

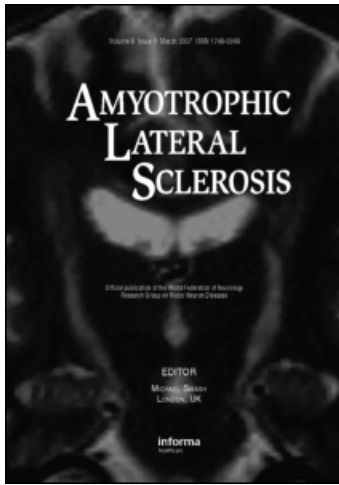
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## Amyotrophic Lateral Sclerosis

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### Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis

Michael J. Strong<sup>a</sup>; Gloria M. Grace<sup>ab</sup>; Morris Freedman<sup>c</sup>; Cathy Lomen-Hoerth<sup>d</sup>; Susan Woolley<sup>e</sup>; Laura H. Goldstein<sup>f</sup>; Jennifer Murphy<sup>g</sup>; Christen Shoesmith<sup>a</sup>; Jeffery Rosenfeld<sup>h</sup>; P. Nigel Leigh<sup>i</sup>; Lucie Bruijn<sup>j</sup>; Paul Ince<sup>k</sup>; Denise Figlewicz<sup>k</sup>

<sup>a</sup> Department of Clinical Neurological Sciences, The University of Western Ontario, London, Ontario, Canada

<sup>b</sup> Psychological Services, London Health Sciences Centre, London, Ontario, Canada <sup>c</sup> Division of Neurology, Behavioural Neurology Program, and Rotman Research Institute, Baycrest Division of Neurology, Department of Medicine, Mt. Sinai Hospital, University Health Network, and University of Toronto, Toronto, Ontario <sup>d</sup>

Department of Neurology, UCSF, San Francisco, California, USA <sup>e</sup> Forbes Norris MDA/ALS Research Center, San Francisco, California, USA <sup>f</sup> MRC Centre for Neurodegeneration Research, King's College London,

Institute of Psychiatry, London, UK <sup>g</sup> Department of Neurology, USCF, San Francisco <sup>h</sup> Division of Neurology, UCSF-Fresno, Fresno, California <sup>i</sup> Research and Development, The ALS Association, Palm Harbor, Florida, USA <sup>j</sup> Department of Neuroscience, University of Sheffield, Sheffield, UK <sup>k</sup> ALS Society of Canada, Toronto, Ontario, Canada

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ORIGINAL ARTICLE

## Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis

MICHAEL J. STRONG<sup>1</sup>, GLORIA M. GRACE<sup>1,2</sup>, MORRIS FREEDMAN<sup>3</sup>,  
CATHY LOMEN-HOERTH<sup>4</sup>, SUSAN WOOLLEY<sup>5</sup>, LAURA H. GOLDSTEIN<sup>6</sup>,  
JENNIFER MURPHY<sup>7</sup>, CHRISTEN SHOESMITH<sup>1</sup>, JEFFERY ROSENFELD<sup>8</sup>,  
P. NIGEL LEIGH<sup>6</sup>, LUCIE BRUIJN<sup>9</sup>, PAUL INCE<sup>10</sup> & DENISE FIGLEWICZ<sup>11</sup>

<sup>1</sup>Department of Clinical Neurological Sciences, The University of Western Ontario, London, Ontario, <sup>2</sup>Psychological Services, London Health Sciences Centre, London, Ontario, Canada, <sup>3</sup>Division of Neurology, Behavioural Neurology Program, and Rotman Research Institute, Baycrest Division of Neurology, Department of Medicine, Mt. Sinai Hospital, University Health Network, and University of Toronto, Toronto, Ontario, <sup>4</sup>Department of Neurology, UCSF, San Francisco, California, <sup>5</sup>Forbes Norris MDA/ALS Research Center, San Francisco, California, USA, <sup>6</sup>MRC Centre for Neurodegeneration Research, King's College London, Institute of Psychiatry, London, UK, <sup>7</sup>Department of Neurology, USCF, San Francisco, <sup>8</sup>Division of Neurology, UCSF-Fresno, Fresno, California, <sup>9</sup>Research and Development, The ALS Association, Palm Harbor, Florida, USA, <sup>10</sup>Department of Neuroscience, University of Sheffield, Sheffield, UK, and <sup>11</sup>ALS Society of Canada, Toronto, Ontario, Canada

### Abstract

Amyotrophic lateral sclerosis (ALS) is increasingly recognized to be a multisystem disorder which includes both clinical and neuropathological features of a frontotemporal lobar degeneration (FTLD). In order to provide a common framework within which to discuss the characteristics of the cognitive and behavioural syndromes of ALS, and with which to conduct clinical and neuropathological research, an international research workshop on frontotemporal dementia (FTD) and ALS was held in London, Canada in June 2007. The recommendations arising from this research workshop address the requirement for a concise clinical diagnosis of the underlying motor neuron disease (Axis I), defining the cognitive and behavioural dysfunction (Axis II), describing additional non-motor manifestations (Axis III) and identifying the presence of disease modifiers (Axis IV).

**Key words:** *Genetics, neuropathology, dementia*

### Introduction

Although amyotrophic lateral sclerosis (ALS) has traditionally been considered to be a progressive neurodegenerative disorder in which the motor system is selectively targeted, the contemporary conceptualization is that ALS is a multisystem disorder in which motor system deficits are prominent, but in which non-motor manifestations can also be observed (1). Among these are impairments in frontotemporal functions that manifest as a spectrum of clinical deficits, including both cognitive and behavioural impairments, with a subgroup developing a frontotemporal dementia (FTD). Collectively, these are referred to as the syndromes

of frontotemporal dysfunction in ALS. To be consistent with the literature, in this consensus document the use of the term FTD will be restricted to the overall clinical spectrum of frontotemporal dementia, including the behavioural variant FTD (bvFTD), progressive non-fluent aphasia (PNFA) and semantic dementia (SD) (2,3). The term frontotemporal lobar degeneration (FTLD) will be restricted to the neuropathological correlate to the majority of FTD patients.

Ascertaining the presence of a frontotemporal syndrome in ALS is of direct relevance in that its presence predicts a shorter survival time (4). Compared to individuals afflicted with Alzheimer's disease, overall survival among those affected with a

FTLD is shorter. This observation is most evident in those patients with FTLT coexistent with motor neuron disease (5,6). A similar impact of the presence of a FTD on survivorship in ALS has been observed (7). Because estimates of the prevalence of cognitive or behavioural impairment in ALS range from 10% to 75% (8,9), with the prevalence of dementia ranging from 15% to 41% (10,11), these issues are of critical importance not only in the care of individuals with a motor neuron disease and in the undertaking of key life decisions (e.g. enteral nutrition, non-invasive positive pressure ventilation), but also in the design of pharmacological trials.

