Cognition and behaviour in motor neurone disease
Patricia Lillo and John R. Hodges

Introduction
Motor neurone disease (MND) has long been considered a pure motor syndrome which spares aspects of cognition and behaviour, although in recent years it has been suggested that up to 50% of patients with motor neurone disease may develop frontal dysfunction which, in some cases, is severe enough to reach criteria for frontotemporal dementia. We review the cognitive and behavioural changes in motor neurone disease emphasizing the recent advances.

Recent findings
A major advance in pathology has been the recent discovery of TDP-43 and FUS inclusions as the key components in cases of motor neurone disease, frontotemporal dementia–motor neurone disease and some cases with pure frontotemporal dementia. In addition, mutations in TARDBP and FUS genes have been reported in recent years. Longitudinal studies showed that progression of cognitive impairment over the course of motor neurone disease appears to be mild and occurs only in a proportion of motor neurone disease patients. The presence of cognitive impairment seems to be related to a faster disease and a shorter survival.

Pathological overlap with frontotemporal dementia
A major advance has been the finding that TDP-43 is the principal component in frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U), currently classified as FTLD-TDP. The condition is found in those patients who present with FTD but develop frank MND (FTD-MND), approximately a half of those with uncomplicated FTD and the majority of patients with both sporadic and familial MND. TDP-43 is a nuclear protein of 43 kDa, which participates in various critical biological processes by binding DNA and RNA. Normally, it is localized in nuclei of neurons and glial cells. Pathologically, normal nuclear TDP-43 staining is absent, and cytoplasmic and nuclear TDP-43 inclusions are detectable [4]. Five patterns of TDP-43 aggregation are recognized. Pure MND, type 5, is characterized by cytoplasmic inclusions (skein-like or dense granular), affecting principally the motor cortex, the spinal cord, basal ganglia and thalamus. FTD-MND is usually associated with type 2, which is characterized by neuronal cytoplasmic inclusions (granulated), affecting principally the motor cortex, the spinal cord, basal ganglia and thalamus. FTLD-MND is usually associated with type 2, which is characterized by neuronal cytoplasmic inclusions in superficial and deep cortical layers involving the temporal and frontal cortices, dentate gyrus, amygdala and subcortical white matter [5]. As expected, the degree of neuronal loss is more in FTD-MND than in pure MND and affects primarily the anterior cingulate gyrus, substantia nigra and amygdala [6,7].

Keywords
amyotrophic lateral sclerosis, behavioural changes, cognitive impairment, frontotemporal dementia, motor neurone disease


Purpose of review
Motor neurone disease has traditionally been considered a pure motor syndrome which spares aspects of cognition and behaviour, although in recent years it has been suggested that up to 50% of patients with motor neurone disease may develop frontal dysfunction which, in some cases, is severe enough to reach criteria for frontotemporal dementia. We review the cognitive and behavioural changes in motor neurone disease emphasizing the recent advances.

Recent findings
A major advance in pathology has been the recent discovery of TDP-43 and FUS inclusions as the key components in cases of motor neurone disease, frontotemporal dementia–motor neurone disease and some cases with pure frontotemporal dementia. In addition, mutations in TARDBP and FUS genes have been reported in recent years. Longitudinal studies showed that progression of cognitive impairment over the course of motor neurone disease appears to be mild and occurs only in a proportion of motor neurone disease patients. The presence of cognitive impairment seems to be related to a faster disease and a shorter survival.

Summary
Motor neurone disease is a multi-system disorder which overlaps with frontotemporal dementia. Behavioural and cognitive changes appear to occur in a subset of patients with motor neurone disease, but the cause of this variability remains unclear.

Keywords
amyotrophic lateral sclerosis, behavioural changes, cognitive impairment, frontotemporal dementia, motor neurone disease


© 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
1350-7540

1350-7540 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

DOI:10.1097/WCO.0b013e3283400b41

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
In addition, another protein called FUS/TLS (fused in sarcoma, translated into liposarcoma), a 526-amino-acid DNA/RNA binding protein, has been very recently identified in pathological cases of FTLD-U without TDP-43 inclusions [8]. The disorder is characterized by neuronal cytoplasmic and intra-nuclear inclusions immunoreactive for FUS. This pattern has been also been found in cases with pure MND, MND-FTD and cases of behavioural variant FTD [9,10].

Genetics

There has been a recent explosion of knowledge in MND and FTD genetics, although the exact relationship between the identified genes and pathology remains unclear. A prominent family history is present in around 5–10% of the patients with MND. It is interesting to note that the Cu–Zn superoxide dismutase 1 (SOD1) mutation, which accounts for 15–20% of autosomal dominant familial cases, is characterized by lack of TDP-43 and FUS inclusions and an apparent absence of cognitive involvement [9,11**].

A second gene now linked to both familial and sporadic MND is the TAR DNA binding protein (TARDBP) gene on chromosome 1p36.22, designated ALS10. It is present in 1–3% of MND cases, and over 30 mutations have been identified with an autosomal dominant pattern of inheritance. Two cases presenting with FTD-MND have been reported; one with language deficits and the other with behavioural impairment. Only one sporadic case with pure FTD with a TARDBP mutation has, so far, been reported [11**].

