test (verbal memory). This correlation was absent in a control group with similar age, education level, anxiety and depression scores and white matter lesion
scores. Although “just” a correlation, the hippocampus involvement is in line with a previous imaging study and with post mortem findings (pathological inclusions), which are frequently encountered in the dentate gyrus of the hippocampus in ALS-FTD patients and to a lesser extent in ALS patients without FTD.\textsuperscript{38, 195} Opposed to the majority of structural MRI studies in ALS which did not find hippocampal changes, a few MRI studies did, but could not relate this to cognitive dysfunction (i.e. memory impairment) as neuropsychological assessment had not been performed.\textsuperscript{232} We concluded from chapters 8 and 9 that fMRI and VBM provide useful insights in the brain regions beyond the motor cortex that are associated with cognitive dysfunction in patients with PMA and ALS.
REFERENCES


References


ABBREVIATIONS

ALS = Amyotrophic Lateral Sclerosis
ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Questionnaire
ALSbi = ALS with behavioral changes
ALSci = ALS with mild cognitive impairment
ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
AMC = Academic Medical Centre
ANCOVA = Analysis of covariance
ANOVA = Analysis of variance
ARWMC = Age Related White Matter Changes
BA = Brodmann area
BNT = Boston Naming Test
BOLD = Blood Oxygenation-Level Dependent
bvFTD = behavioral variant of Frontotemporal Dementia
C9ORF72 = Chromosome 9 open reading frame 72
CBI = Cambridge Behavioral Inventory
CI = Confidence Interval
CNS = Central Nervous System
COWAT = Controlled Oral Word Association Test
CSF = Cerebrospinal fluid
DART = National Adult Reading Test, Dutch version
DARTEL = Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra
DAT = Differential Aptitude Test
DSM = Diagnostic and Statistical Manual of Mental Disorders
EPI = Echo Planar Imaging
FAB = Frontal Assessment Battery
FBI = Frontal Behavior Inventory
fMRI = Functional Magnetic Resonance Imaging
FrSBe = Frontal Systems Behavior scale
FTD = Frontotemporal Dementia
FWE = Family Wise Error
GLM = General Linear Model
Chapter 11

GM = Grey Matter
HADS = Hospital Anxiety and Depression Scale
HC = Healthy Controls
IBM = Inclusion Body Myositis
IFG = Inferior Frontal Gyrus
ISCED = International Standard Classification of Education
JOLO = Judgment Of Line Orientation;
LGMD 2A = Limb Girdle Dystrophy 2A
LMN = Lower Motor Neuron
MMSE = Mini Mental State Examination
MND = Motor Neuron Disease
MNI = Montreal Neurological Institute
MWCST = Modified Wisconsin Card Sorting Test;
NIPPV = Non Invasive Positive Pressure Ventilation
NIV = Non Invasive Ventilation
OPMD = Oculopharyngeal Muscular Dystrophy
OSAS = Obstructive Sleep Apnoea Syndrome
PAN = Population-based epidemiological ALS-study in the Netherlands
pCO2 = Partial Pressure of Carbon Dioxide
PET = Positron Emission Tomography
PFC = Prefrontal cortex
PLS = Primary Lateral Sclerosis
PMA = Progressive Muscular Atrophy
predVC = percentage of predicted value of VC
RAVLT = Rey Auditory Verbal Learning Test,
RBMT = Rivermead Behavioral Memory Test;
RD = Respiratory dysfunction
ROI = Regions of interest
SD = Standard deviation
SNIP = Sniff Nasal Inspiratory Pressure
SOD1 = Superoxide dismutase 1
SPM = Statistical Parametric Mapping software

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Abbreviations

TARDBP = Trans Active Response DNA Binding Protein
UMN = Upper Motor Neuron
VBM = Voxel based morphometry
VC = Vital Capacity
VFI = Verbal Fluency Index
VSOP = Visual Space and Object Perception
WFU = Wake Forest University
WM = White Matter
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**NEDERLANDSE SAMENVATTING**

Progressieve spinale spier atrofie (PSMA) en amyotrofische lateraal sclerose (ALS) zijn zgn. motorische voorhoornaandoeningen. Afhankelijk van de klinische betrokkenheid van het perifeer motorisch neuron en het centraal motorisch neuron wordt de diagnose PSMA (perifeer motorisch neuron) of ALS (perifeer en centraal motorisch neuron) gesteld.\(^1\) Negentig procent van patiënten met een motorische voorhoornaandoening heeft een sporadische vorm en 10% een familiaire vorm, vaak met een autosomaal dominant overervingspatroon. Het beloop van de ziekte is progressief en de meeste patiënten overlijden aan de gevolgen van respiratoire insufficiëntie.