The presence of FTLT in ALS is of biological importance in that it raises the possibility of an overlap syndrome in which both ALS and FTLT exist within a continuum. This has been highlighted by the observation that abnormal protein aggregation of the TAR DNA binding protein of 43 kDa (TDP-43) has been associated with ubiquitinated inclusions in both ALS and FTLT (12–15). Cortical neurons in both FTLT and ALS show a loss of the normal nuclear staining of TDP-43 with a predominance of cytosolic staining. Furthermore, in both FTLT and ALS, intranuclear TDP-43 immunoreactive aggregates are prominent in neocortical neurons together with previously under-reported glial inclusions.

Even prior to the discovery of TDP-43, a proportion of ALS cases, including the western Pacific variant of ALS and a number of sporadic forms of ALS, had been shown to demonstrate the pathological findings typical of a FTLT. These include superficial linear spongiosis with prominent neuronal loss in the anterior cingulate gyrus and the superior frontal gyrus. Although typically this process is associated with ubiquitin-positive, tau- and  $\alpha$ -synuclein-negative neuronal inclusions, a subgroup of ALS cases also demonstrates microtubule associated tau protein (tau) immunoreactive aggregates in neuronal and non-neuronal cells (16–18). Among patients with FTLT, there also exists a subgroup of patients with no obvious ante mortem evidence of a motor neuron disease, but in whom the neuropathology has demonstrated ubiquitin immunoreactive intraneuronal aggregates within both bulbar and spinal motor neurons (19,20). Therefore, there is significant neuropathological evidence of an overlap of ALS with FTLT.

This greater neuropathological knowledge of FTLT and ALS, coupled with advances in our understanding of the genetics of these disorders, highlights the critical need to clarify the terminology surrounding the definitions of the frontotemporal syndromes that may occur in ALS, in order to further define their clinicopathological characteristics. To this end, a workshop on FTD in ALS was convened in June 2007 in London, Canada to

develop consensus criteria for diagnosis and classification of frontotemporal syndromes in ALS. The following recommendations reflect the results of this workshop and are meant to provide a common framework for the discussion of frontotemporal syndromes in the context of motor neuron diseases, both for the conduct of clinical research and to inform future clinicopathological studies. The participants noted that a percentage of ALS patients with no previous diagnosis of FTD will have early behavioural changes that precede the onset of the symptoms of ALS. Although the behavioural changes may not have justified an evaluation or diagnosis of FTD, the changes can be noticeable, disturbing to the family, and undiagnosed (21,22). This paper does not address directly the diagnostic variations for the 15% of FTD patients who later develop ALS or a related motor neuron disease (23).

Because of the complexity of motor neuron disorders, participants recommended that the approach to the clinical characterization of the frontotemporal syndromes in ALS or related motor neuron diseases would be based on four primary 'diagnostic axes', including the following: Axis I – defining the motor neuron disease variant; Axis II – defining the cognitive and behavioural dysfunction; Axis III – additional non-motor disease manifestations; Axis IV – presence of disease modifiers. The following article summarizes these discussions and recommendations.

## Axis I

### *Defining the motor neuron disease variant*

The motor neuron diseases are a heterogeneous group of disorders that have in common progressive degeneration of the motor neurons. Such diseases can involve exclusively the upper motor neurons (UMN), lower motor neurons (LMN) of either spinal or bulbar origin, or can present as combined UMN and LMN disorders. Motor neuron disease can also remain isolated in a specific segment or, more typically, become widespread. Specific disease phenotypes include ALS, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), spinal muscular atrophy (SMA), spinal bulbar muscular atrophy (Kennedy's disease), progressive bulbar palsy, bibrachial amyotrophy, and monomelic amyotrophy. The diagnostic criteria for the diagnosis of the motor neuron diseases have been well established and are summarized in Table I. Rates of progression vary enormously and can be anticipated by a number of prognostic determinants including the specific disease phenotype. Because the most common presentation of the adult-onset motor neuron diseases is ALS (UMN and LMN dysfunction in multiple spinal levels), participants focused on the specific recognition of a frontotemporal

Table I. Clinical features of adult onset motor neuron diseases (from Strong & Rosenfeld, 2003) (146).

	Amyotrophic lateral sclerosis	Progressive muscular atrophy	Spinal muscular atrophy	Primary lateral sclerosis	Kennedy's disease	Progressive bulbar palsy	Monomelic amyotrophy	Brachial amyotrophic diplegia
Typical distribution of weakness	Asymmetrical	Asymmetrical	Symmetrical Proximal or distal	Asymmetrical	Symmetrical Proximal	Initially limited to bulbar muscles	Asymmetrical Restricted to 1-2 extremities	Symmetric Proximal upper extremities
UMN signs	Present	Absent	Absent	Present	Absent	Present	Absent	Absent
LMN signs	Present	Present	Present	Absent	Present	Present	Present	Present
Sensory loss	Absent	Absent	Absent	Absent	Modest	Absent	20%	Absent
Genetics	AD (10%) SOD mutation (2%)	Unknown	AR, AD SMN gene implicated	Unknown (no reported familial cases)	XLR CAG repeats >40	Unknown	Unknown	Unknown
Distinct features	UMN and LMN signs with usually rapid progression	Pure LMN disorder with usually indolent course	Pure LMN disorder usually with progressive proximal weakness over decades	Pure UMN disorder with indolent course	Gynaecomastia, diabetes mellitus, impotence, infertility	Weakness initially limited to bulbar muscles. May progress rapidly to ALS or be relatively indolent.	Progression over 2-3 years with subsequent stabilization	Preservation of respiratory and bulbar function with slow progression

Abbreviations: AD: autosomal dominant; AR: autosomal recessive; CAG: cytosine-adenine-uracine nucleotide; LMN: lower motor neuron; SOD: superoxide dismutase; SMN: survival motor neuron; UMN: upper motor neuron; XLR: X-linked recessive.

syndrome within the context of ALS. However, the participants noted that the diagnostic recommendations could be applied across the spectrum of motor neuron diseases.

*Axis I diagnostic criteria.* The El Escorial criteria (revised) for the diagnosis of ALS form the core of any diagnosis of ALS (24,25). In their revised format, these criteria make use of clinical, electrophysiological, genetic and neuroimaging modalities to apply a level of certainty to the diagnosis of ALS. The sensitivity and specificity of the El Escorial criteria as diagnostic criteria for ALS have been validated in neuropathological studies (26).

