Neuropsychological impairment in amyotrophic lateral sclerosis–frontotemporal spectrum disorder

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Abstract | Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a rapid course, characterized by motor neuron dysfunction, leading to progressive disability and death. This Review, which is aimed at neurologists, psychologists and other health professionals who follow evidence-based practice relating to ALS and frontotemporal dementia (FTD), examines the neuropsychological evidence that has driven the reconceptualization of ALS as a spectrum disorder ranging from a pure motor phenotype to ALS–FTD. It focuses on changes in cognition and behaviour, which vary in severity across the spectrum: around 50% individuals with ALS are within the normal range, 15% meet the criteria for ALS–FTD, and the remaining 35% are in the mid-spectrum range with milder and more focal impairments. The cognitive impairments include deficits in verbal fluency, executive functions, social cognition and language, and apathy is the most prevalent behavioural change. The pattern and severity of cognitive and behavioural change predicts underlying regional cerebral dysfunction from brain imaging and post-mortem pathology. Our increased recognition of cognition and behaviour as part of the ALS phenotype has led to the development and standardization of assessment tools, which have been incorporated into research and clinical care. Measuring change over the course of the disease is vital for clinical trials, and neuropsychology is proving to be a biomarker for the earliest preclinical changes.

[H1] Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disease that is characterized by degeneration of both upper and lower motor neurons. The disease is

considered to be rare, affecting around 1.75 in 100,000 individuals worldwide[1], although the prevalence might vary between different ethnic groups[2]. The first symptoms include muscle weakness, fasciculation or brisk reflexes and spasticity in the limbs or bulbar region. Affected individuals often present with difficulties with fine motor coordination, such as doing up buttons, or leg weakness and foot drop, and occasionally respiratory weakness. Diagnostic delay from onset of symptoms is substantial — commonly over 10 months[3]. The course of the disease is rapid, with progressive disability and a mean survival of 3–5 years from symptom onset.

In recent years, we have seen a shift in our understanding of ALS as a pure neurodegenerative motor disorder to a multisystem disorder with a spectrum of phenotypes ranging from pure motor ALS to ALS–frontotemporal dementia (ALS–FTD). This reconceptualization of the condition as ALS–frontotemporal spectrum disorder[4] (ALS–FTSD; Figure 1) has been partly driven by the discovery of neuropsychological impairment as a key characteristic of the clinical phenotype in many cases, as well as genetic and pathological overlap between ALS and FTD.

This Review focuses on the types of cognitive impairment, behavioural dysfunction and underlying cerebral dysfunction that are found in the mid-range of the ALS–FTD spectrum. Brain imaging studies are discussed from a neuropsychological perspective when considering the different cognitive and/or behavioural functions that can be impaired in ALS. I also explore the development and validation of assessment tools and provide recommendations for intervention. The Review is particularly relevant for scientists, clinicians and other health-care professionals who are engaged in evidence-based research and practice relating to neurodegenerative diseases and dementia.

[H1] ALS–FTSD

The term ALS–FTSD refers to a spectrum that ranges from pure motor ALS with no evidence of cognitive or behavioural impairment or cerebral dysfunction beyond the motor pathways to ALS with full-blown FTD (ALS–FTD). Around 35% of patients with ALS lie in the mid-range of this spectrum and have subtle and focal impairments in cognition and/or behaviour[5-11] (Figure 1). This radical shift in our understanding away from ALS as a pure motor neurodegenerative

disorder to incorporate other systems gained momentum in the 1980s with several neuropsychological studies[12-14], followed by confirmation in neuroimaging studies[15-17]. The association between ALS and FTD, which were previously regarded as disparate conditions, has now been shown to have clinical, pathological and genetic underpinnings, pointing away from a comorbidity, which implies the co-presentation of two distinct disorders, to a multisystem disorder with a heterogeneous presentation.

FTD without ALS is itself heterogeneous, and the type of FTD found in ALS is typically the behavioural variant (bvFTD); the other two types of FTD, semantic dementia and progressive non-fluent aphasia, occur infrequently with ALS[18]. Behavioural change is a prominent feature that culminates in the caregiver reporting a personality change. Similar to bvFTD, people with ALS can show one or more of the following five behavioural symptoms: disinhibition (socially inappropriate behaviour, loss of manners and/or impulsivity); apathy; loss of sympathy and/or empathy; stereotyped and/or perseverative behaviour; and hyperorality or increased eating. Other common symptoms include anosognosia — that is, a lack of awareness of their cognitive and behavioural problems, also known as insight— and, on occasion, psychotic behaviour[4].

Consensus criteria based on the degree and type of neuropsychological impairment have been formulated for the diagnosis of frontotemporal dysfunction in ALS[4]. These criteria delineate people into the following categories: ALS; ALS with cognitive impairment (ALSci), behavioural impairment (ALSbi) or both (ALScbi); and ALS–FTD categories. Diagnosis of ALS–FTD is based on the criteria for diagnosing bvFTD without ALS[19], with evidence of at least three of the five behavioural symptoms listed above or two of these behaviours and a cognitive profile of impaired anterior (executive) functions with relatively preserved posterior (memory and visuospatial) functions (Box 1).

The profile of cognitive and behavioural dysfunction in ALS–FTSD is distinct from that found in other common disorders in older adults. Comorbid ALS–Alzheimer disease (AD) is probably the most common differential diagnosis, although AD typically manifests with primary memory deficits, with impairments in the retention of information over time. Executive dysfunction and behavioural change resembling ALSci, ALSbi or FTD can also be found in AD, and a frontal variant of AD has been described[20]. However, the neuropsychological profile

tends to have some element of posterior cerebral dysfunction with disproportionate involvement of visuospatial dysfunction[21], which is rare in ALS.