Het enige medicijn met een bewezen effect is Riluzol, dat een gering effect heeft op de overleving (3-6 maanden).\(^2\)

De mediane overleving van ALS is 3 jaar en van PSMA waarschijnlijk tussen 5 en 8 jaar, alhoewel een deel van de PSMA patiënten een ALS-achtig beloop heeft, wat wordt voorspeld door een vroege daling van de vitale capaciteit (een longfunctiemaat).\(^3\) Er zijn ook op genetische en pathologische gronden overeenkomsten tussen PSMA en ALS.

Alhoewel van oudsher bekend als puur motorische aandoeningen, is het, in ieder geval voor ALS duidelijk geworden dat in een deel van de patiënten (30%) cognitieve stoornissen voorkomen en frontotemporale dementie (5-10%).

De overeenkomsten tussen PSMA en ALS, en het voorkomen van cognitieve stoornissen en frontotemporale dementie in ALS hebben geleid tot het onderwerp van dit proefschrift. In dit proefschrift onderzochten we niet motorische symptomen en hieraan gerelateerde hersenafwijkingen in patiënten met PSMA en ALS.

**Cognitieve stoornissen en gedragsveranderingen**

Cognitieve stoornissen en gedragsveranderingen bij motorische voorhoornaandoeningen worden in toenemende mate herkend en zijn, vooral indien ernstig, relevant voor patiënten, hun familie en behandelend artsen omdat ze van invloed kunnen zijn op (het nemen van beslissingen over) therapeutische interventies, de overleving en de relaties met partners of familieleden.
Het correct vaststellen van deze niet-motorische symptomen is een belangrijk onderdeel van precieze fenotypering, wat op zijn beurt essentieel is voor de juiste interpretatie van pathofysiologische mechanismen en genetische variaties die de aandoening veroorzaken of het risico erop vergroten. Deze inzichten kunnen in de toekomst leiden tot een remmende of genezende behandeling voor deze ernstige aandoeningen.

Deel I: Cognitieve stoornissen in motorische voorhoornaandoeningen: prevalentie, profiel en beoordeling.

In hoofdstuk 2 beschrijven we een meta-analysis van neuropsychologische studies bij ALS-patiënten (16 studies met 554 ALS patiënten zonder dementie), waarin we aantoonden dat het aggregeren van neuropsychologische data het inzicht in het cognitieve profiel van ALS vergroot. Het cognitieve profiel van ALS bestaat uit meer dan alleen executieve stoornissen en omvat ook geheugenproblemen en taalstoornissen. Inmiddels hebben andere onderzoekers deze bevindingen gerepliceerd. Dit heeft gevolgen voor o.a. het ontwerp van cognitieve screeningsinstrumenten, te gebruiken in de medische praktijk.

In hoofdstuk 3 beschrijven we een cross-sectionele neuropsychologische studie in een cohort van 23 PSMA en 30 ALS patiënten en 27 gezonde controles, waarin 17% van de PSMA patiënten cognitieve stoornissen had (letter-nummer sequencing, onmiddellijke en uitgestelde herinnering van een verhaaltje), deels vergelijkbaar met stoornissen bij ALS-patiënten (van wie 27% cognitieve stoornissen hadden). Deze uitkomsten zijn gebaseerd op normscores die gebaseerd zijn op de algemene populatie (gecorrigeerd voor leeftijd, geslacht en opleiding waar mogelijk en noodzakelijk) in combinatie met afkappunten uit de consensuscriteria voor het vaststellen van het frontotemporale syndroom bij ALS. Ook op groepsniveau, vergeleken met een goed vergelijkbare controlegroep, werden subtiele cognitieve stoornissen gevonden bij PSMA-patiënten. Deze bevinding wijst erop dat bij een minderheid van patiënten met een motorische voorhoornaandoening zonder aanwijzingen voor betrokkenheid van het centraal motorisch neuron, er aanwijzingen zijn voor hersendysfunctie, voornamelijk in de voorste hersengebieden.