The diagnostic categories of ALS include clinically definite, probable, possible and suspected. In essence, the diagnosis of ALS requires the presence of both multisegmental (bulbar, cervical, thoracic or lumbosacral) LMN degeneration (by clinical, electrophysiological or neuropathological criteria) and evidence of UMN dysfunction (by clinical examination) accompanied by evidence of progression of symptoms or signs within a region or to other regions (Table II). These features must be present in the absence of an alternative disease process that could explain the findings. A simplified version of these criteria has been developed and validated (Table III) (27). Laboratory and genetically supported categories can be utilized in those individuals in whom the full clinical and electrophysiological criteria are not met (25).

*Axis I molecular diagnostics.* Motor neuron diseases can be classified as either sporadic or familial. Although there is little literature with regard to the occurrence of a frontotemporal syndrome in familial ALS (FALS), it is likely that this reflects poor case ascertainment in that contemporary studies suggest that such syndromes may be more common among this variant of ALS (28,29). There are also neuropathological data indicating widespread involvement of the central nervous system in ALS harbouring copper/zinc superoxide dismutase (SOD1) mutations (mtSOD1, the most common variant of FALS) (30). This reflects not only those cases presenting with typical manifestations of a motor neuron disease, but additional pedigrees in which the initial manifestations of a FTD syndrome are followed by either clinical or electrophysiological manifestations of a motor neuron disease (Table IV).

Given the extent to which neuropsychological evaluations have been undertaken in FALS pedigrees, only limited generalizations can be made. There are few reports of a behavioural syndrome in association with SOD1 mutations (31-33) and a single report in which mtSOD1 FALS patients were shown to be cognitively and behaviourally intact (34). Apart from mtSOD1, a limited number of genetic risk factors for the development of ALS have been identified and, among these, rare associations with neuropsychological syndromes. These include chromosome 3p11.2

Table II. Diagnostic categories for ALS (24,25).

Clinically definite ALS	Clinical evidence of the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions, or the presence of UMN and LMN signs in at least three spinal regions
Clinically definite familial ALS – laboratory supported	May be applied when ALS presents with progressive UMN and/or LMN signs in at least one region (in the absence of another cause for the abnormal neurological signs)
Clinically probable ALS	Clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to the LMN signs
Clinically probable ALS – laboratory supported	Clinical signs of UMN and LMN dysfunction alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes
Clinically possible ALS	Clinical signs of UMN and LMN dysfunction are found together in only one region, or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of clinically probable ALS – laboratory supported cannot be proven
Clinically suspected ALS	Where the diagnosis could not be regarded as sufficiently certain to include the patient in a research study

Abbreviations: LMN: lower motor neuron; UMN: upper motor neuron.

linked CHMP2B (charged multivesicular protein) mutations (35–38) and chromosome 14q11.2 linked angiogenin/vascular endothelial growth factor (ANG/VEGF) mutations (39). In spite of the finding of cortical TDP-43 immunoreactive pathology in ALS, it is not yet possible to determine whether mutations in TARDBP (chromosome 1p36.2 gene encoding TDP-43) are a priori associated with the development of a frontotemporal syndrome. However, because a number of TARDBP mutations have been identified in ALS, it is likely that for a specific subpopulation of patients (Table V), alterations in the metabolism or function of TDP-43 may be a causative factor in the disease process. It is noteworthy that, to date, none of the reported ALS patients with mutations in TARDBP has also been documented to have a frontotemporal syndrome.

Mutations in the microtubule associated protein tau gene (chromosome 17q21.1 encoded MAPT) are most commonly manifested as FTD in association with Parkinson's disease, although Pick's disease, progressive supranuclear palsy (PSP) and rarely amyotrophy with pyramidal findings can also be observed (40–44). To date there have been no reports of ALS with a frontotemporal syndrome associated with MAPT mutations.

Table III. Simplified ALS diagnostic algorithm (27).

Exclude disorders known to mimic ALS
Diagnosis of ALS is tenured if:
● Lower motor neuron signs in at least two regions
● Upper motor neuron signs in at least one region
● Progression
Absence of:
● Sensory signs
● Neurogenic sphincter abnormalities
● Clinically-evident peripheral nervous system disease with natural history of progression, distinct from ALS
● Clinically-evident peripheral nervous system disease with a natural history of progression
● ALS-like syndromes

Although mutations in progranulin (PGRN) are associated with approximately 5.7% of cases of FTD (45), a percentage that increases to approximately 18% in the presence of an autosomal dominant pattern of inheritance, there does not appear to be a significant association between PGRN mutations and ALS with a frontotemporal syndrome (46). The exceptions to this include a single FTD pedigree of individuals with either a corticobasal syndrome, ALS or FTD in association with a PGRN mutation (IVS6-1G >A) (47) and a single missense PGRN mutation identified in an ALS-FTD patient (48) and in a pedigree of FTD and ALS (49).

*Axis I recommendations.* With respect to characterizing the phenotype of the frontotemporal syndromes in the motor neuron diseases, the participants recommended that defining the phenotype of the motor neuron disease should be the first level of categorization. Detailed discussion pertaining to the potential for definition of numerous disease subtypes defined by anatomical variants, regional variants, or disease duration took place. The potential for unnamed disease subtypes to be of significance in the correlation with FTD syndromes was noted. Given that international criteria exist for some of the individual MND syndromes of interest, the participants recommended that these published criteria be used. Where possible, the syndrome should be defined as either sporadic or familial or, in the instance of ALS where endemic foci exist (e.g. western Pacific variant), that this information also be included in the categorization. In the context of familial variants, when present, disease specific genetic mutations should be documented. With respect to specific genetic risk factors for the development of a frontotemporal syndrome, the participants recommended that patients be assessed for SOD1, CHMP2b, ANG, MAPT, TARDBP and PGRN mutations.

Table IV. FALS genotypes and correlation with cognitive dysfunction (from Strong, 2008) (1).

