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COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS: EXPLORING ITS RELATIONSHIP WITH FUNCTIONAL INCAPACITY

Universidade Católica Portuguesa para obtenção do grau de mestre em Neuropsicologia

Por

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Sob a orientação de Filipa Ribeiro, PhD e Simão Cruz, MSc

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Abstract

Amyotrophic Lateral Sclerosis (ALS), traditionally associated with motor dysfunction, also presents cognitive impairments in approximately half of the patients. Significant cognitive and behavioural deficits in ALS affects executive functioning and could have critical implications for prognosis and disease management. Assessing these changes in ALS patients is challenging because their motor disabilities can mask the real extent of their ability to perform daily activities. This study aimed to explore the cognitive impairment in ALS and their relationship with functional incapacity in Activities of Daily Living (ADLs).

In a comparative cross-sectional analysis, twenty-two ALS patients were divided into Low Severity and High Severity groups (*n*=11 each) based on their ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale Revised) scores and compared with twenty-two Healthy Controls. Cognitive, behavioural, emotional, and functional performance were assessed. The results revealed significant cognitive deficits in ALS patients, particularly with High Severity disease. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS), a multidomain evaluation specifically developed for ALS/Motor Neuron Disease, showed pronounced deficits including language, verbal fluency, executive function, and visuospatial abilities. The Mini Mental State Examination (MMSE) was more discriminative between levels of ALS severity, while the Frontal Assessment Battery (FAB) proved beneficial for comparisons with healthy individuals. Correlation analysis indicated a significant negative association between Executive Function and Advanced Instrumental Daily Living tasks.

The results corroborate previous research and emphasize the importance of regular cognitive assessments in ALS patients, and also add value by assessing functional incapacity. Beyond the diagnostic cost, they pave the way for cognitive stimulation programs,, especially those targeting executive functions, which may delay cognitive decline and support complex daily living activities, essential for decision-making and developing coping strategies for the disease. Furthermore, the cognitive decline in a higher level of severity disease accentuates the need for early and comprehensive healthcare planning involving ALS patients and their families.

Key words:

Amyotrophic Lateral Sclerosis, cognitive impairment, neuropsychological assessment, functional incapacity

Resumo

A Esclerose Lateral Amiotrófica (ELA), tradicionalmente associada a disfunções motoras, também apresenta comprometimento a nível cognitivo em aproximadamente metade dos doentes. Os défices cognitivos e comportamentais na ELA afetam o funcionamento executivo e podem ter implicações críticas para o prognóstico e na gestão da doença. A sua avaliação é desafiadora, uma vez que os doentes apresentam limitações motoras que podem mascarar a verdadeira extensão da capacidade de realizar as atividades de vida diárias. Este estudo pretende explorar o comprometimento cognitivo na ELA e a sua relação com a incapacidade funcional nas Atividades da Vida Diária (AVDs).

Numa análise transversal comparativa, vinte e dois pacientes com ELA foram divididos em grupos de Baixa Severidade e Alta Severidade (n=11 em cada) com base nos resultados na ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale Revised) e foram comparados com vinte e dois controlos saudáveis. O desempenho cognitivo, comportamental, emocional e funcional foram avaliados. Verificaram-se défices cognitivos significativos nos doentes com ELA, em particular de Alta Severidade. O ECAS (Edinburgh Cognitive and Behavioral ALS Screen), um instrumento de avaliação multidomínio desenvolvido para doentes com ELA/Doença do Neurónio Motor, revelou défices acentuados na linguagem, fluência verbal, função executiva e capacidade visuoespacial. O Exame Breve do Estado Mental (MMSE) foi mais discriminativo entre os níveis de severidade da ELA, enquanto que a Bateria de Avaliação Frontal (FAB) para comparações com indivíduos saudáveis. A análise de correlação indicou uma associação negativa significativa entre a Função Executiva e as Atividades Instrumentais Avançadas de Vida Diária.

Os resultados corroboram pesquisas anteriores e enfatizam a importância de avaliações cognitivas regulares em doentes com ELA, acrescentando valor ao avaliar a incapacidade funcional. Para além do custo diagnóstico, abrem portas para programas de estimulação cognitiva, especialmente focados nas funções executivas, para retardar o declínio cognitivo e apoiar atividades diárias complexas, essenciais na tomada de decisões e desenvolvimento de estratégias de coping relativas à doença. Além disso, o declínio cognitivo no nível Alto de Severidade da doença acentua a necessidade de um precoce planeamento de cuidados de saúde envolvendo pacientes com ELA e suas famílias.

Palavras-chaves:

Esclerose Lateral Amiotrófica, comprometimento cognitivo, avaliação neuropsicológica, incapacidade funcional

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by a progressive loss of functional capacity. Historically perceived as a disorder confined to motor neuron degeneration, ALS has been described to also encompass cognitive and behavioural dimensions, warranting a broader investigational approach. The implications of such cognitive and behavioural changes in ALS patients are profound, exerting a multifaceted impact on patient functionality which turns important to investigate them.

The functional capacity evaluation, taking in consideration the motor impairment in ALS patients, is the most consensual severity disease measure (Sandstedt, et al., 2018). However, OMS (2001) defined the term 'functionality' to include a person's overall body function, activities, and participation, which transcend the definition of physical and structural integrity. Accordingly, this research advocates for a more holistic understanding of functionality in ALS patients and proposes a comprehensive evaluation of the functional capacity considering the Daily Living Activities (ADLs), taking into account, not just the physical motor deficits. The cognitive and behavioural changes could also compromise the functional capacity. By employing validated assessment tools tailored for the ALS population, this research aims to elucidate the cognitive, emotional, behavioural, and functional profiles of a Portuguese cohort.

Furthermore, this study seeks to explore which cognitive impairments influence the functional incapacity of ALS patients concerning ADLs. Given that such impairments can hinder decision-making capabilities, identifying and characterizing these deficits—relative to functional incapacity—is crucial. Such insights will be instrumental for prognostic evaluations, informing treatment strategies, and establishing the necessity for Advance Directives in a timely manner, contributing to the enhancement of patient care and quality of life.

2. Literature review

2.1. Amyotrophic Lateral Sclerosis

In 1869, the neurologist Jean-Martin Charcot first described Amyotrophic Lateral Sclerosis (ALS) as a rare, progressive neurodegenerative disease that selectively affects motor neurons (Masrori & Van Damme, 2020).

ALS is the most common disease of a larger group of neurologic disorders collectively named Motor Neuron Disease (MND) which affects both the lower (LMN) and the upper motor neurons (UMN). Degeneration of motor neurons involving the cerebral cortex, the brainstem and the anterior horn cells of the spinal cord leads to a variable combination of progressive limb muscle weakness and wasting, spasticity, problems with speech, swallowing and respiratory function (Soriani & Desnuelle, 2017; Masrori & Van Damme, 2020).

2.1.1. Clinical features

The onset of ALS is insidious, with the disease initially manifesting through subtle, focal motor deficits. As ALS progresses, these symptoms typically spread to adjacent anatomical regions. Weakness most commonly starts in the limb muscles (limb-onset disease) and accounts for 60% of patients. Up to 5% present with respiratory problems and about 25-30% have a bulbar onset characterized by dysarthria (difficulty with speech), dysphonia (voice quality change), dysphagia (difficulty swallowing) and sialorrhea (excessive drooling) (Hardiman, et al., 2017; Masrori & Van Damme, 2020). The most common upper motor neuron (UMN) signs are spasticity and hyperreflexia. Conversely, lower motor neurons (LMN) signs include muscle atrophy and fasciculations (Masrori & Van Damme, 2020) (Figure 1 in Appendix).

Moreover, ALS is associated not only with motor impairment. It is well known that up to 50% of patients develop cognitive and/or behavioural impairment during the course of the disease, and 35-40% present mild cognitive and/or behavioural changes (Goldstein & Sharon, 2013; Masrori & Van Damme, 2020). Ten to fifteen percent of cases are diagnosed with the behavioural variant of frontotemporal dementia (bvFTD) (van Es, et al., 2017; Masrori & Van Damme, 2020). The other less common variants of Frontotemporal Dementia (FTD) are

progressive non-fluent aphasia (PNFA) and semantic dementia (svPPA) (Hardiman, et al., 2017; Masrori & Van Damme, 2020; Figure 1 and Tabe 7 in Appendix).

ALS can be classified according to the site of onset (bulbar, spinal, or respiratory onset), the extent of UMN and LMN involvement, and the rate of motor impairment. However, none of these classifications includes the cognitive and behavioural changes (Hardiman, et al., 2017).

2.1.2. Epidemiology

The age of onset, as well as the presentation and progression of the disease, can vary considerably between ALS patients. The incidence of the disease increases with age and peaks between the ages of 65–75 years. However, ALS could manifest at a younger age (< 30 years) and in the elderly (> 80 years). Median survival time is 3–5 years from symptom onset, although up to 10% of patients survive for more than 8 years and, with mechanical ventilation by tracheostomy, survival can increase by a further 15 years or more (Soriani & Desnuelle, 2017).

The worldwide distribution of ALS is heterogeneous. In Europe, ALS incidence and prevalence have been estimated as 1.75-3 per 100 000 persons per year and 2.6-3.0 cases per 100 000 people, respectively (Marin, et al., 2017). Men are more commonly affected (1.2–1.5:1) (van Es, et al., 2017).A large case-control study across three different European countries has demonstrated an association between exogenous estrogens and progestogens and reduced odds of ALS in women (Rooney, et al., 2017).

