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Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria

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Declaration of interest

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Abstract

This article presents the revised consensus criteria for the diagnosis of frontotemporal dysfunction in amyotrophic lateral sclerosis (ALS) based on an international research workshop on frontotemporal dementia (FTD) and ALS held in London, Canada in June 2015. Since the publication of the Strong criteria, there have been considerable advances in the understanding of the neuropsychological profile of patients with ALS. Not only is the breadth and depth of neuropsychological findings broader than previously recognised – – including deficits in social cognition and language – but mixed deficits may also occur. Evidence now shows that the neuropsychological deficits in ALS are extremely heterogeneous, affecting over 50% of persons with ALS. When present, these deficits significantly and adversely impact patient survival. It is the recognition of this clinical heterogeneity in association with neuroimaging, genetic and neuropathological advances that has led to the current re-conceptualisation that neuropsychological deficits in ALS fall along a spectrum. These revised consensus criteria expand upon those of 2009 and embrace the concept of the frontotemporal spectrum disorder of ALS (ALS-FTSD).

Keywords

Amyotrophic lateral sclerosis; frontotemporal dementia; neuropsychology; cognition; behaviour; genetics

Introduction

While the core feature of amyotrophic lateral sclerosis (ALS) is a relentless loss of motor function leading to paralysis and ultimately death, the awareness that it can be associated with one or more features of frontotemporal dysfunction has gained increasing acceptance (1). This in part can be traced to the development of international criteria for the diagnosis of frontotemporal dysfunction in ALS in 2009 (Strong criteria) (2,3). These criteria, which incorporated clinical, electrophysiological, neuropsychological, genetic and neuropathological characteristics, recognised that ALS could exist as a pure motor syndrome but that it can coexist with a frontotemporal dementia (ALS-FTD) as defined by the Neary or Hodges criteria (4,5). The criteria further recognised that both behaviour and/or cognitive features, not sufficient to meet criteria for the diagnosis of dementia but sufficient to be detected and/or give rise to impairment, could exist (termed ALS behavioural impairment [ALSbi] and ALS cognitive impairment [ALSci], respectively). The criteria also acknowledged that a small population of patients could develop dementia not typical of FTD (ALS-Dementia).

Since the introduction of the Strong criteria, our understanding of the breadth and impact of frontotemporal dysfunction has grown considerably. With this has come the realisation that the Strong criteria do not adequately recognise impairments in social cognition, language or memory, or the presence of neuropsychiatric symptoms and that these deficits are manifestations of the spectrum of deficits resulting from frontotemporal dysfunction. It is for this reason that we believe that the term frontotemporal spectrum disorder (ALS-FTSD) is most appropriate to characterise the breadth and severity of frontotemporal dysfunction that can be encountered in association with ALS. Moreover, the Strong criteria were not readily adapted to languages other than English and were insufficiently operationalised for easy use in everyday clinical practice or in clinical trials. Equally important, there have been significant advances in the genetics of ALS which have provided novel insights into the pathobiology of ALS-FTSD. Given this, a consensus conference was convened in the summer of 2015 to revisit the 2009 Strong criteria. A consensus development panel approach was utilised, which consisted of a group of content experts (manuscript authors) who identified key topic areas of relevance to developing these revised international guidelines. The expert panel then identified key international content experts who attended and/or presented at the international consensus conference in the summer of 2015. At the end of day 3 of the consensus conference, a round table discussion was held in which all attendees provided input into the key parameters of the revised criteria. Members of the consensus panel formulated the revised criteria, following which the criteria were provided to the conference attendees for commentary and/or revisions.

To that end, this article presents the revised Strong criteria. In doing so, we have addressed several key issues, including the recognition that any criteria must be sufficiently broad to be adequate for research purposes while at the same time be nimble enough to be of utility clinically. As such, beyond expanding the nature of neuropsychological and neuropsychiatric deficits that characterise ALS- FTSD, a key advance in this revision is the inclusion of three levels of complexity or depth of assessment: criteria which can be applied in everyday clinical use (Level I), those which can be utilised for prognostic stratification in clinical trials (Level II), and those which are considered as research intensive with the goal of better defining the nature and extent of FTSD in ALS (Level III) (Figure 1). The criteria are intentionally hierarchical. Level I incorporates tools that can be easily applied at the bedside and are of low statistical complexity, require the least amount of effort to implement, rely upon well-validated tools that have already been applied in the ALS population, and while not requiring neuropsychological support for implementation, would benefit from neuropsychological support for interpretation. Level III are the most advanced criteria and contain the core elements of the Level I testing but are of high statistical complexity, require a maximum amount of time and effort to complete, include research tools not yet validated in a broader ALS population, and would be considered research grade. Level II criteria are anticipated to be applicable to clinical trials where a moderate amount of effort could be expended. Level II criteria also would consist of a minimum dataset for inclusion in case publications. In contrast to Level I, Level II criteria require the engagement of either neuropsychologists or speech-language pathologists to evaluate the testing paradigms, to oversee or manage test administration and to interpret results.

Participants at the consensus conference also agreed that the core features of the diagnostic algorithm, and most specifically the use of the diagnostic axis model, should remain while recognising that specific components would need either modification or expansion. Given this, the revised criteria continue to use the three primary 'diagnostic axes', including: Axis I – defining the motor neuron disease variant; Axis II – defining the cognitive and behavioural dysfunction; and, Axis III – additional non-motor disease manifestations. It was felt that the use of Axis IV which previously was included in order to define the presence of disease modifiers, did not contribute to the characterisation of the FTSD of ALS and thus it has been omitted in the revised criteria presented here.

Axis I. *Defining the motor neuron disease variant*

The phenotypic variability within ALS is significant and includes variability in age of onset, site of onset, the degree of upper verses lower motor involvement, the rate of disease progression and survival. Until such time as the basis for this heterogeneity is elucidated, it is helpful to recognise distinct clinical syndromes that may be characterised by the predominance of upper motor neuron degeneration (e.g. primary lateral sclerosis [PLS]), lower motor neuron neurodegeneration (e.g. progressive muscular atrophy [PMA]), or a combination of both UMN and LMN degeneration which typifies the most frequent phenotype, namely ALS; by the neuroanatomical region primarily affected (e.g. progressive bulbar palsy [PBP]); or by the absence (e.g. monomelic amyotrophy) or presence of left-right symmetry (e.g. brachial amyotrophic diplegia, also known as flail arm, or leg amyotrophic diplegia).

Axis I diagnostic criteria—Since the publication of the original Strong criteria, there has been considerable debate with respect to the minimal criteria necessary to diagnose ALS, particularly with respect to the presence or absence of active denervation as diagnostic of LMN dysfunction. In the original Strong criteria, it was recommended that the El Escorial criteria (revised) be used for the diagnosis of ALS (6–8). In doing so, a multimodality approach toward identification of both UMN and LMN dysfunction using both clinical and electrodiagnostic studies was recommended, along with incorporation of genetic studies as appropriate. Neuroimaging studies were felt to be contributory when structural pathology was considered a diagnostic possibility but were otherwise relegated to being a research tool. The criteria further required the absence of any disease process that might account for the findings. In this context, the diagnosis of ALS required the presence of multisegmental LMN degeneration by either clinical or electrophysiological criteria combined with evidence of UMN dysfunction, with progression. Progressive upper or lower motor neuron dysfunction in a single segment, even if isolated, was considered sufficient for the diagnosis in the presence of a mutation in a known ALS causative gene.