In hoofdstukken 4 en 5 beschrijven we de resultaten van twee kleine studies over
het vaststellen van stoornissen van de frontaalkwab in motorische voorhoornaandoeningen.

De *Frontal Assessment Battery* (FAB) is een veelgebruikt screeningsinstrument, dat door andere auteurs is gebruikt voor het vaststellen van frontaalkwabdysfunctie bij ALS.

In *hoofdstuk 4* hebben we data gebruikt uit het cohort beschreven in hoofdstuk 7. We hebben aangetoond dat door motorische problemen de FAB minder bruikbaar is bij ALS patiënten, vooral als de ziekteduur langer is dan 1 jaar. 22% van de ALS patiënten kon een of meer items van de FAB (bijvoorbeeld de palm-rand-vuist Luria test) niet uitvoeren.

In *hoofdstuk 5* hebben we normscores berekend voor de *verbal fluency index* (VFI, een letter-fluency test die is aangepast voor vertraagd spreken of schrijven bij ALS). We gebruikten VFI data van 273 gezonde controles (gematched voor leeftijd, geslacht en opleiding met 1009 ALS patiënten) uit de Prospectieve ALS studie Nederland (PAN). Alhoewel de VFI sinds 2000 internationaal gebruikt wordt waren normscores nog niet beschikbaar (in geen enkele taal). We presenteren Nederlandse norm scores voor zowel de 1 en 3-minuut versie van de VFI waarmee het interpreteren van deze belangrijke cognitieve test voor ALS patiënten in Nederland wordt vergemakkelijkt.

**Deel II: Gedragsveranderingen bij motorische voorhoornaandoeningen: prevalentie, profiel en beoordeling.**

*Hoofdstuk 6* is een systematische review over het 1) voorkomen van de gedragsvariant van FTD (bvFTD) bij motorische voorhoornaandoeningen, 2) de gepoolde prevalentie van verschillende bvFTD symptomen bij motorische voorhoornaandoeningen en 3) associaties tussen bvFTD met de plaats van het ontstaan van klachten (keelspieren of ledematen) bij de motorische voorhoornaandoeningen. Acht procent van 705 patiënten met ALS had bvFTD gebaseerd op 5 studies waarin neuropsychologische studies en familie-interviews werden gebruikt (gouden standaard).

Lichte tot matig ernstige gedragsveranderingen waren aanwezig in 17-88% van patiënten met motorische voorhoornaandoeningen (gemeten met uiteenlopende, en veelal niet gevalideerde, instrumenten). Persevereren kwam vaak voor (40%). Het
Nederlandse samenvatting

Profiel van gedragsveranderingen bij patiënten met motorische voorhoornaandoeningen in combinatie met bvFTD verschilt niet opvallend met het profiel bij bvFTD patiënten zonder motorische voorhoornaandoening, voor zover vergelijkbaar.

De meeste vragenlijsten om gedragsveranderingen op te sporen zijn ontwikkeld voor patiënten met dementie of neuropsychiatrische ziektebeelden. In deze lijsten wordt geen rekening gehouden met het gebruik van een rolstoel of minder goed kunnen spreken, zoals dat bij ALS voorkomt. Gebaseerd op de prevalentie van gedragsveranderingen uit hoofdstuk 6 hebben we een 25-item vragenlijst gemaakt die door een naaste wordt ingevuld om gedragsveranderingen in het kader van bvFTD betrouwbaar te meten.

In hoofdstuk 7 presenteren we de interne consistentie, hertestbetrouwbaarheid, construct-validiteit en klinische validiteit van de ALSFTD-Q, die alle goed blijken. De punt-prevalentie van lichte en ernstige gedragsveranderingen zoals gemeten met de ALSFTD-Q waren lager vergeleken met prevalenties verkregen met de Frontal Systems Behavior Scale en de Frontal Behavioral Inventory. In deze studie en gemeten met de ALSFTD-Q had 8% van de ALS-patiënten bvFTD en 11% lichte gedragsveranderingen. We concludeerden dat de ALSFTD-Q een bruikbaar instrument is, dat een overschatting van de gedragsveranderingen bij ALS kan helpen te voorkomen. De 8% zoals gemeten met de ALS-FTD-Q is hetzelfde percentage als de prevalentie van bvFTD bij ALS uit de systematische review.