A meta-analysis of population-based studies assessing the variation of ALS worldwide (Marin, et al., 2017) found a lower incidence of ALS in East Asia as compared to Europe. These results agree with another comparative study reporting a lower incidence in East Asia (Japan) than in the United States of America (Okumara, 2003).

2.1.3. Etiology

Approximately 90% of ALS cases have no family history of this disease (Goldstein & Sharon, 2013). While the exact cause is unknown, research suggests a combination of genetic and environmental factors.

More than 20 genes have been associated with monogenic ALS and together explain about 15% of all cases. A specific mutation such as the superoxide dismutase 1 (SOD1) gene, has been found to be responsible for 20% of familial ALS cases and 1-2% of sporadic cases (Masrori & Van Damme, 2020).

According to a population-based cohort study, the most frequent genetic cause of ALS is a hexanucleotide repeat expansion of the *C9orf72* gene, which accounts for 30-50% of familial and 7-5% of sporadic cases (Goldstein & Sharon, 2013). Those patients are more likely to have a bulbar onset and a clinical presentation with cognitive and behavioural impairment (Masrori & Van Damme, 2020). Furthermore, an expansion of GGGGCC repeats in the first intron of C9orf72 was found to be a common cause of both illnesses (FTD and ALS) (Xu, Poidevin, & Li, 2013). Other findings support that both neurological disorders share phenotypic and pathologic overlap: *TARDBP* (which encodes TDP-43, now established as the major disease-associated protein in ALS) and FUS mutations can cause both ALS and FTD (Goldstein & Sharon, 2013; Xu, Poidevin, & Li, 2013). The presence of abnormal protein aggregates, such as TDP-43 protein, in patients with ALS, as well as in those with ubiquitin-positive, tau-negative, and α-synuclein-negative FTD, provides further evidence of a link between both diseases (Geser, M-Y Lee, & Trojanowski, 2010).

The environmental factors should also be considered. Chio et al., (1999), raised the issue of ALS incidence among migrants from South Italy in Piedmont (North Italy) and the authors identified an increased risk of ALS in migrants from Puglia (Southeast Italy) comparatively with people born in Piedmont, as well as in men migrating from other countries. The evidence of lower socioeconomic status and the professional activity, since most of the migrants were farmers, were two characteristics suggested to be associated with an increased risk of ALS (Chiò, et al., 1999).

In a larger case–control study, part of the Euro-MOTOR project (a multidisciplinary ALS network with the goal of discovering the cure to motor neuron degeneration), the preliminary results suggest that the exposure to smoking increases the risk of developing ALS (Hardiman, et al., 2017). On the other hand, type-2 diabetes mellitus, elevated levels of circulating lipids and exposure to female contraceptives hormones may have a protective role (Hardiman, et al., 2017; Rooney, et al., 2017;).

2.1.4. Diagnosis and Prognosis

The diagnosis of ALS is based on the clinical picture, and it is supported by electromyography. Plausible differential diagnoses must be excluded by additional ancillary tests, mostly brain and/or spine Magnetic Resonance Imaging (MRI) (Masrori & Van Damme, 2020).

Several sets of criteria have been developed to increase the homogeneity of patients recruited for clinical trials (Masrori & Van Damme, 2020). El Escorial criteria were established by the World Federation of Neurology, initially published in 1994 (Brooks, 1994). According to those criteria, when both UMN and LMN signs are present in at least three of four regions (bulbar, cervical, thoracic, lumbar), a definite diagnosis of ALS can be made.

In 1998, El Escorial criteria was revised, considering the importance of laboratory testing and were retitled as Arlie House criteria and included a category called "laboratory-supported probable ALS" that allowed the use of electromyography (EMG) data to substitute for clinical findings and the "suspected ALS" category was excluded (Brooks, Miller, Swash, & Munsat, 2000). To address some perceived problems, in 2008 the Awaji-criteria (de Carvalho, et al., 2008) was introduced to further integrate the electrophysiological data and clinical examination findings and, for the first time, considered fasciculation potentials as an acute denervation sign, equivalent to fibrillation potentials and positive sharp waves (Finsterer & Stöllberger, 2013; Shefner, et al., 2020; Table 5 in Appendix).

Recently, a new simplified set of diagnostic criteria for ALS, the Gold Coast Criteria, has been proposed by a group of experts (Shefner, et al., 2020) and can be useful both in clinical and research settings. Instead of several disease categories, they establish a single diagnostic level which requires either combined UMN and LMN dysfunction in 1 body region or LMN signs in at least 2 regions (Table 6 in Appendix).

Life expectancy in ALS is variable according to different clinical subtypes of the disease (Masrori & Van Damme, 2020).

In classic ALS presentation, signs of combined UMN and LMN loss are present in one or more body regions and the progression is slower than in bulbar onset. Bulbar ALS is characterized by a rapid clinical deterioration, with a median survival of 3 years from disease onset. Respiratory onset ALS has the worst prognosis (Hardiman, et al., 2017; Masrori & Van Damme, 2020).

There are some prognostic factors associated with a shorter survival: a bulbar and respiratory onset, a fast functional decline, a pronounced weight loss, the presence of executive

impairment or FTD, an older age at symptom onset and low forced vital capacity (FVC). Some specific genetic factors also could compromise life expectancy: Ala5Val mutation in SOD1, C9orf72 repeat expansion, P525L mutation in FUS and exceedingly rare variants such as the homozygosity for the C allele of rs12608932 in UNCI13a (Masrori & Van Damme, 2020).

2.1.5. Treatment and Care

European Federation of Neurological Societies (EFNS) recommendations for the management of ALS, proposes a multidisciplinary care in ALS at tertiary centers (ALS centers) to try to increase life expectancy and support ALS patients, their families and caregivers in the control of symptoms and also in the preparation of advanced care planning and the end of life (Soriani & Desnuelle, 2017).

A multidisciplinary team care in ALS usually comprises healthcare practitioners (neurologists, psychologists, nutritionists, physical therapists, pulmonologists, speech therapists) and a social counsellor. Tertiary centers should offer a) appointments covered by a single visit, b) usually proposed, with variations according to disease progression and c) effective communication and good coordination between hospital-based multidisciplinary team, home practitioners and palliative care team (Andersen, 2012; Soriani & Desnuelle, 2017).

Regarding the pharmacological management of ALS, the only drug thus far approved by the European Medicines Agency (EMA) is riluzole (50 mg twice daily), a glutamate antagonist, that had shown efficacy in slowing the course of disease, with an increase in survival around 3-6 months (Soriani & Desnuelle, 2017; Masrori & Van Damme, 2020).
Alpha-tocopherol (500 mg twice daily) may help to slow progression but only in milder ALS states because of its antioxidant properties. The French National Health Authority (HAS) has recommended the combination use with riluzole (Soriani & Desnuelle, 2017).

To ameliorate bothersome non-motor symptoms of ALS (e.g.: pseudobulbar affect and mood disorders, cramps, spasticity, sialorrhea, pain, insomnia, fatigue) and to improve patients quality of life, a wide range of pharmacological and non-pharmacological treatments are available (Soriani & Desnuelle, 2017; Masrori & Van Damme, 2020).

Nutritional issues in ALS should the addressed, as weight loss is an independent factor for poor prognosis (Soriani & Desnuelle, 2017). Swallowing problems are the main cause of malnutrition leading to or worsening weight loss. The management of dysphagia includes: (1)

changing the consistency of food and fluids; (2) prescribing a high-calorie diet with high-protein content and the use of oral nutritional supplements; (3) Percutaneous Endoscopic Gastrostomy (PEG), to circumvent the difficulties regarding oral feeding (Soriani & Desnuelle, 2017).

Respiratory dysfunction should be screened for and monitored across the course of the disease by means of pulmonary function tests and nocturnal oximetry. When symptoms and/or signs of significant respiratory insufficiency or nocturnal hypoventilation are present, it is recommended to consider Non-Invasive Ventilation (NIV). NIV is an established long-term treatment that uses a face or nasal mask and provides positive pressure to support weakened respiratory muscles. When NIV is not tolerated or unable to maintain SaO2>90% and Pa02<30 or to manage the secretions, Invasive Mechanical Ventilation (IMV) can be discussed with patients and their caregivers. IMV is an invasive ventilatory support that is usually provided by a tracheostomy tube (Soriani & Desnuelle, 2017).

Although those treatments and assistive devices may improve quality of life and symptom control, it is not clearly demonstrated their survival benefits (Masrori & Van Damme, 2020).

2.2. Cognitive and Behavioural changes

Amyotrophic Lateral Sclerosis (ALS) is predominantly identified as a Motor Neurone Disease. However, emerging evidence underscores the concomitant cognitive and behavioural phenotypes manifesting in a subset of patients. These cognitive and behavioural changes extend from subtle cognitive impairments—particularly affecting frontal-executive domains—to a more pronounced clinical presentation consistent with Frontotemporal Dementia (FTD) .

Frontotemporal Dementia (FTD) is the second most common cause of dementia in patients under 65 years of age, in which the degenerative process affects the frontal and anterior temporal lobes. This condition is characterized by a progressive decline in behaviour and/or language (Masrori & Van Damme, 2020). Clinical presentation of FTD includes disinhibition, impulsivity, decreased attention and executive functioning, problems with planning, apathy, changes in sleep and eating patterns and language deficits (Irwin, Lippa, & Swearer, 2007). Executive Dysfunction in ALS may also lead to changes in personality, manifesting as altered social conduct, irritability, obsessions, poor insight multitasking difficulties, perseverative behaviour, poor initiation of speech and action and challenges with timekeeping (Abrahams, et

al., 2000). Moreover, some patients may present pervasive deficits on frontal executive tests that involves verbal fluency, working memory and attention (Phukan, Pender, & Hardiman, 2007).