There has since been considerable debate about the genesis of the delay in diagnosing ALS and whether such delays may hamper not only enrolment in therapeutic trials but the ability to impact on the earliest stages of the disease process. This has led to the introduction of alternative diagnostic algorithms, the intent of which are to include greater numbers of patients in clinical studies or trials who may have the potential of developing ALS while not yet fully manifesting the complete syndrome. The Awaji criteria, which emerged from a

consensus conference held in 2006, proposed two fundamental changes to the revised El Escorial (9). The first proposed change was to use both electromyography and clinical data simultaneously to determine the presence of LMN dysfunction. For example, atrophy in an ulnar innervated C8 muscle along with evidence of LMN pathology in the deltoid muscle, would be sufficient to declare the limb/region affected. The second proposed change was to consider fasciculation potentials as evidence of ongoing denervation, equivalent in importance to fibrillation potentials. While controversy has arisen over the notion that fasciculations represent ongoing denervation, there is greater agreement that unstable and complex fasciculations should be accorded greater significance. The Awaji criteria have been shown to have a higher sensitivity than the El Escorial criteria (revised) while maintaining the same specificity, with the diagnostic benefits being most apparent in the bulbar-onset and limb-onset patients (10–12). This increased sensitivity, however, is gained in large part by the combination of two El Escorial criteria (probable and laboratory supported probable) into a single category. The introduction of a ‘possible’ diagnostic category to the Awaji criteria was of particular benefit in enhancing the early diagnosis of ALS and more specifically in the limb-onset subgroup (13).

More recently, the El Escorial criteria have been revisited in an effort to accommodate a postulated broader ALS phenotype (14). The revised iteration of the criteria proposed that the diagnosis of ALS would require, at minimum, progressive UMN and LMN deficits in at least one limb or region (previous possible ALS) or lower motor neuron deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, lumbosacral). The EMG findings needed to include neurogenic potentials and fibrillation potentials and/or sharp waves. In this scheme, restricted phenotypes of ALS would now be considered as including progressive bulbar palsy, flail arm and flail leg syndrome, progressive muscular atrophy and primary lateral sclerosis. In the context of the flail arm and flail leg syndromes, as well as progressive muscular atrophy, the diagnosis of ALS could be rendered in the absence of evidence of UMN dysfunction. It was noted, however that the modifications of the El Escorial criteria as proposed by Ludolph et al. (2015) were as yet to be validated in longitudinal studies, and in particular the inclusion of pure LMN syndromes, as being equivalent to a diagnosis of ALS.

The role of biomarkers in the diagnosis and monitoring of progression in ALS continues to evolve, although to date, no markers specific to the presence of frontotemporal dysfunction have been validated. Thus, while there is evidence to suggest that a number of biomarkers within either cerebrospinal fluid or blood may prove to be of value in the diagnostic work-up of ALS patients with or without frontotemporal dysfunction, including high molecular weight neurofilament, phospho-tau (including measures of total tau), TDP-43, APOE ε2 and beta-amyloid are not yet ready to be included in Level I diagnostic work-up (15–21). Furthermore, while it is increasingly likely that proteomic profiling of CSF will enhance the sensitivity and specificity of biomarker utilisation in the diagnosis when used either independently or within a broader array of investigations including MR imaging (22,23), such testing should remain within the Level III work-up although a restricted number (e.g. pNFH, phospho-tau, TDP-43, APOE ε2) could be considered in Level II.

Axis I genetic diagnosis—Since the publication of the original consensus criteria, significant advances have been made in our understanding of the genetic underpinnings of ALS; there are now over 17 Mendelian variants known to be associated with ALS that are considered causative (Table 1). In addition to these genes, an ever-expanding list of disease-associated or disease-modifying genes are being discovered (Supplemental Table 1). While these discoveries are helping to advance our understanding of ALS, they also add substantial complexity in the clinical realm. While genetic characterisation of patients with ALS and ALS-FTSD is encouraged, it is critical to remember that the identification of a pathogenic variant in an ALS-causing gene does not imply the presence of disease. Moreover, while the term 'familial' remains useful in describing the presence of a family history (i.e. at least two affected biological relatives) and as a surrogate for the likelihood of identifying a genetic cause of disease, it is important to remember that all genes implicated in familial forms of ALS also have been found to harbour mutations in a small subset of patients with apparently sporadic ALS. Moreover, by virtue of factors such as recessive inheritance, compound heterozygosity, de novo mutations, misdiagnosis, small sibship size, reduced penetrance, lack of family information, including paternity, etc., a family history may frequently be lacking in genetic forms of disease. The term 'familial' therefore should not be used interchangeably with 'genetic'(24). Conversely, given a lifetime risk of ALS, which approximates 1:350 for males and 1:400 for females, coincidental familial clustering is a realistic consideration among pedigrees with only two affected individuals which might otherwise be considered to be clinical examples of Mendelian inheritance (24).

Among ALS-disease causing genes, there are several that bear specific mention because their presence is disproportionately associated with frontotemporal dysfunction in ALS, sufficient to warrant genetic testing among those individuals with frontotemporal dysfunction regardless of the presence or absence of a family history. The prototypic gene amongst these is represented by the pathological hexanucleotide repeat (GGGGCC) expansions of C9*orf*72, which is the most common genetic modification affecting FALS (60–70%) as well as those afflicted with familial FTD (approximately 18% of cases). The presence of cognitive impairment in patients carrying a C9*orf*72 expansion is several-fold greater than those without (40–50% vs. 8–9%, respectively) (25). In rare instances in which ALS patients present with psychosis and marked lack of insight, there is also a higher likelihood of harbouring the pathological C9*orf*72 expansion (26).

Axis I recommendation

The classification of frontotemporal dysfunction in ALS should be hierarchical and begin with a description of the motor neuron disorder/syndrome.

While consensus has not yet been achieved with respect to the use of clinical syndromic terms, we perceive value in the use of terms such as progressive muscular atrophy, upper motor neuron predominant ALS and progressive bulbar palsy, for example, and recognise that the clinical syndrome may evolve over time. Such terminology is appropriately used in the clinic (Level I), in clinical trials (Level II) and as part of the broader research endeavour (Level III). Quite distinct from this syndromic nomenclature, however, is the use of diagnostic criteria such as the revised El Escorial and Awaji criteria for clinical trials (Level

II) and research purposes (Level III). It is recommended that patients diagnosed with ALS should fulfil either the El Escorial criteria (revised) or the Awaji criteria (revised).

Genetic testing is recommended when a family history is present (by which we mean that at least one other biological relative has been diagnosed with ALS or FTD), as the El Escorial criteria require only progressive upper or lower motor neuron dysfunction in the presence of a mutation in a gene known to cause ALS. We recommend that the term 'genetic ALS' be used instead of 'familial ALS', especially when a genetic cause of disease is identified despite the absence of a family history. Appropriate genetic counselling should always be provided. For clinical trials (level II) and for research purposes (level III), a full genetic analysis (either a panel of genes established to cause ALS (Table 1)), or whole exome/genome sequencing) is encouraged, and genetic counselling provided whenever genetic test results will be shared with the patient.

Axis II. Defining the neuropsychological deficits

The Strong criteria recognised the potential presence of FTD in ALS and for those patients not reaching threshold for a full FTD diagnosis, also provided a means of classifying the presence of cognitive or behavioural involvement – ALSci and ALSbi, respectively. Since the publication of the consensus criteria in 2009, however, developments in the field have necessitated the revision of these definitions. First, increasing evidence has accrued as to the heterogeneity of cognitive impairment in ALS. Thus, while previous emphasis had been placed on executive dysfunction, there is now evidence that language dysfunction may be as, if not more, common and can occur in patients without executive dysfunction (27,28). Deficits in social cognition also have been highlighted, although it is not entirely clear whether social cognition deficits are completely independent of executive dysfunction in ALS (29–36). Additionally, while the original ALSci and ALSbi classifications have been borne out by cluster analysis, it has been suggested that other cognitively-impaired patients cannot be classified according to the original criteria (36). There is also some controversy (to be considered below) about the role of memory dysfunction in the classification of cognitive impairment in people with ALS. Secondly, revised consensus criteria for the diagnosis of behavioural variant FTD (bvFTD) highlight the need for revising the current consensus criteria (37).