Name	Locus	Gene	Onset	Inheritance	Alternative phenotypes	Associated cognitive syndrome	Reference
<i>ALS1</i>	21q22.1	SOD1	Adult	Dominant	None (pure)	L144F, G41S, D90A mutations; apathy, anxiety, inattention, reduced verbal fluency, hypersexuality	(31–33)
<i>ALS2</i>	2q33	Alsin	Juvenile	Recessive	Infantile-onset spastic paralysis; juvenile onset PLS	Spastic pseudobulbar variant (suggestive of behavioural variant)	(147–150)
<i>ALS3</i>	18q21	unknown	Adult	Dominant	None	None described	(151)
<i>ALS4</i>	9q34	SETX	Juvenile	Dominant	CMT or dHMN	None described	(152)
<i>ALS5</i>	15q15.1–21.1	unknown	Juvenile	Recessive	None	None described	(153)
<i>ALS6</i>	16q12	unknown	Adult	Dominant	None	None described	(154–156)
<i>ALS7</i>	20p13	unknown	Adult	Dominant	None	None described	(155)
<i>ALS8</i>	20q13.33	VAPB	Adult	Dominant	Late-onset spinal muscular atrophy; syndrome of fasciculations, cramping and postural tremor	Single description of ALS with ‘dementia’	(157, 158)
<i>ALS9</i>	14q11	ANG/VEGF	Adult	Dominant	None	Single case with impairment in executive function and behavioural change dominated by apathy and inertia followed by akinetic mutism	(39)
<i>ALS10</i>	1p36.2	TARDBP	Adult	Dominant	None	None described	See Table V
<i>FTD-ALS</i>	17q21.1	MAPT	Adult	Dominant	Disinhibition-dementia-Parkinsonism-amyotrophy complex	FTD, Pick’s disease, Parkinson’s disease, Alzheimer’s disease, progressive supranuclear palsy (PSP); rarely associated with amyotrophy and pyramidal findings	(40–43)
<i>ALSFTD1</i>	9q21-22	unknown	Adult	Dominant	FTD in isolation	ALS, FTD or both	(159)
<i>ALSFTD2</i>	9p13.2-21.3	unknown	Adult	Dominant	FTD in isolation	ALS in association with mild cognitive impairment; single pedigree with motor symptoms followed by personality and behavioural abnormalities	(160–162)

Abbreviations: ANG: angiogenin; CMT: Charcot-Marie-Tooth; dHMN: distal hereditary motor neuronopathy; FTD: frontotemporal dementia; PLS: primary lateral sclerosis; MAPT: microtubule associated protein tau; Setx: senetaxin gene; SOD1: copper/zinc superoxide dismutase; TARDBP: Tar DNA binding protein; VEGF: vascular endothelial growth factor.

Table V. TDP-43 mutations associated with ALS.

Familial ALS	Sporadic ALS	Reference
2/31 (6.5%)	0/134	(163)
2/39 (5.1%)	0/149	(164)
1/154 (0.6%)	2/373 (0.5%)	(165)
1/8 (12.5%)	-	(166)
1/16 (6.3%)	-	(167)
3/80 (3.8%)	6/120 (5.0%)	(168)
2/71 (2.8%)*	0/79	(169)

\*G295S mutation observed in two FTD-ALS pedigrees, with one patient initially presenting with semantic dementia, and another with bvFTD.

## Axis II

### *Defining the cognitive and behavioural dysfunction*

There is considerable evidence supporting the existence of cognitive and behavioural dysfunction in ALS, including a spectrum of frontotemporal syndromes and more classically defined dementias. These include pure ALS in which only motor neuron degeneration occurs in the absence of a clinically-overt frontotemporal syndrome, ALS in association with cognitive impairment (ALS*Sci*), ALS with behavioural impairment (ALS*bi*), and ALS with a concurrent dementia that meets the criteria for a FTD (ALS-FTD). In addition, a more florid dementia that precedes ALS, described among the Japanese population, can be included in this categorization. A frontally predominant variant of Alzheimer's disease can also occur in ALS, although it is not clear whether this is a chance association (50).

FTD can manifest in three clinically recognized subtypes (3,51). The most common (behavioural variant FTD, bvFTD) is a progressive behavioural syndrome marked by insidious onset, altered social conduct, impaired regulation of interpersonal conduct, emotional blunting and loss of insight. In addition, both a progressive non-fluent aphasia (PNFA – characterized by progressive non-fluent spontaneous speech with agrammatism, paraphasias or anomia) and semantic dementia (SD, characterized by fluent speech with impaired understanding of word meaning and/or object identity) are considered to be within the FTD spectrum. Although there is a move to subsume both PNFA and SD within the single terminology of primary progressive aphasia (3), this terminology has not yet become engrained in the literature and thus will not be applied here.

Whereas the classification of patients with frontotemporal syndromes into bvFTD, PNFA and SD has in general proven very useful, this approach does not serve to adequately describe the full spectrum of cognitive and behavioural syndromes associated with ALS. For example, a frontal dysexecutive syndrome may occur in ALS in the absence of the typical behavioural features associated with bvFTD. None

of the standard criteria for FTD speaks directly to the issue of executive dysfunction in ALS, deficits of which may impact directly on the ability to organize information mentally, to shift attention, or to inhibit behaviour. Additionally, the most common frontal lobe impairment in ALS reflects a combination of both cognitive and behavioural dysfunction (21).

In developing these guidelines, the workshop participants felt that defining a minimum set of criteria that will be both sensitive and specific to these various syndromes was important. In part, this is a reflection of the fact that the neuropsychological impairments in ALS are often subtle, with the most commonly observed deficits in the areas of problem solving, attention/mental control, word generation, and frontally-mediated aspects of memory (e.g. verbal learning, source memory, free recall). While sampling the major cognitive domains, neuropsychological assessments should include tests weighted towards executive functioning, including a verbal fluency measure, as well as a caregiver interview measuring emotional and behavioural functioning. The latter is critical for assessing the full spectrum of frontotemporal impairments, as many reported series have not addressed the behavioural aspects, but rather have focused solely on alterations in cognition when assessing frontotemporal dysfunction in ALS. It is also critical to use tests that minimize the impact of speech and motor dysfunction on performance, particularly in the setting of longitudinal analysis.

*ALS-FTD (bvFTD, PNFA, SD).* The core aspect of this diagnostic categorization relates to the presence or absence of a FTLT, the underlying pathological process that can manifest in three distinct clinical syndromes (2,51,52). As described above, these include a bvFTD, PNFA or SD, any of which can be seen in association with ALS. It is critical to recognize that a behavioural impairment is at the core of bvFTD, the most common of the three syndromes. In contrast, impairments in expressive language and word/object meaning are at the core of PNFA and SD, respectively, although these too have some behavioural involvement (53). bvFTD is further characterized by an insidious onset with gradual progression, early decline in social interpersonal conduct, early impairment in regulation of personal conduct, early emotional blunting and early loss of insight. The behavioural disorder must significantly impact the patient's life in some manner, i.e. relationships, occupational functioning, or self care. This should reflect a marked change from premorbid levels and not simply reflect a reaction to physical disability or the development of a mood disorder. Such behavioural symptoms may include disinhibition marked by impulsivity, distractibility, and/or poor quality of social interactions. Others exhibit notable apathy or an alteration in emotional expressiveness. Caregivers may describe personality

changes such as irritability, selfishness or disinterest that are inconsistent with pre-illness disease states.

