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

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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 recognized - 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-conceptualization 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).

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, recognized that ALS could exist as a pure motor syndrome but that it can co-exist with a frontotemporal dementia (ALS-FTD) as defined by the Neary or Hodges criteria (4;5). The criteria further recognized that both behavior 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 behavioral 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 realization that the Strong criteria do not adequately recognize 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 characterize 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 operationalized 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 utilized 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 (attendees listed in the acknowledgement section). 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 suffice for research purposes whilst at the same time be nimble enough to be of utility clinically. As such, beyond expanding the nature of neuropsychological and neuropsychiatric deficits that characterize 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 utilized 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 whilst recognizing 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 characterization of the FTSD of ALS and thus it has been omitted in the revised criteria presented herein.

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 versus 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 recognize distinct clinical syndromes which may be characterized 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 multi-segmental 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 in fact hamper not only enrollment 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 in fact have the potential of developing ALS whilst 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 of 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 and colleagues 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 ϵ 2 and beta-amyloid are not yet ready to be included in Level I diagnostic workup (15-21). Further, while it is increasingly likely that proteomic profiling of CSF will enhance the sensitivity and specificity of biomarker utilization 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 workup although a restricted number (e.g., pNFH, phospho-tau, TDP-43, APOE ϵ 2) 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 which 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 characterization 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 harbor 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 men and 1:400 for women, coincidental familial clustering is a realistic consideration amongst pedigrees with only two affected individuals which might otherwise be considered to be clinical examples of Mendelian inheritance (24).

Amongst 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 *C9orf72* 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 *C9orf72* 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 *C9orf72* expansion (26).

Axis I recommendation. The classification of the 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 recognize 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 endeavor (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 fulfill 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 counseling 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 counseling 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. Firstly, 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). In addition, 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. Firstly, 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 (Table 3).

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 which 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 recognize 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 ALS present with obvious language impairments (65). Moreover, language deficits in ALS 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 ALS 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 likely 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 characterize the spoken language of individuals with ALS including reduced utterance length and lower total word output, features that are likely 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 ALS. 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 standardized instruments (Table 3).

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 characterization 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 co-morbidity 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 (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 amnesic subtype). Qualitative differences in memory distinguish ALS patients from patients with AD (83) and those with the AD prodrome of mild cognitive impairment-amnesic 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 summarizing 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. Table 3 provides a list of screening measures and comprehensive memory tests which 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 (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. 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 co-exist with deficits in cognitive domains (see ALSbi; see table 3). 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 Table 4.

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 (Table 3). 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 firstly 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 Behavioral 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 Table 3. 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;102). 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 which 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 which 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 (103). 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 maximizing 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 Behavioral 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 minimize motor or speech production involvement so patients can be tested during later stages of 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 minutes 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 which 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 ≥ 17 is recommended to exclude cognitive impairment.

The behavioural section comprises a 15-item Likert scale questionnaire completed by an informant 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 cutoff 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 (ie., Level II and III; see Table 3), 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 Table 3).

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 ALS*Sci*.

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 1.5sd 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 (ALS*bi*). 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 ALS*bi* 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 (9 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 ALS*Sci* or ALS*bi*) 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 behaviour 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 operationalizing insight is to analyze standardized score discrepancies between patient self-reports and caregiver reports of patient behavior. One study determined that ALS-FTD patients report significantly less behavioral change over time compared to their caregivers, and report fewer behavioral 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 which 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 3 of the behavioural/cognitive symptoms outlined by Rascovsky et al (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, as defined by Neary et al. (5) or Gorno-Tempini et al. (114). This may co-exist 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 recognized 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 recognized 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 3 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 harmonized classification system for FTLD-TDP recognizes four subtypes (A, B, C and D) depending on the morphological forms and their frequency, characteristic neuroanatomical localization 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 present with bvFTD and FTD-ALS, with 50% of cases harboring *GRN* mutation or *c9orf72* expansion).

For neuropathological analysis, due to regional specificity, representative sections should include (among others) the anterior cingulate gyrus, precentral 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 ($A\beta$) 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 and colleagues (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 dysruptions or dementia, including probable Alzheimer's disease (39;136-139). There is, in fact, remarkable consistency across virtually all studies. The

importance of recognizing 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. And yet, 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 realization 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 ALS*ci*, ALS*bi* or ALS(*cbi*).