Our aim, therefore, is to revise the previous classifications of cognitive and behavioural involvement in ALS to take into account the extended evidence base of potential deficits that may need to be considered in arriving at a classification of impairment and to account for the increased knowledge and heterogeneity of impairment profiles. First, we examine the developments below in specific cognitive domains that have given rise to this need for revision; then we consider revisions to the classification of behavioural and neuropsychiatric symptoms and provide recommendations regarding testing paradigms (Supplemental Table 2).

Neuropsychological domains

a) Executive dysfunction and Social Cognition: Executive dysfunction is characteristic of the profile of cognitive deficits in ALS (38), a finding that has been confirmed through

population based studies (39) and meta-analyses (40). The signature executive functions deficit is demonstrated through assessment of verbal fluency (41–44). This is a commonly used clinical instrument, involving the generation of lists of words beginning with a specified letter (letter fluency) or semantic category (e.g. animal fluency), the former being the more widely recognised marker of impairment in ALS. Letter fluency involves the interaction of a number of cognitive processes, specifically executive processes of initiation, strategy formation, set-shifting, sustained attention and inhibition, but in addition language functions involved in word retrieval. It has been shown that poor letter fluency in ALS is related to executive dysfunction (41). Deficits on letter fluency tasks occur early in the course of the disease (45), correlate with ocular movement abnormalities (46), and are more prominent in but not restricted to patients with pseudobulbar palsy (42). Based on limited published literature, impaired verbal fluency does not appear to be a feature of SOD1-ALS (47).

Verbal fluency deficits in ALS also have been shown to be a marker of frontal lobe dysfunction, in particular the dorsolateral prefrontal cortex and inferior frontal gyrus, as demonstrated with functional and structural neuroimaging (48–51). Performance in verbal fluency can be affected by motor disability with difficulties in writing or in speaking, which magnify deficits. This has necessitated the development of the Verbal Fluency Index that controls for physical motor impairments by incorporating a timed condition in which the person either reads or copies previously generated words and from which an estimate of the average time taken to think of each word is calculated. Using the Verbal Fluency Index, deficits have been repeatedly demonstrated that are independent of motor disability (41).

Executive dysfunction in ALS has been revealed across a range of tests including readily available clinical measures and experimental procedures. Deficits have been reliably shown on standard assessments measuring attention monitoring and switching, rule deduction, and cognitive flexibility, such as the Trail Making Test or the Wisconsin Card Sorting Test (52,53). A recent meta-analysis of studies using the latter revealed that patients with ALS made more errors (continuing to choose the previously correct rule) and took longer to learn new rules (54). Similar impairments have been shown on other card sorting concept formation tasks such as from the Delis-Kaplan Executive Function System Sorting Test (34,55). Furthermore, deficits have been revealed on tests highly reliant on manipulating concepts in working memory such as reverse digit span or the N-Back task and most recently on tests of divided attention in which two tasks are undertaken concurrently, such as visual processing speed task and digit recall (51).

Performance on standard neuropsychological tests of executive function are mostly mediated by functions of the dorsolateral prefrontal cortex, but studies have also revealed deficits using experimental measures more dependent on orbitomedial prefrontal functions. ALS patients have shown abnormal risk taking on the Iowa Gambling Task (29). Deficits have been shown using two more ecologically valid measures of executive functions where patients demonstrate difficulties in reasoning, coordinating rules and mental heuristics – the Medication Scheduling Task (56) and the Holiday Apartment Task (57).

Social cognition has recently become a focus of investigation in ALS, having been a notable feature of the FTD profile for some time. A recently updated meta-analysis noted the new addition of social cognition deficits as integral to the cognitive profile in ALS (40). Nevertheless, there remains some debate as to the source of the deficits in social cognition with some studies showing an independence of executive dysfunction and others not (34,57). Patients with ALS show deficits across a range of social cognitive processes including altered emotional processing and reduced capacity to recognise emotional (particularly negative) facial expressions although this is more likely in those with ALS-FTD (29,58–60). ALS patients also have difficulty on tests specific to Theory of Mind, in which the thoughts or beliefs of another are inferred. One-third of patients have been shown to be impaired at detecting a faux pas (57) and such difficulties have been related to specific problems with understanding social situations (30).

A fundamental process in social cognition is the interpretation of the direction of eye gaze as assessed through the Judgement of Preference Task (29). The finding of a deficit on this task was extended to reveal impaired affective and to a lesser extent cognitive Theory of Mind (35).

In patients meeting criteria for ALS-FTD, executive/social cognition deficits are a virtually ubiquitous feature and cover the range of difficulties described above.

b) Language dysfunction: The last two decades have seen a rising interest in defining the prevalence and the nature of the language impairment in ALS (27,39,61–64). The extent to which impairments in word retrieval, sentence processing, spoken language, and pragmatic language are ‘pure’ language deficits versus downstream manifestations of other disrupted cognitive domains (e.g. executive function) continues to be debated. Not all patients with ALSci present with obvious language impairments (65). Moreover, language deficits in ALSci can be challenging to disentangle from motor speech deficits and also from ALS-FTD, which can present similarly to semantic and non-fluent variants of primary progressive aphasia. Notwithstanding these diagnostic challenges, an estimated 35-40% of individuals with ALS but no dementia may demonstrate language impairments (27). These language impairments are dissociable from motor and executive function impairments (28,62,66–69), raising the possibility that impairments in language may both contribute to the profile of ALS and also occur as part of a mixed cognitive profile that includes executive function impairments or social cognition impairments (27,36).

In ALS, word retrieval for nouns and object knowledge are often reported as mildly impaired compared with controls (28,49,62,70,71). In contrast to nouns, verb naming and action verb processing deficits are a more consistent finding in ALS (27,28,62,69,71–73). Verb deficits in ALS are often associated with atrophy in the dorsolateral prefrontal cortex and motor cortices (69,71,72). As such, they may be an important marker of cognitive impairment in ALS. While the theoretical underpinning of the object-action (i.e. noun-action verb) dissociation observed in ALSci remains unclear (73), these findings suggest that the assessment of word retrieval impairments may benefit from including tests that measure the retrieval and comprehension of both nouns and action verbs.

Sentence processing difficulties also have emerged as a prominent feature in the language profile of ALS (27,28,72,74,75). Recent work suggests that syntax and sentence processing deficits in ALS probably exist on a spectrum with modest impairments emerging in ALS that progress in severity for patients with ALS-FTD (75). While more research is needed, deficits in syntax processing have been dissociated from both executive function and motor speech impairments (28), suggesting that syntax processing impairments may contribute uniquely to the language profile of ALS.

There is emerging evidence that, in addition to sentence processing deficits, individuals with ALS also produce sentences with a greater number of grammar and morphology errors compared to healthy adults (28,62,66). Grammatical errors reported from studies of spoken language in ALS include incomplete utterances (28,66,68), missing determiners (66), and verb phrase errors (66). Productivity deficits also characterise the spoken language of individuals with ALS including reduced utterance length and lower total word output, features that are probably related to the motor speech and respiratory challenges in ALS (28,67,68). Beyond grammar and productivity impairments, other linguistic and pragmatic aspects of spoken language are affected in ALS including informativeness (e.g. fewer content or information words in proportion to the total words produced) (68,76); semantic and verbal paraphasias (28,68); poor narrative coherence and cohesion (66); and impaired topic management (76). While it remains an evolving area of research, investigators have reported impaired pragmatic language in ALS including figurative and non-literal language processing, findings that are often attributed to frontal lobe dysfunction (76).