Supportive features of the diagnosis of bvFTD may include impaired executive functioning as determined by neuropsychological assessment. This would occur in the absence of notable posterior visuospatial dysfunction or an amnesic disorder. Speech or language impairments may be present but should not dominate the neuropsychological picture. If so, consideration of PNFA or SD should be made. Rigid or inflexible thinking may be noted, as well as hyperorality, food stuffing, stereotyped behaviours, or frontal release signs.

*ALS-behavioural impairment (ALSbi).* The participants noted that only rarely would the ALS patient meet the full criteria for the diagnosis of bvFTD as described above. However, there is a subgroup of patients who would meet partial criteria. To this end, the diagnosis of ALSbi would require only that the individual meets at least two non-overlapping supportive diagnostic features from either the Neary criteria (i.e. decline in personal hygiene and grooming, mental rigidity and inflexibility, distractibility and imperistence, hyperorality and dietary changes, perseverative and stereotyped behaviour, utilization behaviour) and/or Hodge's criteria (i.e. loss of insight, disinhibition, restlessness, distractibility, reduced empathy or unconcern for others, lack of foresight or planning, impulsiveness, social withdrawal, apathy or loss of spontaneity, reduced verbal output, verbal stereotypes or echolalia, verbal or motor perseveration, poor self care, gluttony, sexual hyperactivity) (54). Although it is possible that meeting only one of the criteria for behavioural impairment would suffice, there was concern that this would lead to over-diagnosis.

The presence of two behavioural abnormalities should be supported by at least two sources from among a patient interview/observation, caregiver report, or structured questionnaire/interview. Ideally, both a clinical interview with both the patient and caregiver and a structured, well-validated questionnaire should be included (see below for recommendations). To diagnose ALSbi, the behavioural changes should not be better explained by a psychiatric condition, a psychological reaction to the motor neuron disease, a premorbid personality disorder, or be due to the presence of pseudobulbar affect.

*ALS-cognitive impairment (ALSci).* To be diagnosed with ALSci, the patient must demonstrate cognitive impairment on standardized neuropsychological testing at or below the 5th percentile, compared to age- and education-matched norms, on at least two distinct cognitive tests sensitive to executive functioning (see below for recommendations). Such impairment must not be better accounted for by the patient's premorbid intellectual level. Domains other than executive functioning should also be

assessed, consistent with a comprehensive neuropsychological assessment, to rule out other cognitive conditions. Measures should control for bulbar dysfunction (dysarthria) and motor weakness.

The participants emphasized that the assessment of cognitive impairment requires a careful delineation of comorbidities to ensure that the cognitive impairment could not be better explained by such comorbid conditions. These comorbidities include neurological (e.g. cerebrovascular disease, pre-existing or concurrent head injury), systemic (e.g. hypothyroidism, diabetes), pharmacological (e.g. substance abuse), or psychiatric (e.g. severe depression, severe anxiety disorder, psychosis) conditions. In addition, a number of ALS-specific associated conditions must be considered as possible explanations for test results indicating impairment in cognition, including the presence of a pseudobulbar affect, respiratory dysfunction (e.g. as measured by forced vital capacity, maximal inspiratory force, nocturnal oximetry, and/or CO<sub>2</sub> ratings), disrupted sleep, delirium, pain, fatigue and medication effect (especially psychotropic and narcotic analgesic medications).

Although patients may meet the criteria for both ALSci and ALSbi concurrently, it is important to recognize that patients suffering from apathy will have poor motivation and hence perform poorly, particularly on demanding tests such as those required for the assessment of executive functions. This raises the risk of misdiagnosis of concurrent ALSci and ALSbi. Patients may also change diagnostic categories as the disease progresses.

*ALS-comorbid dementia.* In this categorization, ALS is associated with a dementia not typical of FTD. Examples include Alzheimer's disease, vascular dementia (55) and mixed dementias.

#### *Axis II recommendations*

*Proposed guidelines for cognitive and behavioural assessment.* Individuals assessing ALS patients for cognitive or behavioural impairment should be familiar with the physical disease state and expected progression. Accommodation may be required for speech deficits resulting from dysarthria, as well as compromised motor speed. Testers should note that for patients who use augmentative communication devices, telegraphic forms of speech are common and should not necessarily be interpreted as reflecting agrammatism or aphasia. When assessing behaviour, reports from family members or friends are essential. Baseline/premorbid psychological and behavioural status must be determined in order to assess whether behavioural abnormalities are 1) new, 2) associated with the onset of ALS (recognizing as stated earlier that a proportion of FTD patients will develop either clinical or electrophysiological features consistent with either ALS or a motor neuron

disease), and 3) disabling or causing clear impairment. Individuals assessing these patients also need to be knowledgeable about pseudobulbar affect, which may be misinterpreted by some as behavioural disinhibition, inappropriateness, or depression.

The participants recognized that due to the complexity of a formal neuropsychological evaluation for a frontotemporal syndrome in an individual with a motor neuron disease, a hierarchical approach might be required. Thus, the participants recommended that the testing paradigms could include a screening assessment (based on empirically-supported screens when available, 2–5 min to maximize efficient use by ALS clinicians or staff), a brief assessment (5–20 min using established cognitive screens, a combination of several cognitive screens, and/or behavioural questionnaires) and, wherever possible, a formal neuropsychological assessment.

A screening assessment should never be used to make the diagnosis of ALS-FTD, ALSbi or ALSci. Although ALS-FTD and ALSbi may be diagnosed without formal neuropsychological testing, this should only occur after a comprehensive neurobehavioural interview is completed, preferably with interviews of both the patient and caregiver, with supporting evidence from a standardized, structured questionnaire.

Similarly, the diagnosis of ALSci requires formal neuropsychological assessment. However, various screening tests, sensitive to executive dysfunction, have been employed in order to determine whether a formal neuropsychological evaluation is warranted.

Recommended screening assessments that can be applied at the bedside include one or more verbal fluency measures. A written or oral verbal fluency test provides maximum sensitivity to identify ALSci. Patients without dysarthria can be administered the oral phonemic and oral category fluency tests that are commonly used in neuropsychological exams (e.g. failure = < 8 verbal fluency D-words and/or < 13 animals in 1 min (11), <8 verbal fluency F-words (56)). Patients with any symptoms of dysarthria should be given a written version that is not affected by their speaking speed (e.g. failure = <9 words for four-letter C words in 4 min, not allowing names of people or places) (57). Ideally, patients can be offered the four-letter C words written version, along with an additional adjustment for motor weakness so that the results are not affected by any signs of hand weakness (57). Patients unable to write can be given an oral test as an alternative. Data for the equivalence of oral and written fluency testing are available for some fluency tests (58). In all cases, the assessor needs to be aware that verbal fluency correlates with IQ (59), and must then account for dysarthria/ impaired writing speed in their interpretation of scores as well as any likely premorbidly low IQ. While caregiver questions addressing cognitive or

behavioural changes may be considered, these have not been validated for use in this population.