Despite the overwhelming commonality between the neuropsychological profiles of bvFTD and ALS–FTD, subtle differences were found in a retrospective cohort[22]. Individuals who had bvFTD without ALS (*n* = 185) exhibited more prominent behavioural abnormalities than those diagnosed with ALS–FTD (*n* = 56); for example, disinhibition and/or socially inappropriate behaviour was reported in 63% of the former group and only 36% of the latter. Executive deficits were found equally in both groups, although language changes, including sentence comprehension impairments and agrammatism, were more common in people with ALS–FTD. The two groups showed some differences in age and disease duration and in the results of genetic screening, with the only overlapping mutation being the *C9or72* repeat expansion, which was found in 7 individuals with ALS–FTD and 18 with bvFTD, *MAPT* and *GRN* mutations were only found in the latter group, albeit at low frequency. The study suggested an incomplete match of symptoms between ALS–FTD and bvFTD, with some characteristics being specific to ALS, raising the question of whether ALS–FTD is a distinct disorder from bvFTD.

The consensus criteria described above are now widely used, although any type of categorization can fail to capture individuals who do not quite reach the relevant threshold. For example, the diagnosis of ALSbi requires the presence of apathy and/or two other non-overlapping behaviours; however, in some instances, such as in the early stages of bvFTD or in ~~presymptomatic individuals with a genetic mutation that places them at risk of developing ALS or FTD~~, disinhibition might be the key presenting symptom. If disinhibition is the sole symptom, the individual will be classified as ALS with cognition and behaviour in the normal range. A symptom-based approach— for example, ALS with disinhibition — might better suited to describe the phenotype and monitor progression in the research setting.

[H1] Neuropsychological impairment

Evidence for a mid-spectrum range in ALS–FTSD initially came from neuropsychological and brain imaging studies, which identified a profile of mild and focal extra-motor dysfunction in people with ALS who did not meet the criteria for ALS–FTD, and was reinforced most recently through the discovery of cerebral pathological changes at post-mortem examination.

[H2] Verbal fluency

Verbal fluency impairments have been the most consistent and striking neuropsychological findings in people with ALS[6,23,24]. The impairment typically manifests in tests of letter (phonemic) fluency, wherein the participant must generate words beginning with a given letter in a limited time period (typically 1 min) while applying rules, such as no proper nouns. One of the most challenging aspects of neuropsychological assessment in ALS is to ensure that performance is not driven by physical disability. This is a particular problem in the case of standardized verbal fluency tests such as Controlled Oral Word Association, which requires rapid spoken generation of words for 3 min. Clearly, speed of speech is likely to be affected by the severity of bulbar dysfunction and resultant dysarthria.

This problem was tackled through the use of the verbal fluency index (VFI)[23,25] — a simple method that was originally developed as an adaptation of the written verbal fluency test and comprises a copy condition in which the person is timed as they copy words previously written in an earlier generation condition. The VFI is an estimate of the average time taken to think of each word and shows independence from functional disability, with no correlation with severity of upper limb dysfunction[25]. A similar procedure was used with oral letter fluency, which involved a read condition in which the person was timed as they read out previously generated words[23]. Reading or copying words are not accurate measures of motor speed as they involve both motor functions and cognitive processes, including word recognition and accessing lexical and orthographic representations. However, options for measuring motor speed using paper and pencil tests are limited. Using reading or copying produces a shortened thinking time and therefore a smaller VFI. Given that longer VFIs indicate impairment, this method produces a conservative estimate of the average time taken to think of each word. The VFI has stood the test of time as a stand-alone sensitive measure of cognitive dysfunction in ALS and has been incorporated into multicomponent assessment protocols[11,26,27], and local normative data have been produced[28].

People with ALS show considerable heterogeneity in performance on verbal fluency tests, supporting the idea of a spectrum. The degree of impairment might differ between ALS subgroups; for example, in one study[25], individuals with bulbar involvement showed longer

VFIs (mean 11.8) than those without bulbar involvement (mean 6.2, compared with 4.9 in individuals without ALS.

This heterogeneity was further cemented by the demonstration of localized cerebral dysfunction in people with ALS who had verbal fluency impairments. In a functional PET study[29], in which letter fluency was used as the activating paradigm, reduced activation in the dorsolateral prefrontal cortex (bilaterally) and the left anterior cingulate cortex was observed in a group of patients with long VFIs. By contrast, individuals with ALS who had VFI scores within the normal range showed little evidence of cerebral dysfunction when compared with a healthy control group. A similar profile of dysfunction has been shown with functional MRI (fMRI)[30], and structural MRI revealed reduced white matter volumes affecting anterior fibres adjacent to the lateral ventricles in people with ALS and a verbal fluency deficit[31].

The question remains as to why verbal fluency is so sensitive to the ALS disease process. Like most clinical neuropsychological tests, verbal fluency relies on several different cognitive processes, including executive functions such as strategy formation, switching and intrinsic initiation, working memory and language processes of word finding. In a study that dissected the different cognitive processes involved[23], deficits in people with ALS were seen across tests involving intrinsic generation, including category fluency, which relies on generation of semantic concepts, and design fluency, which involves the generation of meaningless designs. Through the lens of the eminent cognitive theory of working memory[32], it was hypothesized that verbal fluency requires a person to hold sound-based information and rehearse it silently to aid the generation of the next word. These processes can be understood through the phonological loop of the working memory model, which was assessed using two procedures from the cognitive literature: the word length effect, which reflects functioning of the articulatory loop, and the phonological similarities effect, which reflects functioning of the phonological store. Both of these functions were found to be operating as normal in people with ALS[23]: they remembered more phonologically dissimilar letters than similar letters, which are more phonemically confusing, and remembered more short words than long words, because a larger number of the former words could be silently rehearsed within the articulatory loop. However, on both tasks the participants with ALS showed reduced item span (words or letters immediately recalled), indicating an impairment in working memory capacity.

[H2] Executive functions

Deficits in attention and working memory capacity were investigated further using a dual task paradigm, in which attention is split between two tests — a digit recall task and a visual inspection time task — undertaken in parallel[33] (Figure 2). The visual inspection time task was used to assess information processing speed and involved brief presentation (17–150 ms) of a simple line stimulus in which one arm was longer. The stimulus was then masked and the participant was asked to state which line was longer (left or right). As a group, patients with ALS were able to correctly identify the longer arm as effectively as heathy controls, even with very brief presentations. Both number recall and visual inspection declined when the tasks were combined, and this dual task cost was greater in patients with ALS than in controls, indicating dysfunction in the central executive component of working memory under conditions of divided attention. Diffusion tensor imaging (DTI) revealed that this deficit was related to cerebral dysfunction, with a negative correlation between dual task cost and fractional anisotropy of white matter fibres in the middle frontal gyrus and anterior corona radiata — different from the regions that correlated with verbal fluency.