Collectively, the research over the last decade underscores the importance of considering language impairments in the profile of ALSci. Although analysis of spoken language tasks may be more challenging for typical clinical environments, due to their more labour intensive analyses, clinicians and researchers can glean much about the profile of language impairments in ALS using a number of available standardised instruments (Supplemental Table 2).

The relationship between language impairment and ALS-FTD also is incompletely understood. Progressive non-fluent aphasia (PNFA) and semantic dementia (SD) are clinical forms of frontotemporal lobar degeneration incorporated within previous diagnostic criteria (5). Both PNFA and SD have been reported in association with ALS (77–80). On the other hand, specific language problems, such as in syntactic comprehension, are reported to be common in patients meeting behavioural criteria for ALS-FTD (75). Criteria for ALS-FTD need to recognise that language problems play a contributory role.

c) Memory: Memory deficits in ALS have been studied extensively. However, in the current recommendations, isolated memory impairment does not meet the criteria for a diagnosis of ALSci. The exclusion of memory dysfunction from the current criteria relates in part to the lack of consensus about the characterisation of memory deficits in ALS. Study results are wide ranging and have identified impairments in encoding (81–83), immediate or delayed recall (39,78,81,83–85), recognition (86), or the involvement of a combination of memory processes. Other studies suggest intact recognition memory (39,83,87).

An updated meta-analysis in ALS showed a small effect size for delayed verbal memory as well as executive dysfunction, with larger effect sizes for other domains (fluency, language and social cognition) (40). Although delayed verbal memory recall was associated with a greater effect size than visual memory (40), visual memory deficits have been detected (78). Memory deficits are detected in ALS patients without dementia that correlate with grey matter hippocampal volumes (85) and memory scores may differ significantly from controls even in cognitively-normal ALS patients (78). ALS patients with baseline cognitive impairment demonstrate decline in verbal delayed recall when studied longitudinally (84).

Of importance for further understanding why isolated memory involvement should not be used to classify ALSci, memory impairment in ALS rarely occurs in isolation (4%), which is a comparable rate to that seen in controls (39). The association between executive dysfunction and memory impairment in ALS is asserted repeatedly (78,81– 83,86,87). Variables such as selective attention and mental control explain substantial variance in memory scores. Interestingly, memory deficits are the least common comorbidity in ALSci patients who present with executive dysfunction (39).

With respect to the broader implications of detecting memory impairment in people with ALS, a population based study detected Alzheimer's disease (AD) in 1.9% of ALS patients, compared to 13.8% of the sample who had FTD (39). In a study of 279 ALS patients (78), <2% met diagnostic criteria for AD, a frequency lower than the national rate of AD in 4% of the US population of adults below age 64 years (88). In the ALS study, similarities in cognitive performance across cognitive diagnostic subgroups suggested different levels of severity within the same progressive disease subsumed by executive dysfunction. The results did not support the presence of discrete subtypes (i.e. an amnestic subtype). Qualitative differences in memory distinguish ALS patients from patients with AD (83) and those with the AD prodrome of mild cognitive impairment-amnestic type (86).

Although isolated memory impairment does not qualify for the diagnosis of ALSci, memory impairment may nonetheless be problematic for patients, particularly for those in the older age segment of its distribution. To better understand its nature, assessment of memory in ALS should also analyse domains of attention, language, and executive functioning and age-related changes in the speed of processing. Ideally, research studies investigating memory should analyse multiple variables such as encoding, storage, recall, processing speed, and recognition rather than summarising a single memory composite score, which may obscure the understanding of the specific memory deficit (86). As with any clinical evaluation, memory assessment in ALS should consider alternative conditions that result in memory impairment and factors such as respiratory muscle weakness that may give rise to nocturnal hypoxaemia. Supplemental Table 2 provides a list of screening measures and comprehensive memory tests that can be used in the ALS population.

d) Behavioural changes and neuropsychiatric symptoms: Apathy is the most frequently identified behaviour symptom in ALS, detected in up to 70% of patients (89–95). There is not a clear link to specific ALS phenotypes, apathy being pervasive, and severe apathy being linked to poorer prognosis in ALS (96). ALS patients may present with other types of behaviour change including disinhibition, loss of sympathy/egocentric behaviour,

perseverative and stereotyped behaviour and a change in dietary habits, although not as commonly as apathy (91,97,98).

When assessing behavioural change in ALS, it is important to consider potential confounds of respiratory insufficiency, physical disability and psychological reactions to the disease including mood. Reports from family members or friends are essential, especially in light of the patient's lack of insight. Baseline/premorbid psychological and behavioural status must be determined in order to assess whether behavioural abnormalities are 1) new; 2) associated with the time of onset of ALS (recognising 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. In turn, the distinction between apathy and depression is of great relevance not only for the diagnosis of ALSbi, but also for the clinical management of depression (when present) and provision of family support.

It is important to acknowledge that these behavioural symptoms often coexist with deficits in cognitive domains (see ALScbi; see Table 2). In addition, ALSbi and ALSci can coexist with different levels of severity (99–101). In some patients the combination of behavioural and cognitive changes are sufficient to meet criteria for ALS-FTD.

Behavioural changes and neuropsychiatric symptoms have been merged into one category to align bvFTD current criteria with current research findings, as indicated in Supplementary Table 3.

Axis II recommendations

Since the introduction of the Strong criteria, several reliable screening and assessment tools have been developed with which to describe the cognitive, behavioural and language profile of an ALS patient. These tools have been validated and are readily applied in the clinical setting, allowing for brief screening or testing that can be introduced efficiently into the clinic as an indicator of those ALS patients who may require more intensive study (Supplemental Table 2). As such, therefore, it is recommended that each patient receive a screening assessment as a component of a Level I evaluation and, if impaired, that further testing is warranted.

Screening and brief assessments.—Screening assessments are designed first to identify those individuals who have evidence of frontotemporal dysfunction, and secondly, to provide some degree of differentiation as to the type of dysfunction. Where ALS screening tests are administered, ALSci is identified on the basis of the published cut-off scores. The advantage of using ALS screening tests such as the ECAS and ALS Cognitive Behavioural Screen (ALS-CBS) is that the identification of ALSci may otherwise be based on individual tests of variable levels of complexity, thereby contributing to the heterogeneity of identified samples. While both of these tools allow for the identification of ALSci, where further description of the extent of frontotemporal dysfunction is desirable, patients can then

be assessed in greater detail using the tests proposed in Supplemental Table 2. To that end, it is recommended that either the ECAS or the ALS-CBS be administered to all patients.

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS).—ECAS is a multidomain brief assessment developed for use within the clinic or home visits by non-neuropsychology health professionals (102,103). It assesses a range of functions typically affected in ALS (ALS-Specific: Fluency, Executive Functions, Language Functions) including newly recognised deficits in language and social cognition. In addition, it assesses functions that are not typically affected in ALS but are common in disorders of older adults (ALS Non-specific: Memory, Visuospatial Functions). The ECAS also includes a separate semi-structured behaviour interview that should be undertaken with an informant/caregiver separately from the patient and is based on the five key behavioural domains for diagnosing FTD (see above) using the most recent diagnostic criteria (37) and can therefore be used to aid in the diagnosis of behavioural variant FTD.