Although up to 15% meeting diagnostic criteria for FTD, cognitive and behavioural abnormalities can be observed in over than 50% of non-demented ALS patients (Ringholz, Appel, Bradshaw, & Cooke, 2005). This data implies that pure ALS and FTD syndromes might exist on a spectrum of a single neurodegenerative disease (Ringholz, Appel, Bradshaw, & Cooke, 2005) (Osborne, Sekhon, Johnston, & Kalra, 2014).

Many authors have been investigating clinical, radiological, pathological, and genetic overlap between ALS and FTD. For instance, a study using SPECT identified a similar pattern of abnormalities in the frontal and temporal lobes in patients with FTD/MND which showed a common pattern of cerebral involvement (Talbot, et al., 1995). Moreover, a voxel-based-morphometry study using MRI scanning, found common grey matter loss patterns in both ALS and ALS-FTD patients. In particular, ALS-FTD exhibited significant atrophy in most of the frontal regions, along with decreased cortical activation during frontal lobe function tests (Chang, et al., 2005; Osborne, Sekhon, Johnston, & Kalra, 2014).

The connection between the two diseases his further supported by genetic evidence, showing that ALS and FTD share phenotypic and pathological overlap, namely the TDP-43 protein (Neumann, et al., 2006), the progranulin gene (GRN), chromatin-modifying protein 2B gene (CHMP2B), dynastic 1 gene (DCTN1), and the expansion of GGGGCC repeats in the first intron of C9orf71 (Irwin, Lippa, & Swearer, 2007; Phukan, Pender, & Hardiman, 2007).

In 2017, Strong and colleagues introduced new criteria for delineating cognitive and behavioural changes in ALS patients, using the term frontotemporal spectrum disorder (ALS-FTSD). They proposed a continuum, from cognitively normal ALS patients (ALScn) to the severely affected ALS-FTD patients. Other classifications based on varying symptoms include ALS with cognitive impairment (ALSci), behavioural impairment (ALSbi), or a combination of both (ALScbi) (Strong, et al., 2017).

Historically, the detection of these changes remained elusive, overshadowed by the prominent neuromuscular degeneration inherent to ALS. This has necessitated sophisticated diagnostic expertise, bringing attention to recent developments in neurocognitive pathology (Irwin, Lippa, & Swearer, 2007). Modern neuropsychological assessments and advanced neuroimaging techniques have revealed anomalies, primarily found in the frontal and temporal lobes, exhibit a correlative relationship with diverse neuropsychological deficits (Irwin, Lippa, & Swearer, 2007).

Furthermore, behavioural changes in ALS, notably those aligning with the behavioural variant of Frontotemporal Dementia (bvFTD), demonstrate heterogeneity, reflective of the differential neuropathological involvement of neuroanatomical substrates (Phukan, Pender, & Hardiman, 2007). Characterized by a spectrum encompassing disinhibition, emotional blunting, loss of empathic, ritualistic, or compulsive behaviour, hyperorality, and executive dysfunction, these symptomatic expressions implicate intricate neurodegenerative processes (Masrori & Van Damme, 2020). Some ALS patients display disinhibited and socially inappropriate behaviour, potentially linked to pathology within the orbitomedial frontal and anterior temporal regions (Masrori & Van Damme, 2020). Conversely, others manifest apathy, cognitive rigidity, and signs of extensive frontal lobe pathology, notably in the dorsolateral prefrontal cortex. The term used to appoint this anomaly, the "frontal dysexecutive syndrome", that involves compromised executive function, which affects planning, multitasking, problem solving, behavioural regulation and social interactions (Phukan, Pender, & Hardiman, 2007; Abrahams, Newton, Niven, Foley, & Bak, 2014). Additionally, a distinct patient cohort presents with compulsive, ritualized behaviours, implicating striatal pathology with potential concomitant cortical involvement, often in the temporal lobe (Phukan, Pender, & Hardiman, 2007).

Apathy, a neuropsychiatric symptom distinct from depression, might be exhibited in 50% of the ALS patients and can manifest in three ways: executive (attention, planning deficits), emotional (neutrality or indifference), and initiation (lack of motivation to produce thoughts) with the latter being the most observed in ALS patients. Initiation apathy was the most typical form considered in ALS patients (Marchi, et al., 2021). Behavioural changes, specifically, apathy, had been associated with a poorer prognosis in ALS demonstrated to be an independent and negative prognostic factor in ALS (Caga, et al., 2016). Due to apathy, impulsivity, or other behavioural changes, ALS patients may become non-compliant with essential treatments potentially leading to preventable complications and worsening of their overall health status (Kasper, et al., 2015; Goldstein & Sharon, 2013).

2.2.1. Cognitive impairment

The cognitive profile researchers in ALS have shown that nearly 50% of ALS patients present with neuropsychological alterations, and deficits have been described across various cognitive functions (Beeldman, Raaphorst, & Twennaar, 2015).

In a 2008 meta-analysis of published studies involving ALS patients without dementia, Raaphorst, et al., (2010) included 554 ALS patients and found cognitive impairment in multiple domains, including fluency, executive functions, language, and memory. To provide a more robust assessment considering limited data, an updated meta-analysis was conducted in 2015 with methodological improvements, such as accounting for bias due to motor impairment (Beeldman, Raaphorst, & Twennaar, 2015). This update reinforced the presence of significant cognitive deficits in ALS patients, particularly in areas associated with frontal lobe activity. These areas include fluency, language, executive functions, verbal memory, and notably, social cognition, a newly identified cognitive domain.

As mentioned before, executive function is often affected in ALS patients including difficulties in initiation, planning, attention, organization, decision-making, working memory and cognitive flexibility. In 1996, Abrahams and her colleagues pioneered studies into the neurological underpinnings of cognition in ALS beyond its well-known motor effects. Using PET scans, they quantified cerebral glucose metabolism to identify metabolic abnormalities in the frontal regions of ALS patients' brains. They found a notable decrease in glucose metabolism, suggesting localized dysfunction and reinforcing the idea that ALS affects brain regions tied to cognition and executive functions (Abrahams S. , et al., 1996)

The degradation of neural circuits involved in executive functioning, often observed in the dorsolateral prefrontal cortex of individuals with ALS, can contribute to difficulties in retrieving words or forming coherent sentences. (Irwin, Lippa, & Swearer, 2007). Deficits in verbal fluency in ALS patients highlight damage within brain regions responsible for initiating responses, particularly areas linked to the frontal lobes or circuits connecting the frontal lobes and striatum. This is evident in tasks requiring letter fluency (listing words that start with a specific letter) and category fluency (listing words within a certain category) (Phukan, Pender, & Hardiman, 2007). A decline in both fluencies indicates compromised executive functions. However, if category fluency is especially affected, it implies a broader impairment in semantic memory (Abrahams, et al., 2000; Phukan, Pender, & Hardiman, 2007).

Verbal fluency deficits might also arise from genuine language dysfunction in ALS, but distinguishing this from executive function deficits remains challenging. A functional MRI study (Abrahams, et al., 2004), found that sporadic ALS patients, even those without aphasia or dementia, exhibited unusual brain activation patterns in specific brain regions (inferior frontal gyrus and Broca’s area) when performing verbal fluency and naming tasks. This suggests that

language processing areas might be impacted before overt clinical symptoms emerge (Phukan, Pender, & Hardiman, 2007).

The nature of memory impairments in ALS is not consistently explained. Deficits in delayed recall vary, making it difficult to determine the issue lies in encoding or in the speed of forgetting (Abrahams, Newton, Niven, Foley, & Bak, 2014). Encoding process is an executive function, when compromised involve a neuronal circuit that arises in the left frontal lobe and individuals will also have difficulties in recalling (Phukan, Pender, & Hardiman, 2007). Nevertheless, Beeldman's (2015) meta-analysis emphasized temporal lobe atrophy in ALS patients, which might account for observed deficits in memory and language domains. Significantly, this research highlighted compromised delayed verbal memory, implicating the medial temporal lobe. Recent MRI studies have linked structural changes in this region, especially reduced hippocampal volume, to worsening verbal memory in non-demented ALS patients (Westeneng, et al., 2015).

Additionally, recent studies have proposed that social cognition, the cognitive processes underlying social interactions, might also be impaired in ALS patients (Osborne, Sekhon, Johnston, & Kalra, 2014; Beeldman, Raaphorst, & Twennaar, 2015; Bora, 2017). Social cognition refers to the various cognitive processes that underlie social interactions, including understanding, interpretation, and generation of responses to the intentions, dispositions, and behaviours of others. It encompasses abilities such as emotion recognition, theory of mind (the ability to understand others' mental states), empathy, and social judgment (Marchi, et al., 2021). This underscores the overlap between ALS and FTD, as FTD research has identified severe social cognition impairments related to atrophy in specific brain regions (Beeldman, Raaphorst, & Twennaar, 2015).

Cognitive impairment, especially when severe, has also a negative impact on ALS patients' survival. Notably, executive dysfunction has been shown to be a significant negative prognostic factor, potentially affecting treatment adherence, such as with ventilation techniques (Elamin, et al., 2011; Goldstein & Sharon, 2013; Khin, Minor, Holloway, & Pelleg, 2015).

The extent of structural brain changes and the affected cognitive domains can be variated. Thus, individualized clinical assessments are essential for understanding the specific cognitive profile in ALS.