Other executive functions that are affected in ALS include the processes of abstraction and concept formation, which are assessed using a card sorting test in which participants are required to generate stimuli groupings according to both verbal semantics, such as animals versus transport, and visual semantics, such as width of lines, and to switch between these groupings. Sorting impairment in ALS was related to cortical thinning in the left prefrontal and parietal cortices, as detected using structural MRI[34]. Inhibitory control is also affected in some people with ALS, although to a lesser extent than in bvFTD[35]. Inhibitory control deficits are demonstrated by errors on the Hayling Sentence Completion Test, in which the participant is presented with a sentence with the last word missing and must stop themselves from completing the sentence with a sensible word and generate an unconnected word.

[H2] Social cognition

Dysfunction in social cognition is recognized as a key part of the ALS cognitive profile. Social cognition is typically assessed using paradigms such as Theory of Mind (ToM) and emotion recognition tests, which have been adapted from the bvFTD and autism literature and modified

for individuals with disabilities. A series of ToM studies have shown that patients with ALS have difficulty using social signals — in particular, eye direction — to infer a mental state in the context of both affective (what does X like?) and cognitive (what is X thinking of?) judgements[36,37], and in processing social as opposed to non-social intentions of others, such as asking someone to remove a bag from a seat on a train[38]. A meta-analysis has shown medium effect sizes of ALS on performance in ToM tests and emotion recognition studies, indicating significant and consistent impairments in people with this disease[39]. Emotion recognition is typically assessed by the Ekman faces test[36,40], and patients with ALS have particular problems recognizing negative emotions of disgust, anger, fear and sadness[41]. A test that combines both inference of intention and emotion recognition is the Reading the Mind in the Eyes Test[42], which has been validated in ALS[43]. A short form of this test has been produced[44] and has shown sensitivity in ALS, although like its longer counterpart, it suffers from issues with gender stereotypes and lack of racial diversity. A confounding factor is whether the social cognition deficit is driven by executive functions, and a relationship has been shown between the severity of both types of cognitive functions[39,42]. However, this relationship might make little difference to the overall clinical impact of difficulties with social interactions in people with ALS.

Cerebral correlates of the social cognition deficits in ALS have been investigated using resting-state fMRI. Reduced connectivity in regions including the frontal and temporal lobes in the default mode network and in the frontal parietal network was shown in individuals who scored significantly lower than controls in cognitive and affective ToM at a 6-month follow up[45]. Furthermore, patients with ALS have shown problems with empathy and more selfish behaviour on the Ultimatum game, which was associated with hypometabolism in the anterior Insular and cingulate cortices on ^{18}F-fluorodeoxyglucose (FDG)-PET[46].

[H2] Language functions

In recent years, light has been shed on language dysfunction in ALS. These cognitive processes are concerned with the comprehension and expression of thoughts and words and are distinct from the physical aspects of speech production that are commonly affected in ALS and result in dysarthria. Impairments have been shown in naming, spelling, verb processing and reception

of grammar, among other functions, in people with ALS[47]. Agrammatism has also been described in ALS–FTD[22]. The frequency of language impairment reported in ALS differs between studies. One study indicated that it is at least as common as executive dysfunction in people with ALSci, with 43% of a cohort of 51 individuals showing abnormal scores on language tests[47]. A similar profile of impairment was shown in a large sample (*n* = 117), using tests from the Psycholinguistic Assessments of Language Processing in Aphasia, although the frequency of impairment was relatively low, ranging from 3–23% on different subtests[48]. Executive dysfunction was considered to be a driving factor, although the evidence came from regression involving phonemic fluency, which involves a number of language processes, including word retrieval and lexicon search, in addition to executive functions, so a correlation would be expected.

[H2] Episodic memory

Although memory dysfunction is sometimes reported in ALS, the question remains as to whether this is a secondary effect of attentional dysfunction affecting encoding and retrieval or whether it represents a primary memory consolidation and retention deficit. One study showed that in a group of patients with ALS, only those who had executive dysfunction exhibited a visual memory deficit in the recall of a complex figure[49]. In another study[8], memory dysfunction was found in 11% of a sample of over 100 patients with ALS but was only present as a single cognitive domain deficit in 3.8% and mostly occurred in combination with executive dysfunction. Together, these findings suggest that memory dysfunction in ALS may be secondary to attentional and executive problems in many individuals.

Among individuals with ALS, verbal memory was found to be disproportionately affected in those with a *C9orf72* mutation, although no differences in visual memory were found between mutation carriers and non-carriers[50]. The two groups also differed on fluency and the Trail Making Test, possibly implicating executive dysfunction. However, some evidence from brain imaging indicates mesial temporal lobe involvement, with correlations being observed between immediate and delayed story recall and grey matter hippocampal volumes, pointing towards hippocampal damage as the cause of a primary memory impairment[51]. Further evidence suggests that a disconnection between the frontal and temporal lobes with

reduced integrity of the uncinate fasciculus, as revealed through DTI, correlates with performance on verbal memory tests[52]. Temporal lobe involvement has also been be implicated in later stages of ALS[53,54], although interpretation of findings at these stages is complicated by respiratory failure and nutritional factors.

[H2] Behaviour

Behavioural abnormalities can be present in ALS, either in addition to cognitive deficits or as a stand-alone impairment[4]. Apathy is the most prevalent behavioural symptom, although loss of sympathy, disinhibition, perseverative and stereotyped behaviours and hyperorality and/or increased eating have also been reported[55,56]. Apathy is a multidimensional construct, as conceptualized through the Dimensional Apathy Framework[57]. This framework comprises three dimensions: initiation apathy characterized by lack of generation of thought or behaviour; emotional apathy, characterized by emotional blunting and neutrality; and executive apathy, which manifests as problems in goal management. Increased initiation apathy in people with ALS has been reported by both the patients themselves and their carers[58]. The cerebral correlates underlying the different dimensions of apathy in ALS have been investigated, and reduced grey matter volumes in the superior frontal gyrus in particular were associated with increased self-rated initiation apathy, whereas increased emotional apathy was associated with reductions in the middle frontal gyrus, frontal pole and anterior cingulate.