The cognitive tests were specifically designed to allow for verbal and motor disability, incorporating the Verbal Fluency Index, and the whole assessment can be undertaken in either spoken or written format. The screen has been validated against extensive neuropsychological assessment and shows good sensitivity (85%) and specificity (85%) to cognitive impairment in ALS patients without dementia (104). In the English versions, abnormality cut-off scores were 105/136 for ECAS-Total Score and 77/100 for ALS-Specific Score. A five-point borderline range (105–110) and (77–82) produced optimal values maximising sensitivity without a significant reduction of specificity and is recommended particularly for highly educated patients. Additionally, the ECAS has been validated in German (104), Italian (105) and Chinese (106) and shows convergent validity with other general cognitive screening tools, including the Frontal Assessment Battery and the Montreal Cognitive Assessment. The ECAS has been translated into a number of other languages and adapted for a North American population.

ALS Cognitive Behavioural Screen (ALS-CBS).—The ALS-CBS (107) was developed as a quick, practical tool to aid in the identification of ALSci, ALSbi, and FTD in the clinical setting. It includes a cognitive section and a caregiver questionnaire. It has high concurrent validity with other ALS-specific measures (44) and has excellent accuracy (107). High inter-rater reliability and ease of use was demonstrated in a large, multicentre study (44). The ALS CBS has been translated into six languages and it has been validated in Portuguese (108) and Spanish (109). It is freely available and non-copyrighted, as is ECAS.

The ALS-CBS was developed to minimise motor or speech production involvement so patients can be tested during later stages of the disease. Responses can be provided verbally or in writing and can be generated with speech output devices or communicated with eye movements or mouthing. It can be administered by any clinical staff member, and requires approximately 5 min to complete. The cognitive section measures attention, concentration, working memory, fluency and tracking. Only the verbal fluency item is timed. Certain cognitive items were chosen based on research that identified an association between errors made on specific items and the severity of cognitive impairment in ALS. Scoring combines correct responses minus deductions for errors, with a total possible score of 20. Lower

scores reflect greater impairment. Optimal cut-off scores were determined in the initial validation study (107). A cut-off of ≤10 for the cognitive section achieved 100% accuracy for identifying FTD in the study of ALS patients diagnosed with dementia based on a comprehensive neuropsychological battery. Scores at or below this cut-off raise strong suspicion of FTD and should prompt further assessment to confirm the diagnosis. A cut-off score of ≤16 suggests any cognitive impairment (either ALSci or ALS-FTD), and a score of ≥17 is recommended to exclude cognitive impairment.

The behavioural section comprises a 15-item Likert scale questionnaire completed by an inform- ant and assesses change since disease onset. Behavioural domains were selected to assess a variety of abnormalities known to occur in ALS and FTD, including alterations in empathy, personality, judgment, language, and insight. Total scores range from 0 to 45; lower scores indicate more pathology. For the behavioural section, a cut-off of ≤32 achieved 86% accuracy for correctly classifying ALS patients with FTD and a score of ≤36 best detects any behavioural impairment (ALSbi or ALS-FTD). Scores above ≥37 are suggestive of normal behaviour.

Domain-specific recommendations

ALS with cognitive impairment (ALSci)—A diagnosis of ALSci depends on evidence of either executive dysfunction (including social cognition) or language dysfunction or a combination of the two.

Executive impairment is defined as:

1. Impaired verbal fluency (letter). Verbal fluency deficits must control for motor and/or speech impairments (41) to be valid.

   OR

2. Impairment on two other non-overlapping measures (see below) of executive functions (which may include social cognition).

Language impairment is defined as:

1. Impairment on two non-overlapping tests (which could include pragmatic function).

As the investigator or clinician elects to move to a higher level of complexity or depth of assessment (i.e. Level II and III; see Supplemental Table 2), impairment on individual measures (not screening tests) is defined as a score falling at or below the 5th percentile, compared to age- and education- matched norms. Deficits should not be better accounted for by the person's premorbid intellectual level or native language, although this comparison might be best interpreted within a specialist clinical neuropsychological assessment. At both Level II and III studies, carefully matched control groups will help inform detection of impairment. In addition, at both Level II and III studies, a neuropsychologist and a speech language pathologist are considered mandatory to assist with the administration and interpretation of the test results. Where individual assessment tools (rather than a screening or brief assessment battery) are used, the identification deficits on non-overlapping measures should be guided by the following considerations: measures of impairment should not be

derived from the same test; and, tests on which impairment is identified should not involve a similar format (e.g. investigators would not include impairment on two tests of attention-inhibition, or concept formation or two tests of naming, see Supplemental Table 2).

Although the above criteria will potentially exclude people who have a selective breakdown on only one executive function (other than verbal fluency) or language test, we are concerned not to over-diagnose ALSci.

Clinical assessments and research studies should rule out confounding factors that may or not may be associated with ALS. A comprehensive assessment should rule out other cognitive presentations. Assessment procedures should control for bulbar speech production impairments (dysarthria) and motor deficits wherever possible so that deficits are not primarily identified on the basis of timed tests. Where serial measurements are available, a decline from baseline of at least 1.5 sd on a measure might also be considered to indicate (new) impairment, although caution also has to be taken to evaluate the likely effect of repeated testing on performance where no new deficits are elicited, especially where parallel versions of tests are not available. For this reason, control groups are vitally important in clinical trials and longitudinal research studies.

ALS with behavioural impairment (ALSbi)—While both the ECAS and ALS-CBS contain behavioural measures, the delineation of the behavioural characteristics can be further gained through either the Motor Neuron Disease Behaviour Scale (MiND-B) (110), the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALSFTD-Q) (111) or the Frontal Behavioural Inventory – ALS Version (FBI-ALS) (44,112). In each, the diagnosis of ALSbi is dependent on evidence from informant interviews and clinical observation of alterations in behaviour that cannot be accounted for by disease-related limitations, psychological reaction to the ALS diagnosis, a premorbid personality disorder, the presence of a comorbid psychiatric disorder (e.g. anxiety or depression) or pseudobulbar affect.

MiND-B is a brief assessment (nine items) completed by a proxy informant who knows well the person diagnosed by ALS. It includes three domains: disinhibition, stereotypical behaviour and apathy. It is derived from the Cambridge Behavioural Inventory Revised, which was originally developed to be sensitive for FTD. The MiND-B was validated in ALS with a data driven approach. Two cut-offs to distinguish ALS from ALS plus (defined in MiND-B as patients with either ALSci or ALSbi) or FTD are available: 35/36: 90% sensitivity and 50% specificity and 33/36: 81% sensitivity and 75% specificity.

The ALSFTD-Q is a caregiver questionnaire that was developed to measure abnormal behavior change in ALS and avoid response bias due to physical disability. The 25 items were selected on the basis of a systematic review of the ALS literature and cover apathy, irritability, disinhibition, emotional lability and altered food preference. It shows good construct validity against other measures of behaviour change (Frontal Systems Behaviour Scale and Frontal Behaviour Inventory) and discriminates well ALS-FTD from ALS and controls. The cut-offs for this scale provide distinctions between mild behavioural symptoms (ALSbi) and more severe symptoms, although not for a particular behaviour.

Loss of insight must be established by comparing patients' and informants' accounts of behavioural change and this may require clinical opinion. One means of operationalising insight is to analyse standardised score discrepancies between patient self-reports and caregiver reports of patient behaviour. One study determined that ALS-FTD patients report significantly less behavioural change over time compared to their caregivers, and report fewer behavioural abnormalities overall (113). The extent of patient-caregiver discrepancy was not documented in ALS patients without dementia.

On the basis of information gained from a knowledgeable informant, a diagnosis of ALSbi is defined by:

1. The identification of apathy with or without other behaviour change.

   OR

2. The presence of two or more of the following behavioural symptoms: a) disinhibition, b) loss of sympathy and empathy, c) perseverative, stereotyped or compulsive behaviour, d) hyperorality/dietary change, e) loss of insight (see above), f) psychotic symptoms (e.g. somatic delusions, hallucinations, irrational beliefs). The behavioural features a–d, together with apathy, are drawn from current criteria for behavioural variant FTD (37).