The third group, classified as ALS6, have mutations in the fused sarcoma/translocation in liposarcoma gene (FUS/TLS), on chromosome 16q12. Dominant and recessive mutations have been identified in familial and sporadic MND cases, and one case of sporadic FTD [11**,12,14].

Other mutations linked to MND cases with FTD are missense mutations in angiogenin (ANG) gene and mutations in the p150 subunit of dynactin 1 (DCTN1) gene. In addition, two mutations reported in FTD cases, affecting chromatin-modifying protein 2B (CHMP2B) and progranuline (PGRN) genes, although uncommon, have been found in cases with FTD and MND [12].

There are clearly more genes to be identified which are likely to be more common than some of the known mutations. A significant number of families in which some members have MND, FTD or both have been linked to chromosome 9, but the gene responsible remains elusive [15].

<table>
<thead>
<tr>
<th>Development of motor neurone disease in patients with frontotemporal dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximately, 15% of the patients with FTD develop frank MND in the course of the disease [3,16]. This clinical syndrome has a fairly consistent pattern in which rapidly evolving behavioural and cognitive symptoms are followed after a period of 1–2 years later (sometimes up to 7 years) by bulbar and other signs of motor dysfunction [17,18**]. The presentation may be either behavioural or language impairment, but usually both are present from the start.</td>
</tr>
<tr>
<td>The behavioural changes include poor insight, lack of empathy, obsessions and tendency to eat sweet food and hoard things. Periods of apathy alternate with irritability and disinhibition. The language impairment is characterized by a progressive nonfluent aphasia, leading to mutism [17]. A detailed case study of five patients with marked aphasia in association with MND documented a selective deficit in verb processing involving both production and comprehension. These patients were shown to have pathological involvement of Broca’s area [19].</td>
</tr>
<tr>
<td>Neuropsychological assessment often reveals prominent frontal/executive dysfunction. Although psychotic symptoms appear to be infrequent in FTD, remarkably, delusions have been reported in up to 50% of patients with the FTD-MND phenotype. Recent reports have focused attention on the presence of delusions in early stages of the disease, which have been described as persecutory type, phantom boarder syndrome, erotomania, bodily invasion and delusional pregnancy [18**,20**]. The course of the disease, with survival from diagnosis of 2–3 years, is certainly shorter than in cases with pure FTD [18**].</td>
</tr>
</tbody>
</table>

Executive dysfunction

The greatest body of literature on cognition in MND has related to executive function and by implication to prefrontal lobe abilities [2,21–24] (Table 1). Although estimates of the prevalence of such deficits range from 10 to 70%, in the largest study to date subtle cognitive impairment was found in 50% of 279 patients with sporadic MND [2].

### Table 1 Summary of cognitive and behavioural changes in patients with motor neurone disease

<table>
<thead>
<tr>
<th>Deficits caused by cognitive impairment</th>
<th>Behavioural changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Apathy</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Irritability</td>
</tr>
<tr>
<td>Working memory</td>
<td>Lack of empathy</td>
</tr>
<tr>
<td>Planning/organizing</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Mental shifting</td>
<td>Compulsions</td>
</tr>
<tr>
<td>Stereotyped behaviours</td>
<td></td>
</tr>
</tbody>
</table>

Data from [21–27,28**].
The most prominent deficit reported has been reduction in verbal fluency, which is evident in the letter fluency test [24,25]. This impairment has been associated with dysfunction of anterior cingulate gyrus and middle and inferior frontal gyri as demonstrated by functional MRI [25]. Written rather verbal fluency has been examined in patients with significant dysarthria [24]. Attention (verbal series attention test and paced auditory serial addition test), working memory (reverse digit span test), planning (Tower of Hanoi) and cognitive flexibility (Wisconsin card sorting test) may also be impaired [21–24]. As impaired performance on neuropsychological assessment can be confounded by motor dysfunction, a recent study assessed executive function with a motor-free test. In this study, the performance of MND patients and controls was compared using the Medication Scheduling Task, which includes planning, multitasking, mental set shifting and delaying response components. The participants were asked to assemble a daily safe scheme for the administration of the medication. Despite correction for motor disability, MND patients performed worse than the control group [26].

**Behavioural symptoms**

A range of behavioural symptoms that parallel those found in FTD have been reported although, as with cognitive dysfunction, estimates of prevalence vary considerably. Apathy has been consistently found to be the most common feature. For instance, one study reported apathy in 55% of MND patients, which correlated with deficits in verbal fluency but not with physical disability, mood disturbances or respiratory function [27]. A study on 225 MND patients, which used the Frontal Systems Behaviour Scale (FrSBe) designed to evaluate apathy, executive dysfunction and disinhibition, showed an elevation in the total FrSBe score in a quarter of cases and over a third of cases had impairment in at least one behavioural domain. Patients with cognitive impairment had greater behavioural changes, although the two domains were partially independent [28**]. Finally, two informant-based behavioural interview surveys showed that patients with MND may also present indiscriminate eating, gluttony, compulsions and behavioural stereotypes [29,30] (see Table 1).