In the literature, behavioural changes have been typically considered as a syndrome that is distinct from cognitive dysfunction in ALS. Indeed, the consensus criteria for diagnosing frontotemporal dysfunction place these changes in separate categories[4], and patients with specific types of behavioural change are classified as ALSbi, although an overlap diagnostic category, ALScbi, has been described. Attempts to assign symptoms to these diagnostic categories could lead to confirmation bias. The study of apathy undermines the distinction between cognitive and behavioural changes, as a strong correlation has been observed between initiation apathy and increased VFI. No such association was found for executive or emotional apathy, indicating that the patients were not apathetic in general. Difficulties with initiation of thought could provide a mechanistic link between initiation apathy and

impairments in verbal fluency. Brain imaging studies have shown cerebral involvement in apathy in ALS, and a network of areas including the anterior cingulate gyrus and the dorsomedial, dorsolateral and orbitofrontal cortices is common to apathy and verbal fluency[29-31,59-61] (Table 1). Similarly, accumulation of abnormal TAR DNA-binding protein 43 (TDP43) has been found in Brodmann areas (BA) 11, 24 and 46 (Figure 3) in two-thirds of patients with ALS who have behavioural impairment and in patients with verbal fluency dysfunction[62]. This regional pathology could result in a specific cognitive impairment that manifests behaviourally as a type of apathy.

An association between performance on a face emotion recognition test and emotional apathy scores has also been reported in patients with ALS: those with poor emotion recognition showed increased emotional apathy[63]. Problems with ToM are likely to underlie some of the symptoms of loss of sympathy and/or empathy that are commonly reported in ALS, although studies confirming such an association are lacking at present.

Behavioural change has considerable impact on daily life in people with ALS and is seen as notably burdensome to the carergivers[64]. Predictors of high caregiver burden, as measured using the Zarit Burden Interview, include apathy, disinhibition and executive dysfunction, with total behaviour change scores on the Frontal Systems Behaviour Scale (FrSBe) contributing 31% of caregiver burden in regression analyses, the other major contributors being anxiety and depression[65] (38.5%). In a consecutive sample of patients from an ALS clinic, behavioural abnormalities, measured using the FrSBe, were associated with higher burden and depression and lower quality of life in the caregiver[66]. Of note, however, the FrsBe was not designed for people with physical disability.

When compounded with the cognitive and physical disabilities, behavioural changes in ALS can be challenging to manage. For example, a combination of disinhibition and impulsivity, binge eating and bulbar dysfunction with dysphagia can manifest as an increased risk of aspiration. Behavioural abnormalities might also be associated with non-adherence to treatment (for example, non-invasive ventilation and gastrostomy) although this phenomenon has only been related to FTD and has not been shown in people with milder cognitive and behavioural changes alone[64]. Psychological support is recommended for people with ALS and their caregivers (Box 2).

[H1] Neuropsychological assessment: what, how and why?

Fast and accurate assessment of cognition and behaviour is essential for research and clinical care in ALS. Standardized, validated tools can be widely applied across multicentre studies internationally, thereby facilitating clinical trials.

[H2] Assessment tools

The brief cognitive assessments that have been employed in ALS research include the Addenbrooke's Cognitive Examination[67] (ACE-R and ACE-III) — a widely used test for mild cognitive impairment and dementia — and assessments specifically designed for ALS, such as the ALS Cognitive Behavioural Screen[68] (ALS-CBS) and the Edinburgh Cognitive and Behavioural ALS Screen[27] (ECAS). The ALS-CBS has been combined with the written verbal fluency test (with the VFI calculation) and the Frontal Behavioural Inventory to produce the University of California San Francisco (UCSF) Cognitive Screening Battery[26]. The screen was shown to be effective in detecting ALSci, ALSbi and ALScbi against gold-standard neuropsychological evaluation[26]. Within the ALS Multicentre Study of Oxidative Stress (COSMOS) of 274 people with ALS[11], this screening examination identified that a large number of the participants had ALSci (54%) and a smaller number had ALSbi (14%).

Progressive movement disorders necessitate an assessment tool that can be adapted for physical disability, which in ALS can affect both speech (dysarthria to anarthria) and hand control (writing and drawing). The time required to complete an assessment is also a crucial factor to avoid fatigue. Finally, the tool must assess those abilities that are affected in ALS, namely, executive functions, verbal fluency, language function and behaviour.

The ECAS was designed to accommodate these requirements. It is a multidomain tool that includes assessments of executive and language functions and verbal fluency, producing an ALS-specific score, and a semi-structured caregiver interview to assess behavioural abnormalities. A neuropsychological profile can be used to aid differential diagnosis and, with this in mind, the ECAS includes not only tests that have been shown to be sensitive to ALS but also functions that are less commonly affected in ALS, namely, episodic memory and

visuospatial abilities, producing an ALS non-specific score. Both of these domains are more likely to be affected in AD than in ALS, and the ALS non-specific score has been shown to be effective at discriminating people with AD from healthy controls (97% sensitivity and 96% specificity) and in differentiating between AD and ALS (96% sensitivity and 91% specificity)[69-71].

The ECAS can be undertaken either in writing or orally, and the participant can switch the method of responding halfway through the assessment if they become physically fatigued. The test in its full form might not appropriate for individuals with severe disabilities (for example, with marked problems speaking or writing) as although most subtests require simple, short responses or pointing, some subtests, such as verbal fluency and memory, require long responses, which might be impractical with eye gaze technology, particularly in the case of fluency tests, where predictive text should be switched off. However, a proof-of-principle study was conducted in which a mobile brain–machine interface was applied to some subtests in which responding is simple[72] (for example, naming). The full test battery needs to be undertaken in its entirety in one sitting, given that it includes delayed recall and recognition subtests, and, therefore, it might not be advisable for individuals who will fatigue within 20 min or lack motivation. Nevertheless, it is brief, lasting only 20–30 min, which is preferable to the typical 90–120 min required for comprehensive assessment.