A brief assessment of 5–20 min duration can include any of the following: Penn State Rapid Screening Battery (PSRSB) (60), The ALS Cognitive Behavioural Screen (ALS-CBS) (61), UCSF Brief Screening Battery (Murphy et al., unpublished), Addenbrooke's Cognitive Examination (ACE-R) (62), Montreal Cognitive Assessment (MOCA) (63) and/or a combination of several cognitive screens including written or verbal word generation tasks, digit span, Trail Making Test parts A and B, and behavioural questionnaires such as the Frontal Behavioural Inventory (FBI) (64,65), the Neuropsychiatric Inventory (NPI) (66) or the Frontal Systems Behaviour Scale (FrSBe) (67). Although the MMSE is widely used to assess cognitive dysfunction and dementia, it is not effective in assessing the executive dysfunction common to ALS and has no means of evaluating behaviour. It is thus of limited utility. However, any of the other global cognitive screens noted above should be applied at least once to help rule out other causes of cognitive dysfunction, such as Alzheimer's disease.

Again, the examiner must account for patients' dysarthria/impaired writing speed in their interpretation of scores.

A formal neuropsychological assessment is mandated in the scenario where either the screening or brief assessment suggests pathology. No single testing paradigm will address the full spectrum of deficits observed in the frontotemporal syndromes of ALS. Hence, workshop participants recommended that while sampling the major neuropsychological domains, testing batteries for assessment of cognitive functioning in MND should be weighted toward assessment of executive functioning. In addition to an emphasis on executive function, domains should include memory, attention/concentration, language, visual-spatial skills and emotional functioning (e.g. depression, anxiety). Testing measures should minimize the need for speech and fine motor skills, or procedures should be put in place to control for such factors (e.g. correction procedure for oral/written word fluency) (57). A formal measure of change in behaviour/personality functioning is recommended, preferably one which is administered to a caregiver (e.g. NPI, FBI, FrSBe). To date, only the FrSBe and the NPI have been studied in the context of ALS (68). Note, however, that because these testing paradigms do not take into account the physical disability or the terminal nature of ALS, there is the possibility of over-diagnosis.

A number of measures have been used in identifying impairment in ALS and should be considered when evaluating an ALS patient. The domains that have been examined and which have proven useful include:

- Executive measures (e.g. oral word fluency tasks, such as controlled oral word association test (COWAT (69); also referred to as FAS (70)), D words (69), Animal Fluency (71), written word fluency ('s' and 'c' words) (57), design fluency (70), Wisconsin Card Sorting Test (72) or California Card Sorting Test (73), Stroop Colour-Word Interference Test (74), and the Trail Making Test (controlling for motor speed by comparing times taken on Parts A and B) (75)). More experimental testing paradigms include delayed alternation/object alternation and tests of social cognition.
- Memory/Learning (e.g. Rey Auditory Verbal Learning Test (76), California Verbal Learning Test-II (77), Warrington Recognition Memory Test (78,79), Wechsler Logical Memory and Visual Reproduction (80), Wechsler Paired Associate Learning (80), Kendrick Object Learning Test (81)).
- Attention/Concentration (e.g. Verbal Serial Attention Test (82), Consonant Trigrams Test (83), Symbol Digit Modalities Test (84), Paced Auditory Serial Addition Task (PASAT) (85), Digit Span (86)).
- Language (e.g. Boston Naming Test (87), Graded Naming Test (88), Pyramid and Palm Trees (89), Peabody Picture Vocabulary Test (90), British Picture Vocabulary Test (91), Test for the Reception of Grammar (92)).
- Visual-Spatial (e.g. Judgement of Line Orientation (93), Benton Facial Recognition Test (94), Block Design (86), Motor-Free Visual Perception Test-Revised (95), Visual Object and Space Perception Battery (96)).

The assessment of premorbid intellectual functioning may be performed (e.g. National Adult Reading Test – Revised (NART-R) (97), North American Adult Reading Test (NAART) (98), Wechsler Test of Adult Reading (WTAR) (99)), although significant dysarthria may confound findings, so demographics-based estimates may need to be used (e.g. from the WTAR). Alternatively, Spot-the-word Test from the Speed and Capacity of Language Processing battery (100,101) could be used, although its utility is reduced in cases of mild/moderate dementia (102). The undertaking of a measure of premorbid functioning will assist the evaluation of whether deficits are specific and likely to have been acquired, rather than being due to premorbidly low levels of functioning (e.g. many executive tests correlate with IQ). If time permits, assessment of current intellectual functioning would be helpful (Wechsler Abbreviated Scale of Intelligence (WASI) (103), Wechsler Adult Intelligence Scale – III (WAIS-III) (86,104)).

The use of a depression scale is recommended (e.g. Geriatric Depression Scale (GDS) (105),

Hamilton Assessment of Depression Scale (106), Beck Depression Inventory-II (BDI-II) (107,108), Hospital Anxiety and Depression Scale (109), the Chicago Multiscale Depression Inventory (110)), recognizing that different scales may yield different estimates of depression (111).

*Diagnostic caveats.* A behavioural disturbance can occur in the context of a delirium, but typically the symptoms of delirium fluctuate while the symptoms of ALS-FTD are relatively stable. Behavioural disturbances and cognitive impairments are seen in both Alzheimer's disease (AD) (71) and vascular dementia (55). Patients with AD have a preponderance of memory disturbances, which often present as an amnesic state, while ALS patients with frontotemporal dysfunction syndrome tend to have relatively preserved memory. Note, however, that executive dysfunction in ALS may interfere with the appropriate retrieval of some information.

*Neuroimaging studies in the diagnosis of a frontotemporal syndrome in ALS.* An extensive array of neuroimaging modalities has been applied to the diagnosis of a frontotemporal syndrome in ALS (1). These include both static (e.g. computerized axial tomography (CT), magnetic resonance imaging (MRI)) and dynamic imaging modalities (e.g. single positron emission tomography (SPECT), MR spectroscopy, functional MR, positron emission tomography (PET)). As independent predictors of the development of a frontotemporal syndrome, these modalities are not yet suitable for clinical use. However, the presence of frontotemporal atrophy, whether defined by CT scan or MR imaging, may be a sensitive early indicator of a frontotemporal lobar degeneration in ALS. More dynamic tests of metabolic function, cerebral perfusion, astrocytic proliferation, or microglial activation remain investigative tools at this time but do show significant promise.