These revised criteria (Table 5) 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 etiology 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 recognized 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 etiologies, 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 etiologies. 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 etiology. 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 recognized 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.

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Listing of conference attendees: Michael Strong (conference organizer and chair), Sharon Abrahams, Thomas Bak, Emma Beeldman, Steve Bell, Michael Benatar, Mervin Blair, Robert Bowser, Emanuele Buratti, Danae Campos-Melos, Marvin Chum, Kristy Coleman, Chris Crockford, Karen Dunkerley, Marwa Elamin, Sali Farhan, Elizabeth Finger, Claire Flaherty, Tania Gendron, Laura Goldstein, Rosanne Govaarts, Francois Gros-Louis, Murray Grossman, Tibor Hortobagyi, Sarah Jesso, Kalyani Kansal, Yasumasa Kokubo, Suzee Lee, Julia MacKinley, Paula McLaughlin, Eneida Mioshi, Hiroshi Mitsumoto, Jennifer Murphy, Catherine Lomen-Hoerth, Lindsay Oliver, Chiadi Onyike, JB Orange, Markus Otto, Erik Pioro, Joost Raaphorst, Angela Roberts, Jonathon Rohrer, Jeffrey Rosenfeld, Vincenzo Silani, Julie Snowden, Carmela Tartaglia, Tamara Tavares, Christine Vande Velde, Kathryn Volkening, Susan Woolley

Figure legends

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 within the clinic (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.

ReferencesReference List

- (1) Strong MJ. The syndromes of frontotemporal dysfunction in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008;9:323-38.
- (2) Strong MJ, Grace GM, Freedman M, Lomen-Hoerth C, Woolley S, Goldstein LH, et al. Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2009;10:131-46.
- (3) Woolley SC, Strong MJ. Frontotemporal Dysfunction and Dementia in Amyotrophic Lateral Sclerosis. *Neurol Clin* 2015;33:787-805.
- (4) Hodges JR, Miller B. The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: part 1. *Neurocase* 2001;7:31-5.
- (5) Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546-54.
- (6) World Federation of Neurology Research Group on Neuromuscular Disease. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci* 1994;124 (suppl.):96-107.
- (7) Brooks BR, Miller RG, Swash M, Munsat TL, for the World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000;1:293-9.
- (8) Chaudhari KR, Crump S, Al-Sarraj S, Anderson V, Cavanagh J, Leigh PN. The validation of El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis: a clinicopathological study. *J Neurol Sci* 1995;129:11-2.
- (9) de CM, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. *Clin Neurophysiol* 2008;119:497-503.
- (10) de Carvalho M, Swash M. Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis. *Amyotroph Lateral Scler* 2009;10:53-7.
- (11) Costa J, Swash M, de CM. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis: a systematic review. *Arch Neurol* 2012;69:1410-6.
- (12) Geevasinga N, Menon P, Scherman DB, Simon N, Yiannikas C, Henderson RD, et al. Diagnostic criteria in amyotrophic lateral sclerosis: A multicenter prospective study. *Neurology* 2016.