The ECAS performs well against full comprehensive neuropsychological assessment[73], with 85% sensitivity and 85% specificity (positive predictive value 0.73, negative predictive value 0.92), which increased to 92% sensitivity when a 5-point borderline was used to determine ALSci[73]. Similar findings have been shown with versions of the ECAS in languages other than UK English[74]. Use of either the ECAS total score or the ALS-specific score produced the greatest accuracy in comparison with full neuropsychological assessment. Good concordance has also been shown between deficits in specific cognitive domains against the corresponding domains in the full assessment[75]. Guidelines for using the ECAS are outlined in Box 1.

In a consecutive sample of patients with ALS from an ALS clinic, 33% were classified as ALSci using the ECAS[27]. Among these individuals, the most common impairments were in language (35%), executive functions and verbal fluency (23% each), with much less common deficits in memory (4%) and visuospatial functions (2%). Similar levels of language dysfunction

have been found in both German and Italian populations[76,77]. The ECAS has also been shown to be a valid assessment method for individuals who have FTD without ALS[69,78]. The ALS-specific and ECAS total scores were particularly accurate in identifying people with FTD (94% sensitivity and 96% specificity) and were superior to the ACE-III (79% sensitivity and 98% specificity).

The ECAS has a comprehensive range of short tests of executive functions that measure working memory (reverse digit span), cognitive inhibition (similar to the Hayling Sentence Completion Test), attention switching and monitoring (oral Trail Making Test) and social cognition (judgement of preference on the basis of eye gaze). These features distinguish the ECAS from the ACE-III, which lacks specific assessment of executive functions, but like the ALS-CBS includes some tests of attention and working memory (serial sevens in ACE-III and reverse digit span in ALS-CBS).

All three assessments include phonemic fluency, although the ECAS assesses both free fluency and four-letter fixed fluency, which requires greater search of the lexical store. Both fluency tests have been found to be sensitive to ALS[11,23] and, like the UCSF Cognitive Screening Battery, include calculation of the VFI to account for performance decrements owing to physical disability. The ECAS and the ACE-III also include some assessment of language functions. The ECAS includes naming, comprehension and spelling, whereas the ACE-III is more comprehensive, with naming, repetition, comprehension, writing and sentence structure and reading of irregular words, and was designed to screen for language variants of FTD. Some of the subtests included in the ACE-III — for example, repetition and sentence writing — would not be suitable for ALS assessments.

Ease of administration is another key issue for cognitive screening. The ECAS, ACE-III and ALS-CBS all involve paper-and-pen administration, which is still commonly used within multidisciplinary care. Automated computerized tablet tests are reliable for producing a metric, but might fail to record nuances of cognitive and, in particular, behavioural change in ALS, which may be noted and explored using a less rigid interview with a clinician. However, remote assessment is becoming increasingly important, and a telephone-based version of the ALS-CBS has been described[79].

Standardized procedures enable collaboration across multiple centres and countries, which is essential for clinical trials and genetic–phenotype studies. To aid this effort, the tools described above are available in multiple languages with cultural adaptations[72,76,80-83].

[H2] Assessing behaviour

Several quantitative tools have been developed specifically for the assessment of behaviour in neurological disorders such as ALS, including the Beaumont Behavioural Inventory (BBI), which is completed by the caregiver[84] and comprises 41 questions on the range of symptoms defined in the consensus diagnostic criteria for FTD[19,85] to produce a total score of the severity of behavioural abnormalities. Other tools, such as the Dimensional Apathy Scale (DAS), focus on a single symptom that is prevalent in ALS[58].

The DAS comprises questions assessing the three apathy dimensions: initiation apathy ("I set goals for myself"; "I try new things"), emotional apathy ("I am concerned about how my family feel"; "before I do something I think about how others would feel") and executive apathy ("I am able to focus on a task until it is finished"; "I get easily confused when doing several things at once"). The three subscores enable a profile of apathy to be determined for different disorders. The profile in ALS is of increased initiation apathy[57], as reported by both the person with ALS and a caregiver, whereas people with Parkinson disease show both initiation and executive apathy[86] and those with AD have a more global apathy profile[87]. The distinct profiles enhance our understanding of potential therapeutic targets. For example, in ALS, the lack of initiation of ideas could be addressed through education of the caregiver with simple strategies including replacement of open questions such as "what would you like to do today?" with closed questions that restrict choice, such as "would you like to do A or B?". This approach enables the patient to continue to engage in daily decisions and, together with other strategies such as cueing through strategic placement of objects, will help to maintain participation in daily life.

Assessment of behavioural issues in ALS is challenging owing to the degree of physical disability, which influences engagement in activities and is accounted for to some extent by some tools (for example, the BBI and DAS) but not others (for example, the FrSBe). Distinguishing symptoms of apathy from depression is also an issue, although within the

dimensional apathy framework, emotional apathy is conceptualized as emotional blunting and neutrality rather than negative thinking.

The questionable distinction between cognitive and behavioural syndromes in ALS might partly stem from differences in measurement of cognition (quantitative) and behaviour (qualitative). Although some questionnaires successfully measure discrete symptoms, such as apathy, overall, the assessment of all behaviour does not lend itself well to quantitative techniques. Qualitative assessment through semi-structured interviews can pick up the nuances of behaviours, their changes over time and their impact, thereby identifying potential targets for intervention. In the case of disinhibition, for example, context plays an important part: taking your shoes and socks off in public might be socially acceptable near a beach but not in a restaurant. Cultural norms within and outside the patient's family and close circle of friends can also influence the perception of behavioural change. The BBI can be used to assess a range of abnormal behaviours but does not necessarily lend itself to assessing the impact of a single behaviour type. For example, disinhibition is one of the most burdensome symptoms in ALS and can present in isolation. Developing scales for each type of abnormal behaviour might be impractical in a clinical setting. Measuring behavioural change from premorbid or baseline levels is also challenging, and caregiver reports are vital. Owing to the complexities of behavioural assessment, a clinical interview and opinion might be more valuable than a cut-off score on a questionnaire.