2.2.2. Neuropsychological Assessment

Since the revised diagnostic criteria for ALS-FTSD were introduced by Strong et al. (2017), numerous studies concentrated on the development of novel, accurate neuropsychological tools. However, cognitive changes remain challenging to evaluate, primarily because motor and speech impairments can obstruct cognitive assessment (Osborne, Sekhon, Johnston, & Kalra, 2014). On one hand, tests requiring visuomotor coordination under time pressure, especially when dysarthria is present, mainly in Bulbar involvement, can result in poor performance by ALS patients (Irwin, Lippa, & Swearer, 2007). On the other hand, well established screening tests, such as Mini Mental Status Examination (MMSE), are insensitive to the executive deficits that are prevalent in ALS (Osborne, Sekhon, Johnston, & Kalra, 2014). To deal with those limitations, some studies are using screening tests to detect cognitive impairment in ALS patients with advanced physical disability by using adjust total score for missed item or modifying tasks (Floris, et al., 2012; Osborne, Sekhon, Johnston, & Kalra, 2014).

The most consistent cognitive impairment in ALS is related to the executive system (Abrahams, et al., 2000; Kasper, et al., 2015; Beeldman, et al., 2020). Executive dysfunction has been evident through various tests that assess verbal reasoning, visual attention, picture sequencing and category formation, such as the Wisconsin Card Sorting Test (WCST) (Kasper, et al., 2015). Notably, verbal fluency tasks (which reflect working memory and executive functioning), are the most striking and consistent tests used in ALS patients (Abrahams, et al., 1996; Abrahams, et al., 2000). The Frontal Assessment Battery (FAB), as a short screening test, is used to assess frontal lobe functions and has been showed to be a useful measure for detecting executive function impairment in ALS (Floris, et al., 2012; Osborne, Sekhon, Johnston, & Kalra, 2014).

Evidence about memory deficits is still inconsistent (Phukan, Pender, & Hardiman, 2007). MMSE items used to assess immediate recall, might not be affected and is not a very sensitive memory test, but it still be used as a screening test in ALS. Additionally, visuospatial abilities are expected to be preserved in ALS patients, however, Strong and colleagues (1999) noted some deficits.

Lately, neuropsychological assessments have been tailored to account for motor impairments in these patients. The Arrows and Colours Cognitive Test (ACCT), an eye-tracking assessment, effectively measures cognitive flexibility and differentiates ALS patients from healthy subjects (Poletti, et al., 2018).

Social cognition deficits in ALS include abnormalities in Theory of Mind (ToM), include "Reading the Mind in the Eyes," the "Faux-pas Test" and “Judgment of Preference” for

assessing ToM, which in a simple test, was observed an increased egocentric responses (Girardi, MacPherson, & Abrahams, 2011). Moreover, apathy in ALS, an important behavioural domain which could be affected, can be assessed the three dimensions with the Dimensional Apathy Scale (DAS), which is validated and independent of physical disabilities (Girardi, MacPherson, & Abrahams, 2011).

Additionally, comprehensive tools like the Edinburgh Cognitive and Behavioral ALS Screen (ECAS) (Abrahams, Newton, Niven, Foley, & Bak, 2014) and the ALS Cognitive Behavioral Screen (ALS-CBS) (Woolley, et al., 2010), along with focused tests like the Trail Making Test and backward Digit Span, demonstrate precision in cognitive evaluation (Marchi, et al., 2021).

The ECAS is a multidomain evaluation specifically developed for ALS/Motor Neurone Disease. This tool is adapted to minimize the bias that physical disabilities could introduce, offering a more accurate reflection of the cognitive and behavioural status of ALS patients. This screening battery, conceptualized by Sharon Abrahams and collaborators (2014), has been adapted into approximately twenty-five different languages, including in Portuguese (Tomšič, 2015). Designed explicitly for detecting cognitive and behavioural changes in ALS, the ECAS proves effective not only in determining the presence, severity, and nature of these changes but also in differentiating them from other disorders. Furthermore, the ECAS serves as a tool that broader medical teams can use to confirm a clinical diagnosis when impairments are identified (Abrahams, Newton, Niven, Foley, & Bak, 2014). Specific domains of ALS, such as the executive function – particularly in commonly affected areas like social cognition, inhibitory control, and executive function - are evaluated separately from fluency and language. The language function includes object naming, comprehension, and spelling. Verbal fluency, given its unique sensitivity in ALS, is assessed using two different letters (P and C), and a Verbal Fluency Index (VFI) is calculated to account for variations in motor speed and speaking time. Non-specific ALS functions, including immediate memory recall, delayed memory recall, recognition, and visuospatial skills, are also part of the assessment. By evaluating these areas, the ECAS distinguishes ALS-related cognitive changes from those observed in typical age-related conditions, like Alzheimer's disease (AD). Especially, the memory segment, which emphasizes retention and recognition processes, aids in differentiating the cognitive profiles of ALS and AD (Abrahams, Newton, Niven, Foley, & Bak, 2014). An integral component of the ECAS is a separate caregiver interview, which is structured based on the current criteria for diagnosing behavioural variant frontotemporal dementia (bvFTD) and tailored for ALS specifics (Abrahams, Newton, Niven, Foley, & Bak, 2014).

2.3. Functional Impairment

The World Health Organization introduced a system in 2001 called the International Classification of Functioning, Disability and Health (ICF) to help describe the effects of a disease in three ways: on the person's body, their personal life, and within society. Functioning refers to the neutral aspects of health, while disability covers the problems, including difficulties with body functions, doing activities, and being involved in community life. Disability is influenced by the disease itself, the person's environment, and personal factors (Sandstedt, et al., 2018).

Functional capacity encompasses specific abilities to carry out activities of daily living (ADLs) without assistance (Sousa, Prieto, Vilar, Firmino, & Simões, 2014). These activities are crucial for self-care and comprise Basic Activities of Daily Living (BADLs) tasks, including bathing, dressing, feeding, toileting, transferring (getting in and out of a bed or chair), and maintaining continence. The concept extends to Instrumental Activities of Daily Living (IADLs), which are essential for independent community living, including shopping, cooking, managing finances, housekeeping, and managing medications (Edemekong, Bomgaars, Sukumaran, & Schoo, 2023). In clinical practice, functional capacity assessment requires a comprehensive evaluation that includes ADL and several instruments have been developed for specific medical conditions, namely in Alzheimer's Disease (Alzheimer's Disease Cooperative Study Scale for ADL), in Mild Cognitive Impairment (ADCS MCI ADL; Galasko, et al., 1997) and other dementia conditions (Disability Assessment for Dementia Scale, DAD; Gélinas, Gauthier, McIntyre, & Gauthier, 1999).

In ALS patients, functional assessment considering the motor impairment is a widely accepted measure to evaluate the severity of the disease. Functional rating scales like the ALS Functional Rating Scale (ALSFRS) and ALSFRS–Revised (ALSFRS-R) are useful to measure functional decline and have been used to evaluate treatment effects on function in clinical trials (Chiò, Hammond, Mora, & Bonito, 2013). However, those functional scales might not capture the functional characteristics of later-stage ALS progression. Healthcare professionals should be aware of its limitations to give an overall picture of ALS functional capacity and to improve patient care and management (Sandstedt, et al., 2018; Edemekong, Bomgaars, Sukumaran, & Schoo, 2023).

More recently, has been proposed systems for ALS for staging disease severity to develop a universal and objective measure of disease progression. The first proposed system

was the “King's Clinical Staging” (Roche, et al., 2012). The system delineates four stages based on involved anatomical regions and clinical examinations. The scoring ranges from 1 for early disease affecting one region to 4 for advanced disease affecting multiple regions. Milano Torino Staging system (MiToS), derives from ALSFRS-R scale and quantifies disability progression in ALS by evaluating four key functional areas: communication, swallowing, moving, and breathing. Each functional loss counts as one point in the staging score, which totals from 0 to 4. A score of 0 means no functional loss, while 4 indicates impairment in all areas. The King and MiToS staging systems accurately represent the level of motor impairment experienced by patients (Chiò, Hammond, Mora, Bonito, & Filippini, 2015). Nonetheless, those system staging do not include measures of the severity of cognitive deficits and, the real functional capacity of ALS patients.

As mentioned, functionality encompasses all body functions, activities, and participation (WHO, 2001). It is not restricted to functional and structural integrity. Although ALS is known to affect daily life significantly, there are not many studies on how it limits activities or social involvement (Sandstedt, et al., 2018).

Research involving patients with the behavioural variant presentation of Motor Neurone Disease (bMND) (Mioshi, Lillo, Kiernan, & Hodges, 2012), used a measure to assess ADLs, the adapted Disability Assessment of Dementia (DAD) to explore its influence in disease progression. According with those findings, patients with bMND experience a decline in functional performance influenced by motor impairments and behavioural changes, affecting their ability to perform ADLs. However, the impairment in the ADLs MND and the combined impacts of cognitive, behavioural, and motor changes on functional performance have yet to be fully investigated (Mioshi, Lillo, Kiernan, & Hodges, 2012).

Previous studies identified that cognitive impairment in ALS patients, particularly, executive dysfunction, has been linked to a rapid decline in motor function (Elamin, et al., 2013). Also, using ECAS, has shown that ALS specific cognitive deficits and behavioural impairment are more frequent and severe within advanced stages (Crockford, et al., 2018). In a longitudinal study, Chiò and colleagues (2019) used the King's Clinical Staging System and MiToS to explore this relationship between the severity of motor impairment and the severity of cognitive deficits. Their findings revealed that ALS patients more frequently exhibited mild or severe deficits during the disease’s advanced stages than its early stages.

The cognitive deficits can have a profound impacts on coping and disease management meant that executive dysfunction in ALS may also result in disorganized behaviour, poor time management, and multitasking difficulties. These issues compromise simple daily tasks,

ranging from cooking, and self-care to more advanced cognitive process like making decision about treatments (Abrahams, et al., 2000; Khin Khin, Minor, Holloway, & Pelleg, 2015).