Deel III: Functionele en structurele beeldvorming: correlaten van cognitieve stoornissen buiten de motorische cortex bij PSMA en ALS.

In hoofdstuk 8 onderzochten we patronen van hersenactivatie tijdens het uitvoeren van een letter-fluency taak bij patiënten met PSMA en ALS. Er was een groepseffect in de linker inferieure frontale gyrus (IFG): PSMA patiënten vertoonden in dit gebied minder activatie dan controlepersonen, en meer activatie dan ALS-patiënten. Dit groepsverschil was onafhankelijk van de prestatie op de test, en van wittestofafwijkingen en het volume van de IFG. Deze fMRI bevindingen wijzen op betrokkenheid van de prefrontale cortex bij PSMA (en bij ALS) en zijn grotendeels in overeenstemming met fMRI bevindingen uit een eerdere studie bij ALS patiënten.
tijdens een fluency taak. De resultaten uit deze studie onderschrijven de resultaten uit hoofdstuk 3 waarin we suggereerden dat frontale hersenafwijkingen voorkomen bij PSMA.

_Hoofdstuk 9_ is een zgn. *voxel based morphometry* studie bij ALS patiënten en gezonde controles waarin we aantoonden dat er een correlatie is ($r=0.5$) tussen het volume van de hippocampus en de score op onmiddellijk en uitgesteld verbaal geheugen bij ALS patiënten. Deze correlatie was afwezig in een controlegroep met een vergelijkbare leeftijd, opleidingsduur, ernst van symptomen van angst of depressie, en mate van witte stofafwijkingen. Er werd voor geen van de 3 geheugentaken een groepseffect (ALS vs. controlepersonen) gevonden. Dit heeft mogelijk te maken met een te klein aantal patiënten ($n=26$) in onze studie om dit verschil aan te kunnen tonen. De betrokkenheid van de hippocampus, ondanks het feit dat het ‘slechts’ een correlatie is, is in overeenstemming met twee recent gepubliceerde onderzoeken waarvan er 1 een groepseffect op een verbale geheugentaak vond (in een twee keer zo groot cohort).

De bevindingen houden waarschijnlijk ook verband met post-mortem bevindingen van pathologische insluitsels in zenuwcellen van de hippocampus, zoals gevonden bij patiënten met ALS-FTD en in mindere mate bij ALS patiënten zonder dementie. De hoofdstukken 8 en 9 leidden tot de conclusie dat fMRI, en VBM in combinatie met cognitieve testen, bruikbare inzichten geven in de betrokken hersengebieden buiten de motorische cortex bij patiënten met PSMA en ALS.
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ABOUT THE AUTHOR

Joost Raaphorst was born on September 23rd, 1977 in Eefde, the Netherlands. After pre-university school (Baudartius College, Zutphen) he studied Medicine at the Free University, Amsterdam (1996-2003). In 1999 he did a scientific internship on coagulation and sepsis at the Department of Intensive Care, VU University Medical Center, Amsterdam (prof. dr. A.B.J. Groeneveld) and received a nomination for the Organon young research talent prize.


In 2008 he started working as a PhD candidate on cognition and behavior in motor neuron disease at the department of Neurology of the AMC, supervised by prof. dr. M. de Visser and prof. dr. B. Schmand, which resulted in this thesis. He received a 1st and 3rd prize for presentations at the International Research Workshops on FTD and ALS in London, Ontario, Canada.

Joost worked as a neuromuscular fellow on behalf of the Prinses Beatrix Spierfonds at the department of Neurology of the AMC, Amsterdam.

He received a grant from the Dutch ALS foundation to continue investigations on the frontotemporal syndrome of ALS in collaboration with the Alzheimer centre of the VUmc Medical Centre, Amsterdam.

In 2014 he joined the staff of the Neurology department at the Radboud University Medical Centre in Nijmegen (prof. dr. M.A.A.P. Willemsen). At the Radboudumc he will continue his research on brain dysfunction in neuromuscular disorders.

Joost lives together with Laura van de Pol, Kyra, Amber and Luit.