[H2] Brain imaging and pathology

A wide range of brain imaging methods have been applied to shed light on the neuropsychology of ALS. Table 1 shows the breadth of the methodologies that have been used, together with the affected cortical regions or subcortical white matter tracts and the associated cognitive and/or behavioural dysfunction. Findings from neuroimaging, ranging from early functional PET studies to structural MRI and FDG-PET, reflect the heterogeneity of cognitive and behavioural presentations in ALS. When ALS patients with cognitive impairment in the form of letter fluency deficit or executive dysfunction are compared with ALS patients matched for clinical variables but without cognitive impairment, a range of cortical

involvement is revealed, which is even more widespread in ALS–FTD[29-31]. The white matter tracts that are affected are typically those that project to the frontal lobe (Figure 3b).

Brain imaging has also aided the validation of the brief cognitive and behavioural assessments that are used in ALS. DTI has revealed correlates of performance on the ECAS, such as relationships between the integrity of frontal, temporal and parietal association fibres, including the superior longitudinal fasciculus, and verbal fluency, executive functions and ALS-specific ECAS scores[88,89]. The patterns of deficits on the ECAS correlated closely with a DTI-based disease-staging model[53]. fMRI paradigms of the ECAS social cognition and verbal fluency tasks showed reduced activation in the orbitofrontal cortex during the former task in individuals with ALSbi, and a pattern of increased activation during the social cognition task, interpreted as a compensatory strategy, in patients with mild cognitive changes[90]. In addition, transcranial magnetic stimulation has revealed cortical hyperexcitability in people with ALSci, as determined by the ECAS[91].

Robust evidence of brain changes underlying performance on the ECAS came from a post-mortem pathological study of 27 people with ALS who had undertaken the ECAS during the course of their illness[62]. Seven of the participants were classified as ALSci, and all of these individuals showed TDP43 accumulation — a pathological hallmark of ALS and FTD —in extramotor regions of the brain. Furthermore, TDP43 pathology in distinct regions, which were selected a priori on the basis of the neuropsychological literature, corresponded to specific cognitive deficits. Three patients with deficits on the executive functions score had pathology in regions including the dorsolateral prefrontal cortex (BA46 and BA9), eight patients with language deficits had pathology in both the inferior frontal gyrus and temporal regions (BA44, BA45 and BA20), and four patients with verbal fluency impairment showed involvement of the inferior and middle frontal gyrus (BA9 and BA44). This study represented the first demonstration of regional TDP43 accumulation associated with the mid-spectrum range of cognitive impairment in predicted regions, and the findings suggest that ECAS deficits are a biomarker for pathological change.

One of the most promising biomarkers of cognitive and behavioural change in ALS and FTD is neurofilament light chain (NfL), which is an indicator of neuroaxonal degeneration[92]. Plasma and cerebrospinal fluid levels of NfL are raised in frontotemporal lobar degeneration syndromes[93], and were shown to be related to global cognitive scores in a combined group of

individuals with FTD (*n* = 86) or ALS (*n* = 38), but not in the ALS group alone[94]. Longitudinal data from the Genetic Frontotemporal Dementia Initiative (GENFI) has shown that levels of this biomarker increase when presymptomatic individuals with a known genetic mutation, such as a *C9orf72* expansion, convert to symptomatic disease[95]. Rates of NfL change were associated with rate of decline on the Mini-Mental State Examination, although this scale is not well suited to detect changes found within frontotemporal syndromes. Evidence of an association of NfL levels with cognitive measures in ALS is lacking.

[H2] Measuring change over time

A relationship has been demonstrated between cognitive and behavioural dysfunction and the clinical stage of disease of ALS[96]. This study used the King's Staging System, in which the disease stage is based on regional involvement, namely, bulbar, upper limb, lower limb and respiratory or nutritional domains. The stages relate to how far along a person is through the disease course, with Stage 1 being defined as the involvement of a single bodily region and subsequent stages reflecting the cumulative involvement of additional regions or functions[97]. A cross sectional analysis revealed a marked increase in neuropsychological dysfunction with ALS progression, with 58% of patients remaining neuropsychologically intact (no cognitive or behavioural dysfunction) at Stage 1, decreasing to only 20% at Stage 4[54].

Although these studies suggest that cognitive and behavioural functions decline with disease progression in ALS, they are cross-sectional, and demonstrating cognitive and behavioural change longitudinally through the disease course has proved difficult. From the few longitudinal studies that have been conducted, a heterogeneous pattern has emerged, with approximately one-third of patients, including some who had normal functions at baseline, showing deterioration in cognition[98,99]. Another study demonstrated cognitive decline in individuals who presented with executive dysfunction at baseline[100].

Longitudinal studies are fraught with methodological issues, most notably attrition bias. Cognitive impairment has been shown to be a negative prognostic factor in ALS and is associated with shorter survival, resulting in increased attrition in individuals with cognitive deficits at baseline[99,101]. ECAS total scores have been shown to predict survival time at 6-month follow-up[102]. In addition, some of the earlier studies did not use repeatable assessments that

limit practice effects. Such assessments are now being developed, so future studies should be able to measure change more accurately[103-105].

[H2] Neuropsychological change at the presymptomatic stage

Measurement of neuropsychological change is of particular relevance to the study of presymptomatic patients who are at a high risk of developing ALS and/or FTD and could be suitable candidates for drug intervention. In 2011, a genetic mutation was identified that cemented the concept of the ALS–FTD spectrum[106,107]. The hexanucleotide repeat expansion in the *C9orf72* gene was found in both familial and, to a lesser extent, sporadic ALS and FTD (25% of familial FTD, 40% of familial ALS, 80% of familial ALS–FTD, 10% of sporadic ALS and 6% of sporadic FTD). In some[108,109] but not all[11,110] studies, the presence of this mutation has been associated with a greater likelihood of cognitive and behavioural impairment in people with ALS. One study showed that presymptomatic *C9orf72* mutation carriers without clinical symptoms had significantly impaired verbal fluency and visual memory and reduced white matter integrity (measured using DTI) in the orbitofrontal cortical areas, although there was no evidence of further change at 12-month follow up[111]. This new area of research is gaining attention, and new diagnostic criteria to categorize neuropsychological impairment in presymptomatic individuals have been proposed from the fields of ALS[112] and FTD[113].