3.Objectives

This study aims to:

a) Describe a sample of Portuguese ALS patients in terms of onset region, disease duration, motor impairment severity and cognitive impairment.

b) Characterize and compare the cognitive, behavioural, emotional, and functional capacity performances within the ALS patients groups (Low Severity and High Severity) and Healthy Control (HC) group.

c) Examine the relationship between specific cognitive domains affected in ALS (Executive Functions, Fluency, and Language) and the Functional Incapacity.

To address the established research questions, the following hypotheses were formulated:

H1: Individuals with ALS will demonstrate poorer performance in cognitive and emotional tests compared to Healthy Control group.

H2: Low-severity ALS patients will exhibit a lower level of cognitive, behavioural, emotional, and functional incapacity than High Severity ALS patients.

H3: In individuals with ALS, specific cognitive domains will negatively correlate with functional incapacity.

H3a: The domain of Executive Functions will display the most pronounced correlation with Functional Incapacity.

4. Method

4.1 Participants

The study drew ALS patients from the Neurology Services of two public hospitals in the Lisbon Metropolitan Area. Two neurologists at each hospital made the ALS diagnosis and proposed inclusion in this study.

Inclusion criteria for these patients comprise being diagnosed with ALS based on the Gold Coast Criteria, the capability to communicate either orally or in writing (even if aided by communication tools), and the ability to provide either oral or written consent.

Healthy Control group comprised volunteers from an Active Aging program of the same metropolitan area. These Healthy Controls were chosen based on age, gender, and educational background to match the ALS patients.

Both groups, the ALS patients, and the Healthy Control participants, had certain exclusion criteria. Individuals were excluded from this study if were illiterate, had untreated vision or hearing impairments, had a history of neurological disease or lesion (like major stroke or head trauma), had a present history of alcohol or drug addiction, or any diagnosed and currently in treatment psychiatric disorder. For the Healthy Control group, participants were excluded if a cognitive deficit was suspected according to MMSE score ($\leq$ to the cut-off related to normative data).

4.2 Instruments

All participants were asked to complete a sociodemographic questionnaire that gathered data on age, gender, education level, and professional activity.

For the ALS clinical data, details were initially sourced from clinical records and then verified through a questionnaire. This questionnaire addressed the region of onset, disease duration, severity of motor impairment (measured by ALSFRS-R), and the usage of VNI and RIPPEG.

The following neuropsychological tests were administered to all participants:

a) Edinburgh Cognitive and Behavioural ALS Screen (ECAS; Abrahams et al., 2013; Tomšič, 2015) is a 15-20 min screen, includes an ALS specific domain score (total maximum of 100), an ALS Non-specific score (total maximum of 36) with a total score of 136. Additionally, include a carer behaviour screen of five domains characteristic of FTD (behavioural disinhibition, apathy, or inertia; loss of sympathy or empathy, perseverative, stereotyped, compulsive or ritualistic behaviour and hyperorality and/or altered food preferences) and an ALS Psychosis Screen.

b) Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975; Guerreiro, Silva & Botelho, 1994) is a brief 30-point questionnaire that is used to screen for

cognitive impairment. It assesses functions including orientation, attention and arithmetic, retention and delay recall, language, and visuo-construction ability.

c) Frontal Assessment Battery (FAB, Dubois, Slachevsky, Litvan & Pillon, 2000; Lima et al., 2008) is six tasks including abstraction, verbal fluency, motor programming, conflicting instructions, inhibitory control and prehension behaviour. Each task could have a maximum of 3 points for a total maximum score of 18.

d) Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a scale which comprises two subscales of anxiety and depression seven items each. The scale ranges from 0 to 21, with higher scores indicating more impairment and a score ≥ 8 was used as a cut-off, meaning probable impairment in the respectively subscale.

e) ALS Functional Rating Scale – Revised (ALSFRS-R, Cedarbaum, et al., 1999; Guedes, Pereira, Pavan & Valério, 2010) used to assess disease severity. The scale is composed by 12 items of clinical measurement scale that records changes in four functional domains: bulbar, gross motor, fine motor and respiratory parameters. The items scale ranges from 0 to 48, which a higher score means less severity. Mioshi and colleagues (2012) segmented disease severity into three stages using this measure: mild (scores 37-48), moderate (scores 25-36), and severe (scores 0-24).

f) Adult and Older Adults Functional Assessment Inventory (IAFAI, Sousa, Vilar, Simões, 2013) – a comprehensive instrument to assess the functional incapacity of adults and older adults assessing basic and instrumental daily living activities. The instrument has 53 questions divided into three categories: 18 are for Basic Activities of Daily Living (BADL), covering areas like eating, dressing, washing, controlling bodily functions, and moving around; 18 are for Household Instrumental Activities of Daily Living (IADL-H), which include tasks like conversing, using the phone, cooking, cleaning, and maintaining home safety; and 17 are for Advanced Instrumental Activities of Daily Living (IADL-A), which assess skills in understanding, communication, making health decisions, finances, navigating transportation, and maintaining social and leisure activities. The total results can determine three different functional incapacities: 1) leading to BADL, IADL-H and the IADL-A; 2) the total sum of the three categories; 3) the functional incapacity due to Physical, Cognitive and Emotional reasons. Items responses are scored including various levels of independence from a range of completely independent without difficulty (1) or with a presence of difficulty (0) to being completely unable to do a task, the extreme level of functional incapacity (dependence) (0).

To mitigate potential interference effects, all tests were administered in the same sequence for every participant.

4.3. Procedures

Participants for this study were recruited between October 2022 and September 2023.

At the Neurology Service of both hospitals, ALS patients underwent assessments during their outpatient consultations. On routine visits, the study's objectives were relayed to the patients by either a neurologist or psychologist. Once informed, patients identified a caregiver or a close family member to participate. This selected individual was contacted later via phone to evaluate the behavioural questionnaire of ECAS and the Functional Incapacity with IAFAI. Sessions with patients were assessed in one time, ranging from 30 to 45 minutes. Both assessments (with patient and caregiver) were undertaken separately and confidently. Some adjustments were made for patients with fine motor deficits. One MMSE subtest, namely the visual construction, and one subtest from FAB, the motor programming, were not administered. Three replacements were made. In Verbal Fluency of FAB, we used the results of ECAS Verbal Fluency since the task was the same and was adapted for patients with dysarthria. For those with severe motor deficits, the standard written sentence in MMSE was altered to a verbal format. In HADS, the item *"I feel slowed down"* was asked to the patients to do not refer to physical incapacity.

The Healthy Control group was assessed, separately, at a room next to a sports hall. Each session, specifically scheduled for this study, took about 25 to 35 minutes. During this time, participants filled out a sociodemographic questionnaire and underwent a neuropsychological evaluation with: ECAS (cognitive), MMSE, FAB, and HADS.

All participants provided written informed consent. The study was conducted according to the Declaration of Helsinki and had been approved by the local medical ethics committee at each hospital.

4.4. Study design

This study employed a cross-sectional observational design, with statistical methods tailored to three specific research questions. We utilized the Statistical Package for Social Studies (SPSS, version 28.0, IBM SPSS, Chicago, IL) for data analysis. For sample characterization, descriptive statistics were applied. Based on the ALS Functional Rating Scale – Revised (ALSFRS-R) scores and the first categorization by Mioshi et al. (2012), ALS patients

were categorized into two groups: Low Severity (scoring between 37 and 48) and High Severity (scoring between 0 and 36). This approach allows for a better characterization of the cognitive and functional limitations.

The study's outcomes were then compared across three groups: ALS Low Severity, ALS High Severity, and the Healthy Control group. The Shapiro-Wilk test was employed to assess data normality and Levene test for variance homogeneity (Table 13 in Appendix). Depending on their parametric properties, group comparisons of dependent neuropsychological variables were conducted. ANOVA analyses were performed for the subtests in which the assumptions were met for all the groups. Given that some datasets did not adhere to a normal distribution, non-parametric tests were chosen for group comparisons. Specifically, the Kruskal-Wallis test was used for tri-group comparisons, while the Mann-Whitney test was reserved for bi-group analysis.

Effect size measures (Cohen's *d* and Glass rank biserial correlation, r_G) were used to quantify the difference between two group means. Cohen's (Cohen's $d = (M2-M1)/SD_{pooled}$), used in parametric tests, in terms of interpretation, Cohen's *d* values can be considered as small (0.2), medium (0.5) or large (0.8) effect sizes. A significance level of 0.05 was considered for all the statistical tests.

Lastly, the correlation between ALS-specific cognitive domains (measured by ECAS) and Functional Incapacity in ADLs (assessed by IAFAI) was explored using the Spearman's correlation coefficient (*rho*).

5. Results

a) Descriptive Statistics

This study involved forty-four participants, ranging in age from 47 to 85, with a mean age of 68.6 years and a standard deviation (SD) of 7.8.

The three groups were similar in age, years of education and gender distribution (Table 1).

Table 1.

Sample demographic characteristics. (n = 44)

		ALS Low Severity (N =11)	ALS High Severity (N =11)	Healthy Control (N=22)	χ^2	p
Gender	Female	5 (45.5%)	4 (36,4%)	15 (68,2%)	3.483	.175
	Male	6 (54.5%)	7 (63,6%)	7 (31,8%)		
					H	
Age	*M ± SD*	67.4±10.4	70.9±9.8	68.14±4.7	2.37	.306
	Min	47	54	47		
	Max	83	85	85		
Education	*M ± SD*	8.36±4.9	7.82±4.6)	9.4±4.9)	.840	.657
	Min	4	4	4		
	Max	17	16	25		

In the ALS LS group, the most common onset region was the upper limb at 45.5%, followed by both the lower limb and bulbar, each accounting for 27.3%. Conversely, in the ALS HS group, the lower limb onset dominated at 72.7% and was trailed by bulbar onset at 18.2% and a single patient (9.1%) who had an upper limb onset.