The ECAS behaviour screen provides a checklist of symptoms from the diagnostic criteria that are marked as present or not. Other ALS-specific behavioural screens like the ALS-CBS and MiND-B provide published cut-off scores which are used to define ALSbi.

ALS with combined cognitive and behavioural impairment (ALS-cbi)—This new classification captures patients who fulfil criteria for both ALSci and ALSbi.

ALS with frontotemporal dementia (ALS-FTD)—A diagnosis of ALS-FTD is made when patients with ALS also show behavioural/cognitive changes in keeping with FTD.

A diagnosis of ALS-FTD is defined by:

1. Evidence of progressive deterioration of behaviour and/or cognition by observation or history

   AND

2. The presence of at least three of the behavioural/cognitive symptoms outlined by Rascovsky et al. (37).

   OR

3. The presence of at least two of those behavioural/cognitive symptoms, together with loss of insight and/or psychotic symptoms

   OR

4. The presence of language impairment meeting criteria for semantic dementia/ semantic variant PPA or non-fluent variant PPA, as defined by Neary et al. (5) or

Gorno-Tempini et al. (114). This may coexist with behavioural/cognitive symptoms as outlined above.

Neuroimaging studies in the diagnosis of a frontotemporal spectrum disorder in ALS—Neuroimaging continues to provide unique in vivo pathological insights into the expanding clinical and molecular syndrome of ALS (115). While frontotemporal cerebral atrophy may be noted during CT or MRI performed as part of the routine clinical work-up of ALS patients, both are insensitive and in the clinical setting a subjective assessment must take into account normal age-related atrophy. SPECT, long-recognised to be capable of demonstrating reduced frontal uptake in cases of ALS associated with dementia (116), also lacks essential sensitivity for ALS cases with less marked cognitive or behavioural impairment. Automated assessment tools for detecting more subtle grey matter volume changes on high-resolution T1-weighted MRI (voxel-based morphometry), or frontotemporal white matter tract projections (diffusion tensor imaging), are not yet applicable to the individual patient. However, these more advanced structural MRI sequences continue to advance toward this ultimate aim (117), perhaps through combination with functional MRI connectivity measures (118).

More marked patterns of basal ganglia and cerebellar structural MRI change have been noted in ALS patients carrying pathological hexanucleotide expansions in *C9orf72* compared to apparently sporadic ALS cases (119,120). Furthermore, widespread structural MRI changes have been reported in studies involving pre-symptomatic C9orf72 mutation carriers (121,122), offering the potential to study the evolution of broader cerebral pathology in ALS at a much earlier stage.

Positron emission tomography (PET) imaging continues to provide substantial knowledge regarding the anatomic and cellular topography of neuronal dysfunction in ALS and, increasingly, markers of non-neuronal involvement as critical mediators of the disease process. Advances in neuroimaging and the attendant increase in our understanding of the neural networks or connectome are beginning to provide greater clarity as to the nature of FTSD, and in particular the concept of FTSD as a disconnection syndrome with individual clinical phenotypes predicated on the nature of the neural network damage. Providing crisp clinical correlates to such neuroimaging advances underlies a significant proportion of the impetus to revising the criteria.

Axis III. Additional non-motor disease manifestations

As with the 2009 Strong criteria (2), it is recommended that note be made of the presence or absence of non-motor manifestations, including extrapyramidal signs (bradykinesia, rigidity, tremor), cerebellar degeneration, autonomic dysfunction, sensory impairment disproportionate to age or ocular movement abnormalities.

Axis III recommendation

Members of the Consensus Committee made no changes to this recommendation. As such, it is recommended that observations should be made of specific non-motor manifestations that

are distinct from the neuropsychiatric and neuropsychological manifestations of frontotemporal dysfunction.

Axis IV. Presence of disease modifiers

In reviewing this recommendation, members recognised that the majority of modifiers of the neuropsychological features of ALS would be captured within Axis I studies of the molecular genetics or within the specific tests of neuropsychology. All studies will contain the key variables of site of disease onset, gender and age. Hence, the view of the members of the consensus conference was that Axis IV was no longer required within the diagnostic algorithm of the frontotemporal spectrum disorders of ALS.

Axis IV recommendation

As noted above, members recommend that Axis IV is no longer required and be supplanted by information gained through the assessment of Axis I and II.

Neuropathology recommendations—The fundamental recommendations of the Strong criteria with respect to neuropathological diagnosis of ALS-FTSD remain unchanged. However, in keeping with the consideration of levels of complexity, it is recognised that not all cases will be examined as extensively as was proposed, although this remains the goal. As such, a complete neuropathological examination should be considered to be integral to the diagnosis, including examination of the brain and complete spinal cord given the high degree of regional variability of the disease and recent work suggesting a focal onset followed by spread (123–125). Spinal cord sections should continue to include cervical, thoracic and lumbar regions. Due to the pathognomonic involvement by p62 and dipeptide repeat (DPR) pathology in C9FTD/ALS, the cerebellum must be included in the analysis (126,127). In all cases, the degree of involvement of both the UMN and LMN should be ascertained and, for the former, when not clearly evident on routine haematoxylin/eosin staining, identified using immunohistochemical evidence for a microglial neuroinflammatory response (e.g. HLA-DR3, CD68 or Iba1) and astrogliosis (GFAP), and special stain (e.g. Luxol-fast blue/Nissl) for secondary myelin loss. With the increasing recognition that neuronal cytoplasmic and nuclear inclusions within degenerating motor neurons in ALS can be composed of a broad range of cytoskeletal proteins and RNA binding proteins, often with multiple proteins depositing within the same degenerating motor neuron (128), there is now an extensive array of antibodies with which to confirm the presence of ALS. Most commonly, however, immunostaining with antibodies directed towards protein ubiquitination (ubiquitin, p62), TDP-43 and FUS and demonstrating neuronal or glial inclusions would suffice for the diagnosis of LMN involvement in ALS. When full autopsy is possible, peripheral nerves and muscles should be part of the neuropathological work-up. Sampling frozen tissue for future biochemical and genetic analysis also is recommended.

The neuropathological correlate of FTD is frontotemporal lobar degeneration (FTLD). There are three major FTLD types depending on the hallmark pathological protein: FTLD-tau, FTLD-TDP and FTLD-FUS. A small minority of FTD cases are not expressing any of these proteins; those reacting with markers of the ubiquitin-proteasome system (UPS) represent FTLD-UPS whereas the rare, completely immunonegative cases fall into the group of

FTLD-NOS (not otherwise specified). The large majority of cases of ALS with frontotemporal dysfunction belong to the FTLD-TDP type and exhibit TDP-43 immunoreactive inclusions within a range of neocortical and subcortical structures (the remaining cases are FTLD-FUS). They are predominantly in neurons in forms of neuronal cytoplasmic inclusions (NCIs), dystrophic neurites (DNs) and neuronal intranuclear inclusions (NIIs). The harmonised classification system for FTLD-TDP recognises four subtypes (A, B, C and D) depending on the morphological forms and their frequency, characteristic neuroanatomical localisation and presence or absence of other features like hippocampal sclerosis (129). There is good correlation with clinical phenotypes and genetic alterations (for example, the most frequent subtype A often presents with bvFTD and FTD-ALS, with 50% of cases harbouring *GRN* mutation or *c9orf72* expansion).