- (13) Geevasinga N, Loy CT, Menon P, de CM, Swash M, Schrooten M, et al. Awaji criteria improves the diagnostic sensitivity in amyotrophic lateral sclerosis: A systematic review using individual patient data. *Clin Neurophysiol* 2016;127:2684-91.
- (14) Ludolph A, Drory V, Hardiman O, Nakano I, Ravits J, Robberecht W, et al. A revision of the El Escorial criteria - 2015. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:291-2.
- (15) Xu Z, Henderson RD, David M, McCombe PA. Neurofilaments as Biomarkers for Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. *PLoS One* 2016;11:e0164625.
- (16) Pijnenburg YA, Verwey NA, van der Flier WM, Scheltens P, Teunissen CE. Discriminative and prognostic potential of cerebrospinal fluid phosphoTau/tau ratio and neurofilaments for frontotemporal dementia subtypes. *Alzheimers Dement (Amst)* 2015;1:505-12.
- (17) Junttila A, Kuvaja M, Hartikainen P, Siloaho M, Helisalmi S, Moilanen V, et al. Cerebrospinal Fluid TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis Patients with and without the C9ORF72 Hexanucleotide Expansion. *Dement Geriatr Cogn Dis Extra* 2016;6:142-9.
- (18) Wilke C, Deuschle C, Rattay TW, Maetzler W, Synofzik M. Total tau is increased, but phosphorylated tau not decreased, in cerebrospinal fluid in amyotrophic lateral sclerosis. *Neurobiol Aging* 2015;36:1072-4.
- (19) Gaiottino J, Norgren N, Dobson R, Topping J, Nissim A, Malaspina A, et al. Increased neurofilament light chain blood levels in neurodegenerative neurological diseases. *PLoS One* 2013;8:e75091.
- (20) Steinacker P, Fang L, Kuhle J, Petzold A, Tumani H, Ludolph AC, et al. Soluble beta-amyloid precursor protein is related to disease progression in amyotrophic lateral sclerosis. *PLoS One* 2011;6:e23600.
- (21) Chio A, Brunetti M, Barberis M, Iazzolino B, Montuschi A, Ilardi A, et al. The Role of APOE in the Occurrence of Frontotemporal Dementia in Amyotrophic Lateral Sclerosis. *JAMA Neurol* 2016;73:425-30.
- (22) Collins MA, An J, Hood BL, Conrads TP, Bowser RP. Label-Free LC-MS/MS Proteomic Analysis of Cerebrospinal Fluid Identifies Protein/Pathway Alterations and Candidate Biomarkers for Amyotrophic Lateral Sclerosis. *J Proteome Res* 2015;14:4486-501.
- (23) Turner MR, Bowser R, Bruijn L, Dupuis L, Ludolph A, McGrath M, et al. Mechanisms, models and biomarkers in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14 Suppl 1:19-32.
- (24) Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol* 2013;9:617-28.
- (25) Sabatelli M, Marangi G, Conte A, Tasca G, Zollino M, Lattante S. New ALS-Related Genes Expand the Spectrum Paradigm of Amyotrophic Lateral Sclerosis. *Brain Pathol* 2016;26:266-75.

- (26) Khan BK, Yokoyama JS, Takada LT, Sha SJ, Rutherford NJ, Fong JC, et al. Atypical, slowly progressive behavioural variant frontotemporal dementia associated with C9ORF72 hexanucleotide expansion. *J Neurol Neurosurg Psychiatry* 2012;83:358-64.
- (27) Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, et al. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? *J Neurol Neurosurg Psychiatry* 2013;84:494-8.
- (28) Tsermentseli S, Leigh PN, Taylor LJ, Radunovic A, Catani M, Goldstein LH. Syntactic processing as a marker for cognitive impairment in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;17:69-76.
- (29) Girardi A, Macpherson SE, Abrahams S. Deficits in emotional and social cognition in amyotrophic lateral sclerosis. *Neuropsychology* 2011;25:53-65.
- (30) Cavallo M, Adenzato M, Macpherson SE, Karwig G, Enrici I, Abrahams S. Evidence of social understanding impairment in patients with amyotrophic lateral sclerosis. *PLoS One* 2011;6:e25948.
- (31) Cerami C, Dodich A, Canessa N, Crespi C, Iannaccone S, Corbo M, et al. Emotional empathy in amyotrophic lateral sclerosis: a behavioural and voxel-based morphometry study. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:21-9.
- (32) Carlier L, Mondou A, Buhour MS, Laisney M, Pelerin A, Eustache F, et al. Neural substrate of cognitive theory of mind impairment in amyotrophic lateral sclerosis. *Cortex* 2015;65:19-30.
- (33) Staios M, Fisher F, Lindell AK, Ong B, Howe J, Reardon K. Exploring sarcasm detection in amyotrophic lateral sclerosis using ecologically valid measures. *Front Hum Neurosci* 2013;7:178.
- (34) Watermeyer TJ, Brown RG, Sidle KC, Oliver DJ, Allen C, Karlsson J, et al. Executive dysfunction predicts social cognition impairment in amyotrophic lateral sclerosis. *J Neurol* 2015;262:1681-90.
- (35) van der Hulst EJ, Bak TH, Abrahams S. Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2015;86:1208-15.
- (36) Consonni M, Catricala E, Dalla BE, Gessa VC, Lauria G, Cappa SF. Beyond the consensus criteria: multiple cognitive profiles in amyotrophic lateral sclerosis? *Cortex* 2016;81:162-7.
- (37) Rascofsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134:2456-77.
- (38) Goldstein LH, Abrahams S. Changes in cognition and behaviour in amyotrophic lateral sclerosis: nature of impairment and implications for assessment. *Lancet Neurol* 2013;12:368-80.