### Axis III

#### *Additional non-motor disease manifestations*

In addition to frontotemporal impairments, patients with motor neuron disease may have other non-motor manifestations. The participants felt that the presence or absence of these non-motor manifestations should also be critically documented. Drawing upon the literature of the hereditary spastic paraparesis (HSP), for those motor neuron diseases in which progressive LMN or UMN dysfunction was observed in isolation, the terminology of a 'pure' motor neuron disease would be appropriate (112). In contrast, in a 'complicated' phenotype, additional disease manifestations can be evident, including extrapyramidal signs (bradykinesia, cogwheel rigidity, tremor), cerebellar degeneration, autonomic dysfunction (abnormal cardiovascular reflexes, bowel or bladder dysfunction), sensory impairment

(decreased vibration, blunting of temperature discrimination) or ocular movement abnormalities (112).

*Axis III recommendation.* Note should be made of specific non-motor manifestations that are distinct from the cognitive and behavioural manifestations.

#### Axis IV

##### *Presence of disease modifiers*

While the average survival in ALS is two to three years after the onset of symptoms, this value is misleading in that survival curves are skewed towards short-term survival (113). There are several disease modifiers that have an impact on survival, apart from specific disease phenotypes. Some patients have an indolent rate of progression with survival greater than 10 years. In general, longer survival is associated with a younger age at symptom onset (<age 45 years), being male, and having limb-onset symptoms in contrast to onset with bulbar dysfunction (114–116). A slight male preponderance tends to be lost with increasing age (117,118). These population characteristics are of some importance in that they can impact on the primary trial outcomes (e.g. the impact of an over-representation in either the treatment or placebo limb of a drug trial of young male patients with limb-onset symptoms thereby conferring an enhanced survivorship). Both smoking and an increased body mass index (greater than predicted for age) have been suggested as risk factors for the development of ALS (119,120), although there is no evidence linking these to disease course.

*Axis IV recommendations.* The following variables should be recorded: age at symptom onset, disease duration (from symptom onset), site of disease onset (bulbar or limb), and gender.

##### *Neuropathological recommendations*

The previous sections speak to the clinical characterization of a frontotemporal syndrome in the context of a motor neuron disease. The intent of these consensus guidelines is to provide a rigorous clinical framework upon which a clinicopathological diagnosis can be built, and as such will include clinical, neuroimaging and genetic information where applicable. While the workshop participants recognized that the neuropathology underlying the frontotemporal syndromes of motor neuron diseases is that of FTLD, it was also acknowledged that the FTLDs are a heterogeneous group of diseases sharing features of frontotemporal lobar degeneration but in which there is also considerable overlap in neuropathological features. Furthermore, the neuropathological classification of a FTLD has become increasingly refined by newer neurochemical and immunohistochemical

techniques (121). This was exemplified in an analysis of 29 brain bank cases which had been previously classified neuropathologically as FTLD and in which the majority of cases were non-tauopathies, with the most common diagnosis that of frontotemporal lobar degeneration (FTLD) with ubiquitin-only immunoreactive neuronal changes (122). Other diagnoses included Pick's disease, FTD with Parkinsonism linked to chromosome 17 (FTDP-17), FTLD (also known as dementia lacking distinctive histopathology – DLDDH), FTLD with motor neuron disease (FTLD-MND), and neurofilament inclusion body disease (NIBD). Rather than be definitive in assigning specific neuropathological terminologies, workshop participants recommended a more descriptive approach in order to provide a foundation upon which to define the FTLD of ALS.

The core of the neuropathological diagnosis of motor neuron disease is the delineation of the motor neuron pathology. This is particularly critical for those patients in whom there is no ante mortem evidence of ALS, but in whom the features of FTLD are found concurrently with one or more aspects of the neuropathology of ALS. As with the clinical criteria for the diagnosis of ALS, there are minimum criteria for the neuropathological diagnosis of ALS (24). There must be evidence of motor system degeneration that includes the loss of anterior horn cells (AHC), brainstem motor nuclei, and the descending corticospinal pathways involved in motor function. This degenerative process is accompanied by a wide array of neuropathological features in which both UMN and either brainstem or spinal LMN are involved.

Among the neuropathological hallmarks of ALS is a variety of intracellular inclusions, including Bunina bodies, ubiquitinated inclusions or skein-like structures, and hyaline conglomerates (123–128). Although none of these findings is pathognomic, many are sufficiently unique to ALS to render the diagnosis of ALS highly likely.

While the full extent of the neuropathological basis of frontotemporal dysfunction syndromes of ALS remains to be defined, for those individuals with ALSci, the neuropathological features are typical of FTLD (16,18), including spongiform degeneration in frontal and precentral gyrus cortical layers II and III with diffuse subcortical gliosis (18,51,129–140). There is neuronal loss in the anterior cingulate gyrus, substantia nigra and amygdala (141). These features should be delineated, if present. Prior to the description of TDP-43 aggregation, the neuropathological hallmark of FTLD in ALS was considered to be the presence of ubiquitin immunoreactive intraneuronal inclusions lacking immunoreactivity to either microtubule associated protein tau or  $\alpha$ -synuclein within the dentate granule cells, the superficial frontal and temporal cortical layers, and the entorhinal cortex. The use of

Table VI. Application of Axis I and Axis II diagnostic classification for ALS.

Heading	Subheadings	Existing, synonymous terms within the literature	Characteristics
Axis I. Motor neuron disease variant ALS	Sporadic ALS	SALS; classic ALS; Charcot disease	A progressive motor system disorder with both upper and lower motor neuron involvement, with the degree of diagnostic certainty further defined by the El Escorial criteria (definite ALS, probable ALS, laboratory-supported probable ALS, possible ALS)
	Familial ALS	FALS	As indicated for sporadic ALS with the additional components: 1. confirmed genetic linkage, or 2. clinical evidence of autosomal dominant, autosomal recessive, or X-linked inheritance
	Western Pacific variant	Lytico bodig	ALS arising with a hyper-endemic region of the western Pacific (e.g. Kii Peninsula, Guam, Rota)
Axis II. Cognitive/behavioural characterization Frontotemporal lobar degeneration with ALS			
ALS-FTD	ALS-bvFTD ALS-PNFA ALS-SD	ALS-dementia (ALS-D)*, FTD-MND	ALS patient meeting either the Neary criteria (51) or Hodge's criteria (2) for FTD ALS patient meeting Neary criteria for PNFA ALS patient meeting Neary criteria for SD
ALSbi			ALS patient meeting at least two non-overlapping supportive diagnostic features from either the Neary criteria (51) or Hodge's criteria (2) for FTD
ALSci			Evidence of cognitive impairment at or below the 5th percentile on at least two distinct tests of cognition that are sensitive to executive functioning
FTD-MND-like			A neuropathological diagnosis in which FTLT is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
ALS-dementia	ALS-AD ALS-vascular dementia ALS-mixed dementia	ALS-dementia (ALS-D)*	ALS with dementia, not typical of FTLT ALS in association with AD ALS in association with vascular dementia
ALS-Parkinsonism-dementia complex		Western Pacific variant of ALS; lytico bodig.	ALS concurrent with dementia and/or Parkinsonism occurring in hyperendemic foci of the western Pacific

\*Note that the term 'ALS-dementia' has been used generically within the literature to imply the presence of any clinical or neuropathological evidence of cognitive or behavioural impairment and thus appears in two synonymous categories. The participants recommend restriction of the use of 'ALS-dementia' to refer to specific dementias.