For neuropathological analysis, due to regional specificity, representative sections should include (among others) the anterior cingulate gyrus, pre-central gyrus, superior frontal gyrus, superior temporal gyrus, amygdala, entorhinal cortex, hippocampus, basal ganglia and cerebellum. Immunostaining should include antibodies against TDP-43, FUS, p62, tau (e.g. AT8, pThr175) (130,131), α-synuclein and in specific disease subtypes against neurofilament (in neuronal intermediate filament inclusion disease - NIFID), SOD-1, and various dipeptide repeats (DPRs) (in C9FTD/ ALS) (132). Assessment of the presence of amyloid beta (Aβ) pathology (e.g. amyloid plaques, cerebral amyloid angiopathy) with or without Alzheimer's disease type tau pathology also is mandatory. As discussed in the original Strong criteria, 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. A stepwise approach is recommended for neuropathological work-up with special stains and immunohistochemistry of the relevant brain and spinal cord regions (132). A diagnostic algorithm has been proposed recently for neuropathological diagnosis of ALS, FTD and overlapping syndromes (132). More details about the principles and practice of neuropathological analysis and key morphological features are described in reference textbooks (132–134).

Since the publication of the original Strong criteria, the concept of staging of the frontotemporal degeneration of the neocortical and subcortical involvement in ALS has become increasingly of value in understanding the degree to which ALS-FTD may be a distinct entity from ALSci, ALS bi (and thus potentially ALScbi). Level III studies are thus recommended to include a full staging analysis as delineated by Halliday et al. (135).

Discussion

In contrast to the milieu in which the Strong criteria for the diagnosis of frontotemporal dysfunction were crafted, there is now a clearer appreciation of the significant proportion of ALS patients who will have evidence of multidimensional dysfunction. When the Strong criteria were applied to ALS patients prospectively, more than 50% of ALS patients were

found to have some form of frontotemporal disruptions or dementia, including probable Alzheimer's disease (39,136–139). There is remarkable consistency across virtually all studies. The importance of recognising these deficits lies in their impact on survival for a large proportion of ALS patients, an impact which is not yet integrated into the design of drug trials in ALS. However, executive dysfunction alone is a significant predictor of reduced survival from symptom onset (137). Behavioural dysfunction appears also to have an equal contribution to survival (p<0.001), seemingly in isolation from other variables (140). By increasing the rigor of defining the deficits in ALS, this should be clarified and, ultimately, become a defined variable in the design and analysis of clinical trials in ALS.

Advances in our understanding of the spectrum of frontotemporal dysfunction that can occur in concert with the motor degeneration of ALS mandated a revision of the Strong criteria. Underpinning this is the realisation that there exists a spectrum of deficits which have a degree of overlap, and hence the adoption of the term ALS frontotemporal spectrum disorders (ALS-FTSD). This is not meant to imply that the spectrum is a continuum, and indeed it is less clear that ALS-FTD is the natural endpoint of ALSci, ALSbi or ALS(cbi).

These revised criteria (Table 2) have addressed the issue of genetic testing more critically, in part driven by the explosion in knowledge of genetic mutations that are either causally associated with ALS, or identified as modifiers of the disease process. The discovery that many of these genetic mutations can be observed in ALS patients in whom there is no evidence for inheritance underscores the importance of using the term 'genetic' rather than 'familial ALS' to describe such cases. To that extent, we have proposed that all ALS can be stratified into those cases for which a genetic aetiology is known, versus those for which one is not. Clearly, there remain cases for which the designation of familial is warranted based on a conventional analysis of the patient pedigree; we recommend that these cases also be subsumed under the terminology 'genetic ALS'. We are recommending further that all patients who are diagnosed as ALS-FTSD be offered the opportunity for genetic testing, and in the cases of research protocols, that this be mandatory. While ideally an individual should be tested for all genes identified as being causally linked (Table 1), this is impractical and beyond the resources of many clinics or individuals. Genetic testing should, therefore, be modified according not only to the geography of origin of the patient, but to the nature of the deficit (for instance, a patient presenting with marked behavioural impairment, with or without psychosis, should first be tested for pathological hexanucleotide expansions of *C9orf72*).

Since the introduction of the Strong criteria, there also has been an increasing awareness that the neuropsychological deficits are pervasive across the spectrum of motor neuron diseases. The issue arises that even within the motor manifestations of ALS, it is increasingly recognised that there is considerable clinical phenotypic heterogeneity. This observation has driven controversy as to the degree to which defining this heterogeneity serves any clinical purpose, as opposed to considering all disorders of the motor neuron to simply be, on aggregate, a single disorder (i.e. lumping vs. splitting). Recent attempts at revising the diagnostic criteria for ALS have leaned towards the latter. However, in developing these revised Strong criteria, it is hoped that a clearer and more consistent set of criteria by which to define the specific variants of frontotemporal dysfunction will provide a clearer

understanding of distinct pathophysiology of frontotemporal dysfunction in ALS and, potentially, selective treatment responses. While it remains unresolved whether clinically divergent presentations are due to disparate aetiologies, it is prudent to maintain careful documentation of the clinical phenotype and encourage investigations that may link or associate specific presentations with unique biomarkers or aetiologies. The absence of maintaining awareness of such clinically divergent motor neuron phenotypes, given our current understanding, raises the probability of obscuring a valuable treatment effect or a clinical association (perhaps with FTD spectrum) that could highlight a critical aetiology. Hence, we have elected to maintain Axis I with a focus on defining the motor neuron disease succinctly.

Finally, as with the original Strong criteria, it is recognised that our understanding of the frontotemporal dysfunction which may occur in ALS will continue to evolve rapidly. Even now, the place of memory and language impairments in ALS are works in progress, as is defining the true breadth of behavioural and neuropsychiatric dysfunction which may occur. Moreover, recent investigations have begun to elucidate the influence of gender in ALS disease manifestation, including ALSci and ALSbi (141). At this point in time, however, it is our intention that these revised criteria will provide a greater level of diagnostic certainty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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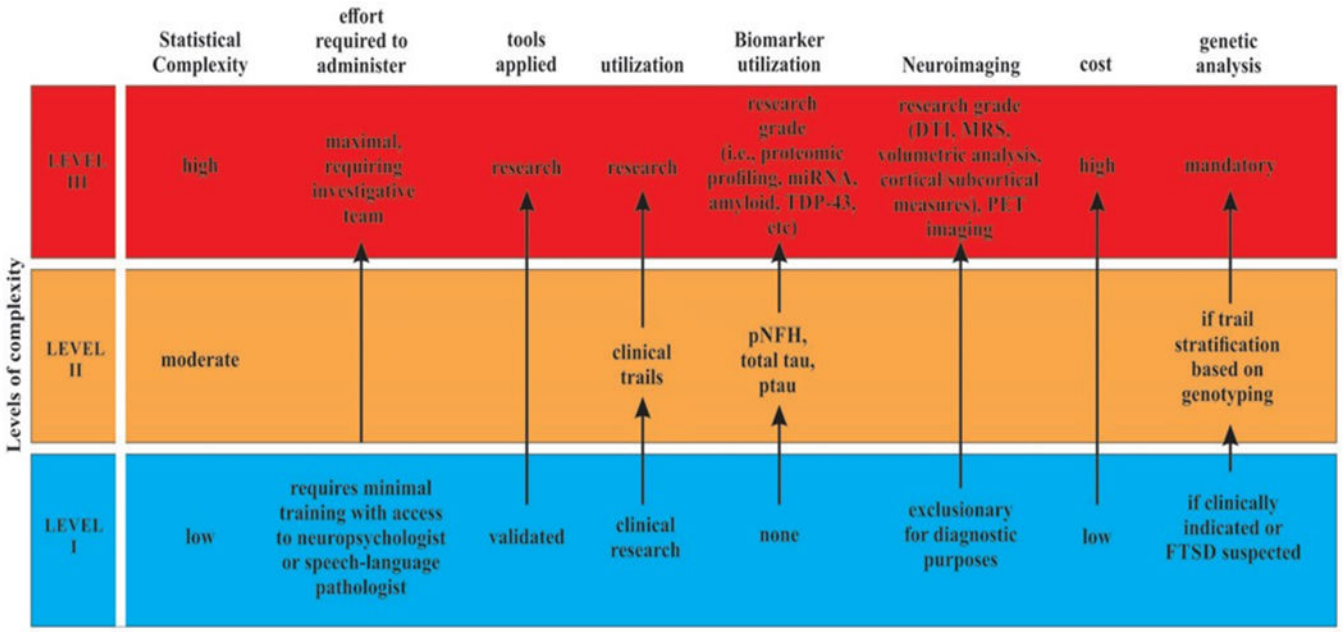

Figure 1.