- (39) Phukan J, Elamin M, Bede P, Jordan N, Gallagher L, Byrne S, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry* 2012;83:102-8.
- (40) Beeldman E, Raaphorst J, Klein TM, de VM, Schmand BA, de Haan RJ. The cognitive profile of ALS: a systematic review and meta-analysis update. *J Neurol Neurosurg Psychiatry* 2016;87:611-9.
- (41) Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia* 2000;38:734-47.
- (42) Abrahams S, Goldstein LH, Al-Chalabi A, Pickering A, Morris RG, Passingham RE, et al. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatr* 1997;62:464-72.
- (43) Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatr* 1996;61:450-5.
- (44) Murphy J, Factor-Litvak P, Goetz R, Lomen-Hoerth C, Nagy PL, Hupf J, et al. Cognitive-behavioral screening reveals prevalent impairment in a large multicenter ALS cohort. *Neurology* 2016;86:813-20.
- (45) Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS. A prospective study. *Neurology* 2005;64:1222-6.
- (46) Donaghy C, Pinnock R, Abrahams S, Cardwell C, Hardiman O, Patterson V, et al. Ocular fixation instabilities in motor neurone disease. A marker of frontal lobe dysfunction? *J Neurol* 2009;256:420-6.
- (47) Wicks P, Abrahams S, Papps B, Al-Chalabi A, Shaw CE, Leigh PN, et al. SOD1 and cognitive dysfunction in familial amyotrophic lateral sclerosis. *J Neurol* 2009;256:234-41.
- (48) Abrahams S, Goldstein LH, Kew JJM, Brooks DJ, Lloyd CM, Frith CD, et al. Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. *Brain* 1996;119:2105-20.
- (49) Abrahams S, Goldstein LH, Simmons A, Brammer M, Williams SCR, Giampietro V, et al. Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. *Brain* 2004;127:1507-17.
- (50) Abrahams S, Goldstein LH, Suckling J, Ng V, Simmons A, Chitnis X, et al. Frontotemporal white matter changes in amyotrophic lateral sclerosis. *J Neurol* 2005;252:321-31.
- (51) Pettit LD, Bastin ME, Smith C, Bak TH, Gillingwater TH, Abrahams S. Executive deficits, not processing speed relates to abnormalities in distinct prefrontal tracts in amyotrophic lateral sclerosis. *Brain* 2013;136:3290-304.

- (52) Reitan RM, Wolfson D. A selective and critical review of neuropsychological deficits and the frontal lobes. *Neuropsychology Review* 1994;4:161-98.
- (53) Grant DA, Berg ED. Wisconsin Card Sorting Test. Odessa: Psychological Assessment Resources, 1990.
- (54) Lange F, Vogts MB, Seer C, Furkotter S, Abdulla S, Dengler R, et al. Impaired set-shifting in amyotrophic lateral sclerosis: An event-related potential study of executive function. *Neuropsychology* 2016;30:120-34.
- (55) Libon DJ, McMillan C, Avants B, Boller A, Morgan B, Burkholder L, et al. Deficits in concept formation in amyotrophic lateral sclerosis. *Neuropsychology* 2012;26:422-9.
- (56) Stukovnik V, Zidar J, Podnar S, Repovs G. Amyotrophic lateral sclerosis patients show executive impairments on standard neuropsychological measures and an ecologically valid motor-free test of executive functions. *J Clin Exp Neuropsychol* 2010;32:1095-109.
- (57) Meier SL, Charleston AJ, Tippet L. Cognitive and behavioural deficits associated with the orbitomedial prefrontal cortex in amyotrophic lateral sclerosis. *Brain* 2010;133:3444-57.
- (58) Crespi C, Cerami C, Dodich A, Canessa N, Arpone M, Iannaccone S, et al. Microstructural white matter correlates of emotion recognition impairment in Amyotrophic Lateral Sclerosis. *Cortex* 2014;53:1-8.
- (59) Palmieri A, Naccarato M, Abrahams S, Bonato M, D'Ascenzo C, Balestreri S, et al. Right hemisphere dysfunction and emotional processing in ALS: an fMRI study. *J Neurol* 2010;257:1970-8.
- (60) Savage SA, Lillo P, Kumfor F, Kiernan MC, Piguet O, Hodges JR. Emotion processing deficits distinguish pure amyotrophic lateral sclerosis from frontotemporal dementia. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:39-46.
- (61) Strong MJ, Grace GM. Cognitive changes in amyotrophic lateral sclerosis. In: Kertesz A, Munoz DA, editors. *Pick's Disease and Pick Complex*. New York: John Wiley & Sons, Inc.; 1998.
- (62) Bak TH, Hodges JR. The effects of motor neurone disease on language: further evidence. *Brain Lang* 2004;89:354-61.
- (63) Cobble M. Language impairment in motor neurone disease. *J Neurol Sci* 1998;160 Suppl 1:S47-S52.
- (64) Moretti R, Torre P, Antonello RM, Carraro N, Cazzato G, Bava A. Complex cognitive disruption in motor neuron disease. *Dement Geriatr Cogn Disord* 2002;14:141-50.
- (65) Neary D, Snowden JS, Mann DM. Cognitive change in motor neurone disease/amyotrophic lateral sclerosis (MND/ALS). *J Neurol Sci* 2000;180:15-20.
- (66) Ash S, Olm C, McMillan CT, Boller A, Irwin DJ, McCluskey L, et al. Deficits in sentence expression in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:31-9.