The duration from the first symptoms to diagnosis varied considerably. ALS LS patients reported an average duration of 14.6 months (SD=12.4), while ALS HS patients had an average of 17.9 months (SD=12.6). On the Functional Rating Scale, ALS LS patients scored an average of 41.8 (SD=3.5), in contrast to ALS HS patients who averaged at 26.6 (SD=6.7).

Regarding medical devices, 45.5% of ALS LS patients (five out of eleven) used non-invasive ventilation (NIV). In the ALS HS group, 90.9% (ten out of eleven) required ventilation. Only two patients from the ALS HS group had a feeding tube (RIPPEG) inserted (Table 2).

Table 2.

Clinical characterization for ALS group (n=22)

		ALS Low Severity (*N* =11)	ALS High Severity (*N* =11)
Region of onset	Upper Limb	5 (45.5%)	1 (9.1%)
	Lower Limp	3 (27.3%)	8 (72.7%)
	Bulbar	3 (27.3%)	2 (18.2%)

Diagnostic Durations	*M* ± *SD*	14.6 (12.4)	17.9 (12.6)
(in months)	*Min*	1	4
	Max	46	45
ALSFRS-R	*M* ± *SD*	41.8±3.5	26.6±6.7
NIV		5 (45.5%)	10 (90.9%)
RIPPEG		0	2 (18.2%)

Notes: NIV=Non-Invasive Ventilation; ALSFRSR-R=ALS Functional Rating Scale Revised; RIPPEG=Feeding tube inserted.

b) Cognitive, behavioural, emotional and functionality comparisons

Comparisons between ALS Patients (Low Severity LS and High Severity HS) and Healthy Control (HC) are presented in Table 3. Discriminative comparation data between groups are in Appendix, table 8-11.

All the domains of ECAS showed significant differences, namely Language, Verbal Fluency, Executive, ALS Specific, Visuospatial, and ECAS TOTAL, except on the Memory and ALS Non-specific subtests. Additionally, a pronounced difference was observed in FAB, between the LS ALS group and HC, as well, between HS ALS group and HC, both with a medium effect size (r=62; r=-.74, respectively). Notably, there were no significant differences in MMSE and HAD scores among the groups. However, a significant difference appeared in the MMSE scores, between ALS patients Low-Severity group (M=28.64, SD=1.4) averaging higher than the High-Severity group (M=26.82, SD=2) with a medium effect size (r=0.53).

Regarding Functional Incapacity, except Physical and Emotional total scores, all categories showed significant differences between the two ALS groups, with large effect sizes ranging from r=-.51 to r=-.82. Of particular emphasis is the pronounced effect size (r=-0.82) seen for the IAFAI TOTAL score.

The comparation analyse between LS ALS group and HC group, generally manifested reduced scores in the ECAS subtests. Significant differences were found in Verbal Fluency domain, with a medium effect size (r=-0.56). Similar patterns were seen in the specific ALS domains and the ECAS total score, both with a large effect size (d=-0.82; d=0.76, respectively). The FAB test further delineated these differences, with the HC group scoring considerably higher (M=15.95; SD=1.8) than the LS group (M=13.63, SD=2; r=0.62).

Results in HS ALS patients were even more reduced comparatively to HC group. The results in ECAS revealed significant differences except for the Memory domain, all ECAS

cognitive domains highlighted significant differences, emphasized by exceptionally large effect sizes ranging from r=-.5 to d=-1.21.

Table 3.

Comparison between groups based on cognitive, behavioural, emotional, and functional incapacity scores (n=44)

	ALS Patients		Control		
	LS (n=11)	HS (n=11)	HC (n=22)	*Test*	*Significant Differences*
	M±SD	*M±SD*	*M±SD*		
ECAS					
Language	22.82±3.3	20.91±5.6	24.59±2.3	F=3.986*	HS ≠** HC
Verbal	5.82±4.6	6.55±5.1	11.73±5.7	H=9.19**	LS≠**HC≠*HS
Executive	26.82±9.4	22.36±10.9	30.95±9	F=3.013	HS ≠*HC
Specific T	55.45±15.2	49.82±19.3	67.27±13.9	F=5.155**	LS≠*HC≠**HS
Memory	17.55±4.2	14.27±5.9	17.41±3	H=1.69	-
Visuospatial	10.64±1.4	9.27±2.4	11.27±1.1	H=6.79*	HS ≠**HC
N-Specific T	28.18±5.2	23.55±7.4	28.68±2.9	F=4.244*	HS≠**HC
TOTAL	83.64±18.6	73.36±24.4	95.95±15.1	F=5.682**	LS≠*HC≠**HS
Behavioural	.09±.3	.55±.93	-	U=73	-
Psychoses	0	.27±.91	-	U=66	-
MMSE	28.64±1.4	26.82±2	28.18±1.5	H=3.902	LS ≠*HS
FAB	13.73±2	12.73±2.7	15.95±1.8	H=9.982**	LS≠**HC≠**HS
HAD-A	4.36±3.78	4.45±3.86	5.73±3.48	F=.720	-
HAD-D	2.82±3.49	4.45±4.41	3.27±2.6	H=.720	-
IAFAI					
BADL	8.23± 10.33	32.82±17.68	-	U=15.87**	LS≠**HS
IADL_H	2.51±3.7	10.47±9.54	-	U=6.641*	LS≠*HS
IADL_A	4.35±4.27	13.42±8.59	-	U=10.06**	LS≠**HS
TOTAL	14.99±15.24	56.7±26.6	-	U=10.15**	LS≠**HS
Physical	13.09±4.73	53.98±7.76	-	U=20.24**	LS≠**HS
Cognitive	0	.973±2.53	-	U=1.620	-
Emotional	1.34±2.06	3.22±5.54	-	U=1.113	-

Note: Significant differences at the 0.01 level (**) and at the 0.05 level (*) (2-tailed).

c) Correlations between ECAS ALS Specific domains and IAFAI domains

Spearman's correlations were executed to examine the relationships between specific cognitive domains of ALS (as determined by ECAS) and the IAFAI domains, which reflect Functional Incapacity in ALS patients (Table 4).

Upon correlating the specific cognitive ALS domains with IAFAI domains, diverse associations were found. All domains of ECAS presented a negative correlation with IADL, both A (*Advanced*) and H (*Household*) categories. A moderate negative correlation was seen between the Executive Function and IADL-A, and this was statistically significant.

Both Cognitive and Emotional IAFAI totals showed negative correlations with all the specific ALS cognitive domains. Importantly, the most robust relationship with a strong negative correlation was found between the Specific ALS domains and Cognitive IAFAI. In addition, a moderate but statistically significant negative correlation was seen between Verbal Fluency and Cognitive IAFAI.

Table 4.

Correlations (Spearman's coefficient) between ECAS cognitive ALS-specific (Language, Verbal Fluency, Executive Functions, Total) and IAFAI domains

	BADL	IADL-H	IADL-A	TOTAL	Physical	Cognitive	Emotional
Language	.200	-.182	-.050	.089	.056	-.395	-.106
Fluency	.293	-.082	-.068	.167	.093	-.454*	-.145
Executive	-.042	-.383-	-.473*	-.203	-.243	-.357	-.278
ALS Specific	.318	-.085	-.212	.112	.136	-.646*	-.250

Note: Correlation is significant at the 0.05 level (*) (2-tailed).

6. Discussion

The aim of this study was to examine the relationship between the cognitive impairment in ALS and functional incapacity in Activities of Daily Living (ADLs).

Comparations within the ALS cohort revealed significant disparities in *Mini Mental Screening Examination* (MMSE) and in several categories of *Adult and Older Adults Functional Assessment Inventory* (IAFAI). Patients with Low severity ALS scored lower in MMSE and IAFAI than patients with High Severity, implying milder impairment. This trend of deteriorating cognitive abilities with disease progression aligns with existing literature (Elamin, et al., 2013; Crockford, et al., 2018). Additionally, in contrast to the previous findings (Osborne, Sekhon, Johnston, & Kalra, 2014), our results indicate the effective utility of MMSE and IAFAI in detecting cognitive and functional differences across ALS severity levels.

Previous studies have consistently shown that ALS patients perform worse on cognitive tests than healthy individuals (Raaphorst, de Visser, Linssen, Haan, & Schmand, 2010; Beeldman, Raaphorst, & Twennaar, 2015). This difference was evident in our study between Low-Severity ALS patients, who have minimal motor impairment, and healthy controls and even larger when High Severity were compared. In particularly, the significant differences were found between Low Severity ALS group and Healthy individual in FAB and in Verbal Fluency and ALS Specific domains of ECAS. These underscoring results in ECAS, Verbal Fluency and the Frontal Assessment Battery (FAB), may help differentiate between healthy individuals and ALS patients.

The large effect size comparing the ALS High Severity and Health Control in executive function and the negative correlation between executive function and the performance of Advanced Instrumental Daily Living (IADL-A) allowed to reinforce previous research that cognitive deficits are more frequent in advanced stages (Chiò, Hammond, Mora, & Bonito, 2013; Elamin, et al., 2013; Crockford, et al., 2018; Chiò, et al., 2019) based on disease staging severity system. Those results are in line with prior longitudinal study, which revealed that executive dysfunction is associated to a rapid motor decline (Elamin, et al., 2013). However, our study offers new insights by incorporating a broader definition of functionality (OMS, 2001) that extends beyond physical and structural abilities, using the IAFAI to evaluate a comprehensive range of ADLs.