Schematic of levels of investigation. The revised criteria are designed to address the need for rapid, easily applied tools that can be used in the clinical setting (Level I) through to assessment tools that are more appropriate to research studies (Level III). Levels II and III require formal neuropsychological and speech and language expertise to implement, reflect higher statistical complexity, and include tests that may require further validation in the ALS population. Level II is an intermediary level which can be applied in clinical trials and would be appropriate to be included in clinical case reports as minimum datasets.

Table 1.

ALS- causative genes and their association with ALS, FTD or ALS-FTSD (adapted from (142,143)).

Locus	Gene ID	Chromosome	Protein; functional changes	Inheritance	Clinical Phenotype				Reference
					FTD	ALS	ALS-FTSD	other	
ALS1	*SOD1*	21q22.11	Superoxide dismutase 1; Oxidative stress	AD, AR		+		PLS, PMA	(144)
ALS2	*ALS2*	2q33.2	ALSin/Rho guanine nucleotide exchange factors	AR		+		PLS, HSP	(145,146)
ALS4	*SETX*	9q34.13	Senataxin; DNA/RNA processing	AD		+		AOA2	(147)
ALS5	*SPG11*	15q21.1	Spatacsin; transmembrane protein	AR		+		HSP	(148,149)
ALS6	*FUS*	16p11.2	Fused in Sarcoma; RNA binding protein, DNA repair, exon splicing	AD	+ (#)	+	+		(150–152)
ALS7	*Unknown*	20p13	Unknown	AD		+			(153)
ALS8	*VAPB*	20q13.33	Vesicle-associated membrane protein-associated protein B and C; Altered axonal transport	AD		+		SMA	(154)
ALS10	*TARDBP*	1p36.22	TAR DNA binding protein (TDP-43); DNA/RNA processing	AD	+	+	+		(155–157)
ALS12	*OPTN*	10p13	Optineurin; membrane and vesicle trafficking, Protein degradation	AD, AR		+		+ (PDB)	(158)
ALS14	*VCP*	9q13.3	Valosin-containing protein; ATP-binding protein, vesicle transport and fusion	AD	+	+	+	MSP	(159–161)
ALS15	*UBQLN2*	X11p.21	Ubiquilin 2; ubiquitination, protein degradation	X-linked	+	+	+		(162–164)
	PFN1	17p13.2	Profilin 1; actin binding protein, actin polymerisation	AD	+	+			(165–167)
	HnRNPA2B1/A1	7p15.2/12q13.3	Heterogeneous nuclear ribonucleoprotein; mRNA processing	AD		+		MSP	(168,169)
ALS-FTD1	*Unknown*	9q21-q22	Unknown	AD	+	+	+		(170)
ALS-FTD2	*C9orf72*	9p21.2	*Chromosome 9 open reading frame 72; unknown	AD	+	+	+		(171–178)
	TBK1	12q154.2	TANK-binding kinase 1; multifunctional kinase active in autophagosome-mediated degradation of ubiquitinated proteins; also role in inflammatory signalling	AD, sporadic	+	+			(179–184)

AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AOA2, ataxia-ocular apraxia 2;AR, autosomal recessive; FTD, frontotemporal dementia; HSP, hereditary spastic paraplegia; MSP, multisystem proteinopathy (previously referred to as IBMFTD or inclusion body myopathy with Paget's disease and frontotemporal dementia); PMA, progressive muscular atrophy; SMA, spinal muscular atrophy; TANK, TRAF family member-associated NF-kappa-B activator; TBK1, TANK-binding kinase 1

Table 2.

Application of Axis I and Axis II diagnostic classification for ALS and ALS-FTSD (modified from Strong et al., 2009) (2).

Heading	Subheadings	Existing, synonymous terms within the literature	Characteristics
Axis I. Motor neuron disease variant			
ALS	Sporadic ALS	sALS, classic ALS, Charcot disease, motor neuron disease	A progressive motor system disorder with both UMN and LMN involvement, with the degree of diagnostic certainty further defined by either the El Escorial criteria (revised) (6) or the Awaji criteria (9).
	genetic ALS	gALS; familial ALS (fALS)	As indicated for sporadic ALS with the additional components: **1** Confirmed ALS associated genetic mutation, or **2** Clinical evidence of autosomal dominant, autosomal recessive, or X-linked inheritance
	Western Pacific ALS	Lytico bodig	ALS arising within a hyper-endemic region of the western Pacific (e.g., Kii Peninsula, Guam, Rota)
Axis II. Neuropsychological characterisation			
ALSbi			A diagnosis of ALSbi requires: **1** The identification of apathy with or without other behaviour change OR **2** meeting at least two non-overlapping supportive diagnostic features from the Rascovsky criteria (37)
ALSci			A diagnosis of ALSci depends on evidence of either executive dysfunction (including social cognition) or language dysfunction or a combination of the two. Executive impairment is defined as: **1** Impaired verbal fluency (letter). OR **2** Impairment on two other non-overlapping measures of executive functions (which may include social cognition) Language impairment is defined as: **1** Impairment on two non-overlapping tests and in which language impairment is not solely explained by verbal fluency deficits.
ALScbi			Patients who meet the criteria for both ALSci and ALSbi

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Heading	Subheadings	Existing, synonymous terms within the literature	Characteristics
ALS-FTD		ALS-dementia (ALS-D) *, FTD- MND	A diagnosis of ALS-FTD requires: **1** Evidence of progressive deterioration of behaviour and/or cognition by observation or history AND **2** The presence of at least 3 of the behavioural/cognitive symptoms outlined by Rascovsky, Hodges et al 2011 (37) OR **3** The presence of at least 2 of those behavioural/cognitive symptoms, together with loss of insight and/or psychotic symptoms OR **4** The presence of language impairment meeting criteria for semantic dementia/semantic variant PPA or non-fluent variant PPA. This may co-exist with behavioural/cognitive symptoms as outlined above.
ALS-dementia		ALS-D *	ALS with dementia, not typical of FTD
	ALS-AD		ALS in association with Alzheimer's disease
	ALS-vascular dementia		ALS in association with vascular dementia (185)
	ALS-mixed dementia		ALS in association with a mixed dementia (e.g., AD-vascular dementia)
FTD-MND-like			A neuropathological diagnosis in which FTLD is the primary diagnosis but in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS
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

* Although less common than in 2009, the term 'ALS-dementia' continues to be used generically within the literature to describe any clinical or neuropathological evidence of neuropsychological impairment. Its use does not differentiate between the individual entities and as such appears in more than one category. Its use also is not recommended.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ALSbi, ALS with behavioural impairment; ALSci, ALS with cognitive impairment; FTLD, frontotemporal lobar degeneration; FTD, frontotemporal dementia; LMN, lower motor neuron; PNFA, progressive non-fluent aphasia; SD, semantic dementia; UMN, upper motor neuron