[H2] Clinical trials

Neuropsychological assessment has been adopted by a number of clinical trials as a secondary outcome measure[114,115]. In a systematic review published in 2020, nine trials were identified in which cognition and behaviour were assessed using the ECAS, the ACE-III, the Frontal Behavioural Inventory and/or the ALS-CBS. Such trials might not only use these assessments to classify participants at the outset of the trial and to ensure equal distribution between the study arms, but also as an outcome measure to assess the impact of the treatment on these symptoms[116]. This is particularly relevant given the relationship of neuropsychological impairments to other biomarkers (imaging and pathology), caregiver burden and survival, and the ability to perform longitudinal measurements will be vital for future trials.

[H2] Clinical care

The clinical importance of cognitive assessment in ALS has been recognized, as indicated by the inclusion of a specific recommendation in care management guidelines[117]. Surveys that assessed the clinical impact of cognitive assessment in the UK and internationally revealed that the ECAS was widely used in health-care services in the UK and Europe, whereas the ALS-CBS was more commonly used in North America[118,119]. From interviews with health-care professionals and people with ALS and their families, themes emerged on the benefits of assessment, including increased awareness about cognitive and behavioural changes among patients, carers and clinicians. The results of formal assessments might validate the experiences of both patients and caregivers and provide explanations for cognitive and behavioural changes. Conversely, as 50% of people with ALS have normal cognition and behaviour, the findings might reassure the patient and caregiver and, for example, reaffirm the patient's decision to continue working. These assessments can also help to identify patients' needs and inform clinical decision making on the suitability of interventions, including discussions regarding end-of-life care. Given the potential for decline in cognition and behaviour over the course of the disease, and the finding that cognitive impairment predicts shorter survival, the assessments should be conducted at an early stage, and discussion and decision making over interventions that might be needed in the future, such as gastrostomy and non-invasive ventilation, should be encouraged. Intervention from a clinical neuropsychologist was reported as particularly helpful to the care team to manage complex cases[118,120].

Although clinicians recognize the benefits of early assessment, barriers to incorporating this approach into clinical practice might be challenging to overcome. These barriers include the perception that other staff members of the multidisciplinary team will think that cognitive testing of patients is unimportant and may even have negative effects such as increasing anxiety[121]. Such perceptions might be altered through education, the inclusion of assessment in health guidelines and observation of the effectiveness of this approach. Public information is now widely available on charity websites to aid education. UK health guidelines recommend that formal neuropsychological assessment is offered to all patients with ALS as part of routine clinical care, as cognitive and behavioural changes might be hidden or misattributed to increasing physical disability.

Incorporation of neuropsychological assessment into clinical practice with limited resources is an additional concern. Comprehensive neuropsychological assessment by a clinical neuropsychologist is the gold standard, as they can address the whole gamut of factors that might affect cognition, including premorbid functioning, education and occupation, developmental difficulties including dyslexia, and anxiety and depression. They can also consider secondary motivational factors that are not directly related to disease pathology, such as depression, marital discord or reaction to the diagnosis. In addition, they can undertake a mental capacity assessment if required. However, the scarcity of such expert professionals and the difficulties for people with ALS to sit for a 2-h assessment or attend additional clinical sessions, combined with the stigma associated with attending a clinic for dementia or mental health, has necessitated the use of a briefer assessment. Brief cognitive assessment can not only identify people who need to be referred for further evaluation but can also produce results that can be directly implemented. Although these assessments can be undertaken by another member of the multidisciplinary care team, such as a speech and language therapist or a specialist nurse, following the appropriate training, they should preferably be supervised by a psychologist, who can also provide help with interpretation.

Psychological support should be provided to the individual with ALS and their caregivers, particularly those in daily contact such as partners and children. This support should address anxiety and depression, as well as suggesting strategies and education to help manage behavioural issues that are particularly burdensome to the caregiver. Promising approaches such as acceptance and commitment therapy are currently being trialled[122].

[H1] Conclusions

The proposal of an ALS–FTD spectrum has been driven by findings of cognitive and behavioural changes, particularly in patients in the mid-spectrum range. This concept has been further solidified with the common pathological and genetic changes found in both ALS and bvFTD. Our increased understanding of the neuropsychology of ALS has led to it being incorporated as a key component of the ALS phenotype, and cognition also serves a biomarker that reflects the underlying cerebral pathology. Cognitive assessment is now an essential component of both clinical research and care in ALS, and assessment tools have been developed and

validated and are now being widely applied. Neuropsychology is also a potential biomarker for the early manifestations of the disease, and the importance of neuropsychological assessment is being recognized by its incorporation into an increasing number of clinical trials.

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993

996

997 Competing interests

998 S.A. is one of the authors of the Edinburgh Cognitive and Behavioural ALS Screen and the
999 Dimensional Apathy Scale.

1000

1001 Key points

- 1002 Cognitive and behavioural impairment in amyotrophic lateral sclerosis (ALS) is
1003 heterogeneous and represents a spectrum of changes from ALS to ALS–frontotemporal
1004 dementia, also referred to as ALS–frontotemporal spectrum disorder (ALS–FTSD).
- 1005 Neuropsychology has been pivotal in identifying the mid-spectrum range of ALS–FTSD;
1006 executive, verbal fluency, social cognition and language impairments are common, and
1007 apathy is the most prevalent behavioural change.
- 1008 Cerebral dysfunction underlying these impairments has been shown in both grey and
1009 white matter using a range of imaging techniques, and specific cognitive deficits were
1010 shown to predict TAR DNA-binding protein 43 pathology in specific brain regions.
- 1011 Assessment tools including the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)
1012 and the ALS Cognitive Behavioural Screen (ALS-CBS) are well validated and standardized
1013 across different languages and are now incorporated into clinical trials.
- 1014 This Review provides recommendations for neuropsychological assessment and
1015 intervention in ALS.