- (67) Ash S, Menaged A, Olm C, McMillan CT, Boller A, Irwin DJ, et al. Narrative discourse deficits in amyotrophic lateral sclerosis. *Neurology* 2014;83:520-8.
- (68) Roberts-South A, Findlater K, Strong MJ, Orange JB. Longitudinal changes in discourse production in amyotrophic lateral sclerosis. *Semin Speech Lang* 2012;33:79-94.
- (69) York C, Olm C, Boller A, McCluskey L, Elman L, Haley J, et al. Action verb comprehension in amyotrophic lateral sclerosis and Parkinson's disease. *J Neurol* 2014;261:1073-9.
- (70) Rippon GA, Goldstein S, Scarmeas M, Gordon PH, Murphy PL, Albert SA, et al. An observational study of cognitive impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2006;63:345-52.
- (71) Grossman M, Anderson C, Khan A, Avants B, Elman L, McCluskey L. Impaired action knowledge in amyotrophic lateral sclerosis. *Neurology* 2008;71:1396-401.
- (72) Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges JR. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. *Brain* 2001;124:103-20.
- (73) Papeo L, Cecchetto C, Mazzon G, Granello G, Cattaruzza T, Verriello L, et al. The processing of actions and action-words in amyotrophic lateral sclerosis patients. *Cortex* 2015;64:136-47.
- (74) Yoshizawa K, Yasuda N, Fukuda M, Yukimoto Y, Ogino M, Hata W, et al. Syntactic comprehension in patients with amyotrophic lateral sclerosis. *Behav Neurol* 2014;2014:230578.
- (75) Kamminga J, Leslie FV, Hsieh S, Caga J, Mioshi E, Hornberger M, et al. Syntactic comprehension deficits across the FTD-ALS continuum. *Neurobiol Aging* 2016;41:11-8.
- (76) Bambini V, Arcara G, Martinelli I, Bernini S, Alvisi E, Moro A, et al. Communication and pragmatic breakdowns in amyotrophic lateral sclerosis patients. *Brain Lang* 2016;153-154:1-12.
- (77) Caselli RJ, Windebank AJ, Petersen RC, Komori T, Parisi JE, Okazaki E, et al. Rapidly progressing aphasic dementia and motor neuron disease. *Ann Neurol* 1993;33:200-7.
- (78) Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;65:586-90.
- (79) da Rocha AJ, Valerio BC, Buainain RP, Ferraz ME, da Silva CJ, Maia AC, Jr., et al. Motor neuron disease associated with non-fluent rapidly progressive aphasia: case report and review of the literature. *Eur J Neurol* 2007;14:971-5.
- (80) Östberg P, Bogdanovic N. Semantic dementia with lower motor neuron disease showing FTLD type 3 pathology (sensu Mackenzie). *Neuropathology* 2016;31:271-9.
- (81) Christidi F, Zalonis I, Smyrnis N, Evdokimidis I. Selective attention and the three-process memory model for the interpretation of verbal free recall in amyotrophic lateral sclerosis. *J Int Neuropsychol Soc* 2012;18:809-18.