**Memory**

A majority of the studies assessing memory have shown greater impairment of immediate recall than with recognition tasks, suggesting a retrieval disturbance secondary to prefrontal dysfunction [21,31]. A recent meta-analysis of studies to date concluded that some aspects of memory are consistently impaired, notably immediate and delayed visual memory and immediate verbal memory. The pattern is in keeping with frontal lobe dysfunction, but involvement of temporal lobe structures could not be discounted because of the effect size [32**].

**Language**

Language assessment presents particular problems in patients with dysarthria, but even allowing for this it seems that significant aphasia occurs in a proportion of patients with MND and may be more common in patients with bulbar onset disease [33]. The most commonly identified deficits have been reduced speech output and anomia [17,34]. Some patients develop significant aphasia designated progressive nonfluent aphasia with agrammatism in production and impaired syntactic comprehension. Interestingly, a higher order disturbance of motor speech, apraxia of speech, has been reported in patients with bulbar onset disease, frequently associated with spastic or mixed spastic–flaccid dysarthria [35].

**Emotional processing**

The fact that emotion processing is severely and consistently compromised in patients with FTD [36] has understandably led a number of investigators to study this aspect of social cognition in MND. Impaired recognition of emotional faces was found in a group of bulbar MND patients [37]. A selective deficit in the recognition of threat stimuli through faces has also been reported, which parallels that seen in patients with amygdala damage [38].

**Longitudinal studies**

A key question unanswered from cross-sectional studies is whether cognitive dysfunction remains confined to a subset of patients with MND whose condition worsens over time or alternatively whether all patients with MND eventually develop cognitive or behavioural changes. Longitudinal studies have found cognitive dysfunction early in the course of the disease, on the basis of verbal fluency deficits [39] particularly in those with bulbar onset disease [40], although this has not been a universal finding [41,42**].

Progression of cognitive impairment over the course of MND appears to be mild. Older patients, and those with more rapidly progressing disease, may be more predisposed to cognitive impairment, which, in turn, contributes to a shorter survival [42**].

**Neuroimaging**

The principal role of neuroimaging in MND has been to exclude alternative diagnoses, although in more recent years new techniques have been used to assess the integrity of both the motor system and the extra motor regions.
Structural MRI has established that those with subtle cognitive or behavioural impairment showed grey matter loss in frontal, parietal and limbic regions [43]. As expected, patients with MND-FTD have atrophy of frontotemporal lobes and hypointensity of subcortical white matter in medial anterior temporal lobe, similar to that seen in patients with pure FTD [44,45].

A comparison of MND and MND-FTD patient groups using voxel-based morphometry showed a similar pattern of grey matter atrophy involving bilateral motor and premotor cortices, superior, middle and inferior frontal gyri, superior temporal gyri, temporal poles and left posterior thalamus that was, as predicted, greater in the MND-FTD group [46].

Functional MRI (fMRI) studies have shown reduced activation of the middle and inferior frontal gyri and anterior cingulate gyrus in MND patients during letter fluency tasks [29]. Deficits on word fluency and confrontation naming have been shown to correlate with impaired activation of the prefrontal region (Broca area), temporal, parietal and occipital lobes [29,43].

A few recent studies have examined the relationship between social processing and regions of brain activation using fMRI. One study demonstrated that patients with MND presenting altered sensitivity to social–emotional clues had an increased response in the right supramarginal area [47]. Another showed that impaired emotional process in ALS patients was related to right hemisphere dysfunction [48].

**Conclusion**

Recent advances in genetics and pathology have led to the concept of MND as a multisystem disorder which overlaps with frontotemporal dementia. The assessment of patients with MND is challenging, due to the motor disability and the variability of the clinical phenotype. It appears that changes in behaviour and cognition, notably executive function, language and emotional processing, occurs only in a subset of patients, but the cause of this variability in the clinical phenotype remains unclear.

**Acknowledgements**

The study was supported by the Australian Research Council Federation Fellowship, FF0776229 (Prof. Hodges) and CONICYT scholarship (Government of Chile) (Dr Lillo).

J.R.H. serves on editorial boards of Aphasiology, Cognitive Neuropsychiatry, and Cognitive Neuropsychology; receives royalties from publication of Cognitive Assessment for Clinicians (Oxford University Press, 2007) and Frontotemporal Dementia Syndromes (Cambridge University Press, 2007) and receives fellowship support from the Australian Research Council Federation.

Thanks to Dr James Burrell, MBBS (Hons), for his assistance with proofreading.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 708).


6. A complete description of the pathology in MND with specific emphasis on the distribution of TDP-43 inclusions.


13. An excellent update on the genetic findings across motor neuron disease with a brief and clear explanation of the pathogenic mechanism and clinical presentation.


21. Provides interesting data comparing the behavioural symptoms of patients with FTD-MND vs. bvFTD and survival.

Degenerative and cognitive diseases