1016

1017

Table 1 | Regional brain dysfunction and neuropsychological deficits in ALS

Cortical areas or structures	Region or tract	Cognitive and behavioural deficits	Imaging methods
BA44, BA45 and BA46	Dorsolateral prefrontal and inferior frontal cortices[15,29,30,34,60,90,123-129]	Attention, verbal fluency, executive functions, concept formation (card sorting), inhibition (antisaccades), theory of mind, apathy and naming	Functional MRI, functional PET, ^{18}F-fluorodeoxyglucose PET, EEG, sMRI (volumetric and cortical thickness) and DTI
BA9, BA10 and BA32	Anterior cingulate cortex and dorsomedial prefrontal cortex[15,29,30,46,59,126-128,130-132]	Apathy and theory of mind[61]	
BA11 and BA25	Orbitofrontal cortex[60,90,131,133,134]	Behavioural change, disinhibition and apathy	
White matter fasciculi	Superior longitudinal fasciculus[31,89,135,136]	Verbal fluency and executive functions	sMRI and DTI
	Inferior longitudinal fasciculus[31,137]	Verbal fluency, memory, naming and emotion recognition	
	Cingulum[31,33,89,136]	Verbal fluency, executive functions and apathy[138]	

The table highlights a selection of imaging studies that have shown associations between regional cerebral and subcortical dysfunction and cognitive and behavioural deficits in ALS. The regions and fasciculi are depicted in Figure 3. ALS, amyotrophic lateral sclerosis. BA, Brodmann area; sMRI structural MRI, DTI diffusion tensor imaging.

Figure 1 | Amyotrophic lateral sclerosis–frontotemporal disorder spectrum disorder. The figure shows the spectrum of cognitive and behavioural dysfunction that can be observed in people with amyotrophic lateral sclerosis (ALS), along with the approximate proportions of patients who lie at the various points in the spectrum[139,140]. The spectrum from pure motor ALS to ALS with frontotemporal dementia (ALS–FTD) has been termed ALS–frontotemporal spectrum disorder[4] (ALS–FTSD).

Figure 2 | The dual task paradigm. In this paradigm[33], the participant is presented with a series of numbers which they must hold in memory while performing a visual inspection time task for 15 s. In this latter task, they are asked to identify the longer arm in a series of images, each of which is very briefly flashed up (ranging from 17 to 150 ms) and is then masked. The participant must then recall the numbers that were presented at the beginning of the task.

Figure 3 | Cortical and subcortical involvement in cognitive and behavioural impairment in amyotrophic lateral sclerosis. **a** | Lateral view of the brain. **b** | Medial view of the brain. Both images show the Brodmann areas (BA) and fasciculi associated with cognitive and behavioural impairment in amyotrophic lateral sclerosis, based on data from brain imaging studies (Table 1).

Box 1 | Diagnosing ALS–FTSD using the ECAS

These diagnostic criteria for amyotrophic lateral sclerosis–frontotemporal spectrum disorder (ALS–FTSD) are an adaptation of the revised consensus guidelines[4] incorporating the Edinburgh Cognitive and Behavioural ALS Screen[27] (ECAS).

ALS with cognitive impairment (ALSci)*

- A deficit in ALS-specific and/or ECAS total scores using published abnormality cut-offs[27].
- To improve accuracy, use values adjusted for age and education.
- The ALS-specific score includes executive functions, language and verbal fluency. Fluency impairment can be used in isolation according to the consensus criteria[4], although all individuals with a fluency impairment also showed impairment on ECAS total and/or ALS-specific scores, and maximum accuracy for detecting ALSci was achieved through the combined use of these two scores[73].
- The consensus criteria can also be applied when a more comprehensive neuropsychological battery is used[4].

ALS with behavioural impairment (ALSbi)*

- Using the ECAS semi-structured interview with a partner, relative, friend or carer: presence of apathy (with or without another behavioural change), or at least two of four other behavioural symptoms (disinhibition, loss of sympathy, perseveration and/or change in eating behaviour).

ALS–frontotemporal dementia (ALS–FTD)

- Evidence of progressive deterioration in behaviour and/or cognition from observation or history.
- Presence of three of four behavioural symptoms (disinhibition, apathy, loss of sympathy, perseveration and/or change in eating behaviour) or two of the four symptoms together with a deficit on the ALS-specific ECAS score and unimpaired or less affected on the ALS non-specific score, or at least two behavioural symptoms together with psychotic symptoms and/or loss of insight.
- Progressive decline is pivotal to the diagnosis, which should be made by a clinician (neuropsychologist, neurologist or psychiatrist) through a clinical interview, although the ECAS can be used to provide supporting evidence.

*The term ALScbi is used to describe people who meet the criteria for both ALSci and ALSbi.

Box 2 | Recommendations for neuropsychological assessment and intervention in ALS

Psychological support

- Psychological support should be integral to the care plan to help alleviate anxiety and depression and aid acceptance in people with amyotrophic lateral sclerosis (ALS) and their caregivers.
- The support should address caregiver burden and provide strategies and education to aid management of cognitive and behavioural issues.

Assessment

- Cognitive and behavioural assessments should be offered to all people with ALS early in the disease course.
- If a psychologist or neuropsychologist is not available, individual assessments can be undertaken by another member of the multidisciplinary care team, such as a speech and language therapist or a specialist nurse, using one of the brief assessment tools, and multiple cases can then be reviewed together under the supervision of a psychologist. The assessments can be conducted at the patient's home or remotely via a video link.
- It is essential that the health specialist or researcher undertakes training and gains certification, if available, before administering the assessment.
- A caregiver or a person who knows the patient well should provide information on any changes in behaviour through a private semi-structured interview or self-complete questionnaire.
- A diagnosis of frontotemporal dementia (FTD) should only be made following a clinical interview and not on the basis of questionnaire scores.
- When using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) to determine ALS with cognitive impairment (ALSci), the diagnostic criteria outlined in Box 1 should be applied. ECAS subscores can be used to tailor intervention to the individual.
- Repeated assessment can be undertaken using the parallel versions of the tests. To avoid practice effects, assessments should not be repeated too often — once every 4–6 months should be sufficient.

Clinical trials

- Include cognitive and behavioural assessment as an outcome measure.

Pre-symptomatic

- Individuals with genetic mutations that place them at a high risk of ALS and/or FTD should undergo repeated cognitive and behavioural assessments, but leaving sufficient time in between assessments to avoid any practice effects, for example, once every 12–24 months.