TDP-43 immunoreactive pathology, including neuronal intranuclear inclusions, cytoplasmic intranuclear inclusions, dystrophic neurites, and oligodendroglial inclusions (142–145), has largely supplanted this.

*Recommendations for neuropathological evaluation.* Where possible, there should be a complete neuropathological evaluation, including brain and spinal cord, with the latter including sections from the cervical, thoracic and lumbar regions (given the high degree of regional variation in ALS pathology). Where degeneration of the corticospinal tracts is not evident on routine haematoxylin/eosin staining, tract degeneration may be identified using immunohistochemical evidence for an inflammatory response (e.g. HLA Dr3, CD68 or Iba1 immunostaining). Degeneration of motor neurons can be assessed using a panel of antibodies, including neurofilament (SMI31 or equivalent staining for high molecular weight neurofilament aggregates), ubiquitin, peripherin and TDP-43.

The evaluation of neocortical and subcortical structures should be robust and include representative sections from the anterior cingulate gyrus, precentral gyrus, superior frontal gyrus, superior temporal gyrus, amygdala, entorhinal cortex, hippocampus, and basal ganglia. Immunostaining should include TDP-43, ubiquitin, p62, tau (including both physiological tau (e.g. 14/46 antibodies) and pathological hyperphosphorylated tau (e.g. PHF1, AT8),  $\alpha$ -synuclein and neurofilament (SMI 31). Where appropriate, antigen retrieval should be utilized. When reported, neuropathological studies should describe, by region, the extent of neuropathological changes, including the presence or absence of superficial linear spongiosis, the degree of neuronal loss, the presence or absence of hippocampal sclerosis (including subtle focal loss of CA1 neurons), and the nature of inclusions present (including dystrophic neurites, neuronal cytoplasmic inclusions, and neuronal intranuclear inclusions). The presence or absence of glial pathology, whether astrocytic or oligodendroglial, should be delineated.

## Summary

Increasingly, the non-motor cognitive manifestations of ALS can be considered to reflect a heterogeneous group of 'frontotemporal dysfunction syndromes' that include cognitive dysfunction (involving a dysexecutive syndrome), behavioural impairment and, in a small proportion, a FTD (Table VI). However, the impairments in the vast majority of these syndromes are relatively subtle and are not characteristic of a fulminant dementia. Consequently, cognitive and behavioural features are often overlooked in a neurological exam of an ALS patient, even among those attuned to their potential existence. Day-to-day variability in decision making,

impulsivity and emotional lability are less critically documented in an individual in whom the devastating nature of the illness mandates a broadly based multisystem and interdisciplinary approach to management. Although the administration of a detailed neuropsychological examination to detect the nuances of a dysexecutive syndrome exceeds the resources of the majority of clinics, in careful studies of cognitive function in ALS such phenomena are frequent. This suggests that the conceptualization and management of ALS as a pure motor system disorder needs a radical overhaul.

There is some urgency to resolving these issues. If the frontotemporal lobar syndromes of ALS are simply intersecting diseases, independent in their biology from 'pure' ALS, then defining what is 'pure' ALS becomes critical to future therapeutic trials in ALS (112) owing to the difference in prognosis with ALS alone versus ALS with frontotemporal impairments. If, however, a frontotemporal lobar syndrome and its attendant biological processes is an integral component of ALS and related motor neuron disorders, then our research focus needs to dramatically shift from understanding a motor system specific disorder, to one in which motor neurons are but the 'canaries in the coalmine' of the demise of the nervous system. Either way, the recognition and acceptance of the presence of a frontotemporal degenerative state in the context of ALS heralds a new direction in our understanding of this disorder.

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## Appendix

This article is based on discussions held at a research workshop entitled 'The Second International Research Workshop on Frontotemporal Dementia in ALS' that was held in 2007 from 10 to 13 June in London, Ontario, Canada. The workshop was sponsored by the ALS Society of Canada, the ALS Association (ALAS), The Windsor/Essex County ALS Society (Canada), and the Michael Halls' endowment for ALS Research (London Health Sciences Centre, London, Canada). Participants in the workshop were as follows:

Chair: Michael J Strong

Steering Committee (in alphabetical order): Lucie Buijn, Denise Figlewicz, Morris Freedman, Gloria M. Grace, Paul Ince, Nigel Leigh, Cathy Lomen-Hoerth, Jeffery Rosenfeld, Susan Woolley.

Participants (in alphabetical order): Peter M. Andersen, Stanley H. Appel, Tetsuaki Arai, Thomas H. Bak, Thomas Brannstrom, Teresa Salas Campos, Richard J. Caselli, Tiffany Chow, Erin Cooper, Lauren Elman, Howard Feldman, Carmen Borrue Fernandez, Karen Findlater, Elizabeth Finger, John K. Fink, Maria Fraraccio, Roberta Friedman, Jeana Frost, Angela Genge, Laura H. Goldstein, May Gohar, Vladimir Hachinski, A. Brett Hauber, Arthur P. Hays, Samantha He, John Hodges, Nancy Hubbard, Saima Humayun, Carlyne Jackson, Keith A. Josephs, Sanjay Kalra, Jonathan S. Katz, Cindy Kersaitis, Andrew Kertesz, Jillian Kril, Cheryl Leystra-Lantz, Ian Mackenzie, Colin McCabe, Ryan McKee, Katie Moisse, Sarah A. Morrow, Jennifer Murphy, Matthew Murphy, Karin Nilsson, J.B. Orange, Stephen Pasternak, Julie Phukan, Eric Pioro, Joost Raaphorst, Janice Robertson, Howard J. Rosen, Ann Rowe, Alicia Salamone, Teresa Sanelli, Masayuki Satoh, Paul E. Schulz, Christopher E. Shaw, Christen Shoesmith, Zachary Simmons, Richard A. Smith, Jennifer Strong, Wendy Strong, Carmela Tartaglia, Bryan J. Traynor, Paul Valdmanis, Leonard H. van den Berg, Kathryn Volkening, Paul Wicks, Shangxi Xiao, Wencheng Yang, Michele K. York, Lorne Zinman.