So far, only one study has included ADL (Activities of Daily Living) performance as a metric to assess its impact on disease progression in MND (Motor Neurone Disease) patients (Mioshi, Lillo, Kiernan, & Hodges, 2012). According to Mioshi et al. (2012), MND patients showed a decline in functional capacity influenced by motor impairments and behavioural changes, affecting their ability to perform ADLs. Furthermore, they proposed that cognitive, behavioural, and motor changes have a combined impact on functional performance. This study

aimed to investigate the role of cognitive impairment in functional performance and looks to address this gap in the research.

Our correlation analyses indicates that better executive function could reduce functional incapacity on complex ADLs, which remains to activities associated with understanding and communicating medical or financial decisions (Sousa, Prieto, Vilar, Firmino, & Simões, 2014). Additionally, a robust negative correlation between Specific ALS domains and Cognitive IAFAI was seen, reinforcing the importance of improving specific cognitive ALS domains (Language, Verbal Fluency and Executive Functions) which could lead in decreasing functional incapacity due to cognitive reasons. These results emphasize the potential benefits of cognitive stimulation programs, particularly targeting executive functions, to slow the progression of cognitive decline and diminishing the functional incapacity. On the other hand, implementing such interventions can greatly benefit a patient's decision-making in disease management but also diminished negative prognostic indicator associated to executive dysfunction, as noted in prior research (Elamin, et al., 2011; Goldstein & Sharon, 2013; Khin, Minor, Holloway, & Pelleg, 2015).

Lastly, this study has also practical implications for caregivers and family members. It helps them understand a patient's capabilities and set realistic expectations, especially concerning Instrumental Activities of Daily Living that require higher cognitive skills and decision-making abilities, namely, advanced healthcare planning and the formalization of Advance Directives. As the disease progresses, cognitive decline may intensify. Thus, early healthcare planning involving both the ALS patient and their family is crucial to understanding the patient's wishes and ensuring they are fulfilled. Future Research should explore the mechanisms underlying the observed correlation between cognitive impairment in ALS and functional incapacity to develop targeted interventions. That includes investigating the neurobiological correlates of executive function and the functional incapacity to ADLs and studying the efficacy of a cognitive stimulation program specially designed for ALS patients. Additionally, a long-term study assessing the effects of cognitive and functional declines on disease progression is recommended.

The primary limitation of this study was the small sample size. Also, certain exclusion criteria, such as communication ability, restricted the participation in this study. Subsequent studies might include patients with severely compromised oral communication, using advanced communication tools like eye-tracking for assessment. However, this approach is feasible with the ECAS version but is restrictive for other metrics.

Communication challenges and pronounced cognitive deficits, especially in ALS bulbar onset cases, led to some patient exclusions, potentially accounting for the observed insignificant behavioural changes. Moreover, patients were assessed at varying disease stages. Assessments at an earlier and at the same disease stage would better highlight discrepancies among ALS patients.

7. Conclusions

This study has investigated the relationship between cognitive impairment in ALS and the subsequent impact on the performance of ADLs. Our findings reveal that cognitive decline, particularly in executive functions, correlates with increased advanced IADL's in ALS patients. The usage of MMSE and IAFAI has proven effective in distinguishing between varying degrees of ALS severity, while the FAB and ECAS Verbal Fluency, was advantageous for contrasting with healthy individuals. These insights underscore the importance of comprehensive cognitive evaluations in the management of ALS. Future interventions could benefit from focusing on cognitive stimulation to mitigate the progression of functional decline. As the results of this studies confirmed, cognitive decline may worsen with disease severity highlighting the importance of early healthcare planning involving both the ALS patient and their families. Further studies with larger and more diverse cohorts are recommended to deepen our understanding of the interplay between cognitive impairment and functional incapacity in ADLs. This research contributes to the ongoing discourse on ALS management and supplies a foundation for subsequent investigative efforts to enhance patient care.

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9.Appendix

Table 5.

Awaji-Shima criteria to Diagnose ALS, as Applied to the Revised El Escorial Criteria

1. Principles (from the Airlie House criteria)

   The diagnosis of ALS requires:

   A. the presence of

      1. evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological, or neuropathological examination
      2. evidence of upper motor neuron (UMN) degeneration by clinical examination; and
      3. progressive spread of symptoms or signs within a region or to other regions, as determined by history, physical examination, or electro-physiological tests.

   B. the absence of

      1. electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and
      2. neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

2. Diagnostic categories

   Definite ALS

   defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions.

   Probable ALS

   defined on clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

   Possible ALS

defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs.

Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded.

Table 6.

Proposal of a new diagnostic criteria for ALS: the Gold Coast Criteria

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
2. Presence of upper and lower motor neuron dysfunction in at least 1 body region, (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions, and
3. Investigations excluding other disease processes.

Footnotes:

Upper motor neuron dysfunction implies at least one of the following:

1. Increased deep tendon reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles.
2. Presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex.
3. Increase in velocity-dependent tone (spasticity).
4. Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features

Lower motor neuron dysfunction in a given muscle requires either:

- Clinical examination evidence of Muscle weakness, and
- Muscle wasting

or

- EMG abnormalities that must include:

Both evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration and/or increased amplitude, with polyphasia and motor unit instability regarded as supportive but not obligatory evidence.

And evidence of ongoing denervation including:

Fibrillation potentials or positive sharp waves, or fasciculation potentials

Body regions are defined as bulbar, cervical, thoracic, and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in two limb muscles innervated by different roots and nerves, or one bulbar muscle, or one thoracic muscle either by clinical examination or by EMG.

The appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle EMG, MRI or other imaging, fluid studies of blood or CSF, or other modalities as clinically necessary.

Table 7.

Phenotypic presentations of ALS (Masrori & Van Damme, 2020)

Disorder	Variants	Clinical diagnosis	Imaging (18F FDG PET/CT of the Brain)
Primary progressive aphasia (PPA)	Non-fluent agrammatic variant primary progressive aphasia (naPPA)	At least one: • Agrammatism errors and omissions, as well as amplification of grammatical forms • Prosody (the rhythm or melody of speech), as well as speech sound errors (such as motor-based speech planning errors 'apraxia of speech') • At least two of the following criteria must be fulfilled: 1.Impaired comprehension of	Atrophy of anterior peri-Sylvian atrophy involving inferior, opercular and insular portions of the left frontal lobe.

		complex sentences 2.Spared single-word comprehension 3.Spared object knowledge	
	Semantic variant of primary progressive aphasia (svPPA)	• Impaired confrontation naming • Impaired comprehension of single words • At least three of the following criteria must be fulfilled: 1.Degraded object knowledge. 2.Surface dyslexia or dysgraphia, in which sight vocabulary words are pronounced as written 3.Spared repetition 4.Spared speech production	Atrophy of left. anterior temporal atrophy affecting lateral and ventral surfaces as well as the anterior hippocampus and the amygdala
	Logopenic variant primary progressive aphasia (lv-PPA)	• Profound difficulty in wordfinding • Impaired Repetition of phrases, partly as a result of limited auditory verbal short-term memory • At least three of the following criteria must be fulfilled: 1.Speech (phonologic) errors in spontaneous speech and naming 2.Spared single-word comprehension and object knowledge	Atrophy of left. posterior perisylvian or parietal lobe

		3.Spared motor speech 4.Absence of frank agrammatism	
Behavioral variant frontotemporal dementia (bvFTD)		At least three: • Behavioural disinhibition • Apathy or inertia • Loss of sympathy or empathy • Stereotypical, perseverative, or compulsive behaviour • Hyperorality or dietary changes • Executive deficits with relative sparing of visuospatial skills and memory	Prefrontal or anterior temporal cortex loss, particularly in the right hemisphere

Table 8.

Comparison between ALS patients (n=22) and Healthy Control (n=22) groups based on cognitive and emotional tests scores

	ALS patients	Healthy Control		
	M±SD	*M±SD*		*p*
ECAS				
Language	21.86±4.6	24.59±2.3	t=2.51	.016
Verbal	6.18±4.7	11.73±5.7	U=114	.002
Executive	24.59±10.2	30.95±9	t=2.195	.034
Specific T	52.64±17.2	67.27±13.	t=3.109	.003
Memory	15.91±5.3	9	U=214	.516
Visuospatial	9.95±2	17.41±3	U=147	.019
Non Specific	25.86±6.7	11.27±1.1	t=1.817	.076
T	78.50±21.8	28.68±2.9	t=3.087	.004
TOTAL		95.95±15.		
		1		
MMSE	27.73±2	28.18±1.5	U=218	.566
FAB	13.23±2.3	15.95±1.8	U=77	<.001

HAD-A	4.41±3.7	5.73±3.48	t=1.213	.232
HAD-D	3.64±4	3.27±2.6	U=229.5	.766

Table 9.