-
- (82) Mantovan MC, Baggio L, Dalla BG, Smith P, Pegoraro E, Soraru' G, et al. Memory deficits and retrieval processes in ALS. *Eur J Neurol* 2003;10:221-7.
 - (83) Hanagasi HA, Gurvit IH, Ermutlu N, Kaptanoglu G, Karamursel S, Idrisoglu HA, et al. Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials. *Brain Res Cogn Brain Res* 2002;14:234-44.
 - (84) Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B, et al. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. *Neurology* 2013;80:1590-7.
 - (85) Raaphorst J, van Tol MJ, de VM, van der Kooi AJ, Majoie CB, Van den Berg LH, et al. Prose memory impairment in amyotrophic lateral sclerosis patients is related to hippocampus volume. *Eur J Neurol* 2015;22:547-54.
 - (86) Machts J, Bittner V, Kasper E, Schuster C, Prudlo J, Abdulla S, et al. Memory deficits in amyotrophic lateral sclerosis are not exclusively caused by executive dysfunction: a comparative neuropsychological study of amnesic mild cognitive impairment. *BMC Neurosci* 2014;15:83.
 - (87) Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1996;61:450-5.
 - (88) Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003;60:1119-22.
 - (89) Grossman AB, Woolley-Levine S, Bradley WG, Miller RG. Detecting neurobehavioural changes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2007;8:56-61.
 - (90) Tsujimoto M, Senda J, Ishihara T, Niimi Y, Kawai Y, Atsuta N, et al. Behavioral changes in early ALS correlate with voxel-based morphometry and diffusion tensor imaging. *J Neurol Sci* 2011;307:34-40.
 - (91) Witgert M, Salamone AR, Strutt AM, Jawaid A, Massman PJ, Bradshaw M, et al. Frontal-lobe mediated behavioral dysfunction in amyotrophic lateral sclerosis. *Eur J Neurol* 2010;17:103-10.
 - (92) Woolley SC, Zhang Y, Schuff N, Weiner MW, Katz JS. Neuroanatomical correlates of apathy in ALS using 4 Tesla diffusion tensor MRI. *Amyotroph Lateral Scler* 2011;12:52-8.
 - (93) Terada T, Obi T, Yoshizumi M, Murai T, Miyajima H, Mizoguchi K. Frontal lobe-mediated behavioral changes in amyotrophic lateral sclerosis: are they independent of physical disabilities? *J Neurol Sci* 2011;309:136-40.
 - (94) Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? *Amyotroph Lateral Scler* 2011;12:45-51.
 - (95) Radakovic R, Stephenson L, Colville S, Swingle R, Chandran S, Abrahams S. Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale. *J Neurol Neurosurg Psychiatry* 2016;87:663-9.

-
- (96) Caga J, Turner MR, Hsieh S, Ahmed RM, Devenney E, Ramsey E, et al. Apathy is associated with poor prognosis in amyotrophic lateral sclerosis. *Eur J Neurol* 2016;23:891-7.
 - (97) Gibbons ZC, Richardson A, Neary D, Snowden JS. Behaviour in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2008;9:67-74.
 - (98) Ahmed RM, Caga J, Devenney E, Hsieh S, Bartley L, Highton-Williamson E, et al. Cognition and eating behavior in amyotrophic lateral sclerosis: effect on survival. *J Neurol* 2016;263:1593-603.
 - (99) Murphy J, Henry R, Lomen-Hoerth C. Establishing subtypes of the continuum of frontal lobe impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2007;64:330-4.
 - (100) Lillo P, Savage S, Mioshi E, Kiernan MC, Hodges JR. Amyotrophic lateral sclerosis and frontotemporal dementia: A behavioural and cognitive continuum. *Amyotroph Lateral Scler* 2012;13:102-9.
 - (101) Hsieh S, Caga J, Leslie FV, Shibata M, Daveson N, Foxe D, et al. Cognitive and Behavioral Symptoms in ALSFTD: Detection, Differentiation, and Progression. *J Geriatr Psychiatry Neurol* 2016;29:3-10.
 - (102) Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:9-14.
 - (103) Niven E, Newton J, Foley J, Colville S, Swingler R, Chandran S, et al. Validation of the Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS): A cognitive tool for motor disorders. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:172-9.
 - (104) Lule D, Burkhardt C, Abdulla S, Bohm S, Kollewe K, Uttner I, et al. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen: a cross-sectional comparison of established screening tools in a German-Swiss population. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:16-23.
 - (105) Poletti B, Solca F, Carelli L, Madotto F, Lafronza A, Faini A, et al. The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS). *Amyotroph Lateral Scler Frontotemporal Degener* 2016;1-10.
 - (106) Ye S, Ji Y, Li C, He J, Liu X, Fan D. The Edinburgh Cognitive and Behavioural ALS Screen in a Chinese Amyotrophic Lateral Sclerosis Population. *PLoS One* 2016;11:e0155496.
 - (107) Woolley SC, York MK, Moore DH, Strutt AM, Murphy J, Schulz PE, et al. Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS). *Amyotroph Lateral Scler* 2010;11:303-11.
 - (108) Branco LM, Zanao T, De Rezende TJ, Casseb RF, Balthazar MF, Woolley SC, et al. Transcultural validation of the ALS-CBS Cognitive Section for the Brazilian population. *Amyotroph Lateral Scler Frontotemporal Degener* 2016;1-8.