Differences in questionnaires scores between ALS LS (n=11) and ALS HS (n=11)

	ALS Low-Severity	ALS High-Severity	Comparation Analyse		Effect size
	M±SD	*M±SD*		*P*	
ECAS					
Language	22.82±3.3	20.91±5.6	t=.981	.338	d= 0.42
Verbal Fluency	5.82±4.6	6.55±5.1	U= 62.5	.894	r= -003
Executive	26.82±9.4	22.36±10.9	t= 1.030	.315	d= 0.43
Specific T	55.45±15.2	49.82±19.3	t=.761	.455	d= 0.33
Memory	17.55±4.2	14.27±5.9	U= 44	.275	r= 0.27
Visuospatial	10.64±1.4	9.27±2.4	U= 41	.189	r= 0.32
Non-specific T	28.18±5.2	23.55±7.4	t= 1.704	104	d= 0.72
TOTAL	83.64±18.6	73.36±24.4	t= 1.112	.279	d= 0.47
Behavioural	.09±.3	.55±.93	U= 73	.221	r= -0.21
Psychoses	0	.27±.91	U= 66	.317	r= -0.09
MMSE	28.64±1.4	26.82±2	U=28.5	.033	r= 0.53
FAB	13.73±2	12.73±2.7	U=51	.528	r= 0.16
HAD-A	4.36±3.78	4.45±3.86	t=-.965	.346	d= -.02
HAD-D	2.82±3.49	4.45±4.41	U=72.5	.425	r= -0.2
IAFAI					
BADL	8.23± 10.33	32.82±17.68	U=108	.002	r= -.79
IADL_H	2.51±3.7	10.47±9.54	U=91.5	.035	r= -.51
IADL_A	4.35±4.27	13.42±8.59	U=98.5	.012	r= -.63
TOTAL	14.99±15.24	56.7±26.6	U=109	.001	r= -0.8
Physical	13.09±4.73	53.98±7.76	U=110	.001	r= -.82
Cognitive	0	.973±2.53	U=71.5	.148	r= -.18
Emotional	1.34±2.06	3.22±5.54	U=61	.968	r= .01

Table 10.

Differences in questionnaires scores between ALS LS (n=11) and HC (n=22)

	ALS Low-Severity	Healthy Control	Comparation analyse		Effect size
	M±SD	*M±SD*		*p*	
ECAS					
Language	22.82±3.3	24.59±2.3	t=-1.823	.078	d= -.68
Verbal Fluency	5.82±4.6	11.73±5.7	U=188.5	.009	r= -.56
Executive	26.82±9.4	30.95±9	t=-1.224	.230	d= -.46
Specific T	55.45±15.2	67.27±13.9	t=-2.237	.033	d= -.82
Memory	17.55±4.2	17.41±3	U=117.5	.893	r= .03
Visuospatial	10.64±1.4	11.27±1.1	U=155.5	.156	r= -.29
Non-specific T	28.18±5.2	28.68±2.9	t=-.358	.723	d= -.13
TOTAL	83.64±18.6	95.95±15.1	t=-2.044	.050	d= -.76
MMSE	28.64±1.4	28.18±1.5	U=98.5	.378	r= .19
FAB	13.73±2	15.95±1.8	U=196.5	.003	r= .62
HAD-A	4.36±3.78	5.73±3.48	t=-1.032	.310	d= -.38
HAD-D	2.82±3.49	3.27±2.6	U=142.5	.402	r= -.18

Table 11.

Differences in questionnaires scores between ALS HS (n=11) and HC (n=22)

	ALS High-Severity	Healthy Control	Comparation Analyse		Effect size
	M±SD	*M±SD*		*p*	
ECAS					
Language	20.91±5.6	24.59±2.3	t=-2.721	.011	d= -1
Verbal Fluency	6.55±5.1	11.73±5.7	U=181.5	.020	r= -.5
Executive Function	22.36±10.9	30.95±9	t=-2.496	.022	d= -.9
ALS Specific	49.82±19.3	67.27±13.9	t=-2.297	.005	d= -1.1
Memory	14.27±5.9	17.41±3	U=152	.232	r= -.26
Visuospatial	9.27±2.4	11.27±1.1	U=181.5	.014	r= -.5
ALS Non-specific	23.55±7.4	28.68±2.9	t=-2.871	.007	d= -1.06
TOTAL	73.36±24.4	95.95±15.1	t=-3.287	.003	d= -1.21

MMSE	26.82±2	28.18±1.5	U=167.5	.071	r= -.38
FAB	12.73±2.7	15.95±1.8	U=210.5	<.001	r= -.74
HAD-AHAD-D	4.45±3.86	5.73±3.48	t=-.956	.347	d= -.35
	4.45±4.41	3.27±2.6	U=112	.729	r= .07

Table 12.

Normality test (Shapiro-Wilk) for age, education, and questionnaires scores (n=44)

		Z	*P*
Age	ALS LS	.969	.875
	ALS HS	.907	.226
	HC	.933	.145
Education	ALS LS	.835	.027
	ALS HS	.766	.003
	HC	.843	.003
ECAS Language	ALS LS	.882	.110
	ALS HS	.906	.216
	HC	.941	.205
ECAS Verbal	ALS LS	.940	.216
Fluency	ALS HS	.905	.214
	HC	.904	.036
ECAS Executive	ALS LS	.948	.613
Function	ALS HS	.954	.700
	HC	.944	.239
ECAS Specific	ALS LS	.962	.791
	ALS HS	.981	.972
	HC	.962	.530
ECAS Memory	ALS LS	.944	.566
	ALS HS	.754	.002
	HC	.969	.683
ECAS Visuospatial	ALS LS	.881	.108
	ALS HS	.884	.118
	HC	.702	<.001
	ALS LS	.946	.595

ECAS Non-specific	ALS HS	.876	.092
	HC	.970	.704
ECAS Total	ALS LS	.943	.560
	ALS HS	.953	.677
	HC	.969	.698
ECAS Behavioural	ALS LS	.345	<.001
	ALS HS	.572	<.001
ECAS Psychoses	ALS LS	-	-
	ALS HS	.345	<.001
MMSE	ALS LS	.858	.055
	ALS HS	.958	.749
	HC	.879	.012
FAB	ALS LS	.959	.763
	ALS HS	.866	.068
	HC	.808	<.001
HAD-A	ALS LS	.910	.244
	ALS HS	.905	.215
	HC	.946	.259
HAD-D	ALS LS	.738	.001
	ALS HS	.848	.041
	HC	.860	.005
BADL	ALS LS	.812	.014
	ALS HS	.954	.691
IADL-H	ALS LS	.750	.002
	ALS HS	.909	.235
IADL-A	ALS LS	.849	.041
	ALS HS	.961	.783
IAFAI Total	ALS LS	.884	.118
	ALS HS	.861	.059
Physical	ALS LS	.819	.017
	ALS HS	.870	.077
Cognitive	ALS LS	-	-
	ALS HS	.461	<.001

Emotional	ALS LS	.711	<.001
	ALS HS	.603	<.001

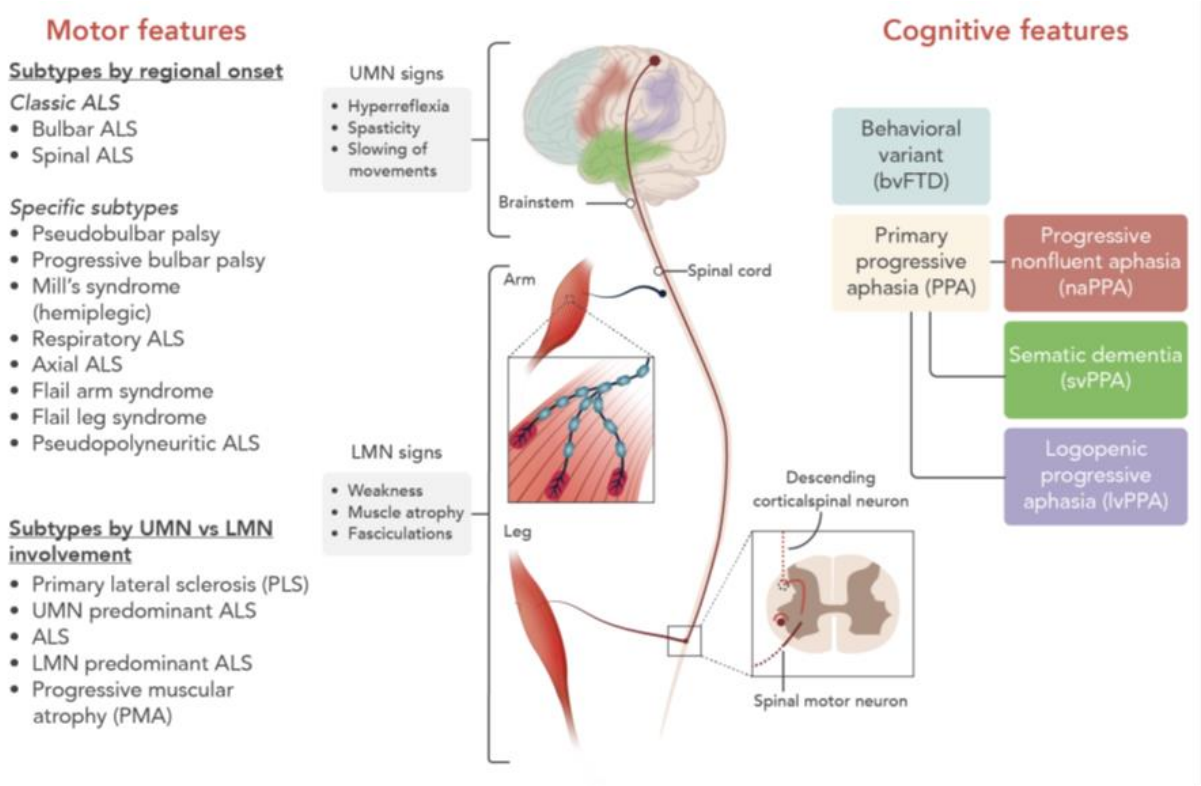

Figure 1. Phenotypic presentations of ALS (Masrori & Van Damme, 2020