- (109) Turon-Sans J, Gascon-Bayarri J, Rene R, Rico I, Gamez C, Paipa A, et al. Cognitive impairment in ALS patients and validation of the Spanish version of the ALS-CBS test. *Amyotroph Lateral Scler Frontotemporal Degener* 2016;17:221-7.
- (110) Mioshi E, Hsieh S, Caga J, Ramsey E, Chen K, Lillo P, et al. A novel tool to detect behavioural symptoms in ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:298-304.
- (111) Raaphorst J, Beeldman E, Schmand B, Berkhout J, Linssen WH, Van den Berg LH, et al. The ALS-FTD-Q: a new screening tool for behavioral disturbances in ALS. *Neurology* 2012;79:1377-83.
- (112) Murphy J, Ahmed F, Lomen-Hoerth C. The UCSF screening exam effectively screens cognitive and behavioral impairment in patients with ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2015;16:24-30.
- (113) Woolley SC, Moore DH, Katz JS. Insight in ALS: Awareness of behavioral change in patients with and without FTD. *Amyotroph Lateral Scler* 2010;11:52-6.
- (114) Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76:1006-14.
- (115) Turner MR, Verstraete E. What does imaging reveal about the pathology of amyotrophic lateral sclerosis? *Curr Neurol Neurosci Rep* 2015;15:45.
- (116) Neary D, Snowden JS, Mann DMA, Northern B, Goulding PJ, MacDermott N. Frontal lobe dementia and motor neuron disease. *J Neurol Neurosurg Psychiat* 1990;53:23-32.
- (117) Agosta F, Ferraro PM, Riva N, Spinelli EG, Chio A, Canu E, et al. Structural brain correlates of cognitive and behavioral impairment in MND. *Hum Brain Mapp* 2016;37:1614-26.
- (118) Douaud G, Filippini N, Knight S, Talbot K, Turner MR. Integration of structural and functional magnetic resonance imaging in amyotrophic lateral sclerosis. *Brain* 2011;134:3470-9.
- (119) Mahoney CJ, Downey LE, Ridgway GR, Beck J, Clegg S, Blair M, et al. Longitudinal neuroimaging and neuropsychological profiles of frontotemporal dementia with C9ORF72 expansions. *Alzheimers Res Ther* 2012;4:41.
- (120) Bede P, Bokde AL, Byrne S, Elamin M, McLaughlin RL, Kenna K, et al. Multiparametric MRI study of ALS stratified for the C9orf72 genotype. *Neurology* 2013;81:361-9.
- (121) Walhout R, Schmidt R, Westeneng HJ, Verstraete E, Seelen M, van RW, et al. Brain morphologic changes in asymptomatic C9orf72 repeat expansion carriers. *Neurology* 2015;85:1780-8.
- (122) Rohrer JD, Nicholas JM, Cash DM, van SJ, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol* 2015;14:253-62.

- (123) Brettschneider J, Del TK, Irwin DJ, Grossman M, Robinson JL, Toledo JB, et al. Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). *Acta Neuropathol* 2014;127:423-39.
- (124) Brettschneider J, Del TK, Irwin DJ, Grossman M, Robinson JL, Toledo JB, et al. Erratum to: Sequential distribution of pTDP-43 pathology in behavioral variant frontotemporal dementia (bvFTD). *Acta Neuropathol* 2015;129:929.
- (125) Brettschneider J, Del TK, Toledo JB, Robinson JL, Irwin DJ, Grossman M, et al. Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Ann Neurol* 2013;74:20-38.
- (126) Al-Sarraj S, King A, Troakes C, Smith B, Maekawa S, Bodi I, et al. p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of C9orf72-linked FTL and MND/ALS. *Acta Neuropathol* 2011;122:691-702.
- (127) Mori K, Arzberger T, Grasser FA, Gijssels I, May S, Rentzsch K, et al. Bidirectional transcripts of the expanded C9orf72 hexanucleotide repeat are translated into aggregating dipeptide repeat proteins. *Acta Neuropathol* 2013;126:881-93.
- (128) Keller BA, Volkening K, Droppelmann CA, Ang LC, Rademakers R, Strong MJ. Co-aggregation of RNA binding proteins in ALS spinal motor neurons: evidence of a common pathogenic mechanism. *Acta Neuropathol* 2012.
- (129) Mackenzie IR, Neumann M, Baborie A, Sampathu DM, Du PD, Jaros E, et al. A harmonized classification system for FTL-TDP pathology. *Acta Neuropathol* 2011;122:111-3.
- (130) Yang W, Strong MJ. Widespread neuronal and glial hyperphosphorylated tau deposition in ALS with cognitive impairment. *Amyotroph Lateral Scler* 2012;13:178-93.
- (131) Behrouzi R, Liu X, Wu D, Robinson AC, Tanaguchi-Watanabe S, Rollinson S, et al. Pathological tau deposition in Motor Neurone Disease and frontotemporal lobar degeneration associated with TDP-43 proteinopathy. *Acta Neuropathol Commun* 2016;4:33.
- (132) Hortobagyi T, Cairns NJ. Amyotrophic lateral sclerosis and frontotemporal dementia. In: Kovacs GG, editor. *Neuropathology of Neurodegenerative Diseases - a Practical Guide*. Cambridge: Cambridge University Press; 2015: 209-48.
- (133) Ince PG, Highley JR, Wharton SB. Motor neuron disorders. In: Love S, Perry A, Ironside J, Budka H, editors. *Greenfield's Neuropathology*. 9th ed. CRC Press; 2015: 817-48.
- (134) Strong MJ, Hortobagyi T, Okamoto K, Kato S. Amyotrophic lateral sclerosis, primary lateral sclerosis and spinal muscular atrophy. In: Weller R, Nixon D, editors. *Neurodegeneration. The molecular pathology of dementia and movement disorders*. Oxford University Press; 2011.
- (135) Fatima M, Tan R, Halliday GM, Kril JJ. Spread of pathology in amyotrophic lateral sclerosis: assessment of phosphorylated TDP-43 along axonal pathways. *Acta Neuropathol Commun* 2015;3:47.

- (136) Consonni M, Iannaccone S, Cerami C, Frasson P, Lacerenza M, Lunetta C, et al. The cognitive and behavioural profile of amyotrophic lateral sclerosis: application of the consensus criteria. *Behav Neurol* 2013;27:143-53.
- (137) Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N, et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. *Neurology* 2011;76:1263-9.
- (138) Montuschi A, Iazzolino B, Calvo A, Moglia C, Lopiano L, Restagno G, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. *J Neurol Neurosurg Psychiatry* 2015;86:168-73.
- (139) Oh SI, Park A, Kim HJ, Oh KW, Choi H, Kwon MJ, et al. Spectrum of cognitive impairment in Korean ALS patients without known genetic mutations. *PLoS One* 2014;9:e87163.
- (140) Hu WT, Shelnutt M, Wilson A, Yarab N, Kelly C, Grossman M, et al. Behavior matters--cognitive predictors of survival in amyotrophic lateral sclerosis. *PLoS One* 2013;8:e57584.
- (141) Bede P, Elamin M, Byrne S, Hardiman O. Sexual dimorphism in ALS: exploring gender-specific neuroimaging signatures. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:235-43.