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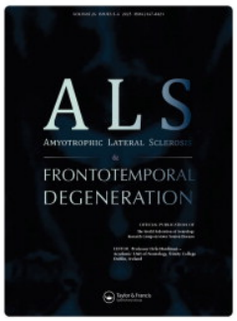

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RESEARCH ARTICLE

Neuropsychological assessment practices in PRECISION-ALS: challenges and opportunities for harmonization

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Abstract

Objective: To gather comprehensive insights regarding current neuropsychological assessment practices in PRECISION-ALS, a pan-European research and industry consortium, to propose areas which can be harmonized and facilitate more robust cross-country comparisons. *Methods*: Representatives from PRECISION-ALS sites were surveyed with a semi-

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structured interview, gathering information on how people with ALS are assessed for cognitive/behavioral change, including how they are initially screened, classified as impaired/unimpaired, and followed up longitudinally. Assessment practices across PRECISION-ALS sites were summarized using descriptive analysis. *Results*: Ten of the eleven PRECISION-ALS sites perform cognitive and/or behavioral screening at least once during the course of the disease, using the Edinburgh Cognitive and Behavioral ALS Screen, either for clinical or research purposes. All centers categorize impairment, but differ how it is defined, with some using local norms, and others using other countries' norms. Most sites account for age and education, but differ in how these factors are considered. Longitudinal protocols vary in terms of the number of assessments, time intervals, and use of alternative versions. Behavioral screening is more consistently implemented, with the ECAS caregiver interview as the standard tool, however there is a lack of clarity in how this data is applied. Many sites supplement cognitive and behavioral screening with additional measures of mood and/or neuropsychiatric symptoms. *Conclusions*: These findings illustrate areas of commonality and divergence in neuropsychological screening practices. Site-specific variations are likely to confound research involving cross-country data-sharing. PRECISION-ALS, in generating prospective population-based datasets, will provide agreed harmonized protocols for neuropsychological assessment across participating sites.

Keywords: *Cognition, behaviour, Amyotrophic Lateral Sclerosis, ECAS*

Introduction

Whilst initially considered an exclusively motor disorder, it is now well established that cognitive impairment and behavioral change are common features of Amyotrophic Lateral Sclerosis (ALS), affecting up to 50% of people with ALS (pwALS) (1). Clinical, neuropathological, and genetic evidence suggests that ALS and Frontotemporal Dementia (FTD) form a disease spectrum, known as frontotemporal-spectrum disorder (ALS-FTSD) (2).

Capturing the heterogeneity of this spectrum remains a key challenge, especially for clinical trial design. Validated tools are urgently needed to assess motor, cognitive, behavioral, and neuronal aspects of the disease, while also being sensitive to change over time to evaluate investigational treatments (3). Robust assessment is also essential for prognosis and care planning, helping clinicians anticipate progression, tailor interventions, and guide pwALS and their families more effectively.

The PRECISION-ALS consortium is a pan-European academic-industry partnership aiming to better characterize ALS heterogeneity using clinical, health service, imaging, and 'omic' data to support a precision medicine approach (4). As sites share data, harmonizing assessment practices is essential to improve quality and consistency—especially for cognitive and behavioral features, which have historically been assessed using diverse measures, professions, definitions of abnormality, and longitudinal protocols (5,6).

The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) is the most widely used cognitive screening tool for ALS in Europe (7), with multiple language translations and alternative versions for repeat use (8,9). However, normative data and its application to define impairment vary across sites and studies (10–12), affecting prevalence estimates. For instance, McMillan et al. (13) reported a 16% impairment rate using local norms versus 35% with UK ECAS cutoffs. They also showed that the choice of statistical method influences results, with regression approaches yielding more conservative estimates than the 2SD method—particularly for non-parametric subscores (e.g. 22.5% vs. 32.4% impairment on visuospatial score), though differences were minimal on total scores (15% vs. 16%).

Another source of inconsistency is how sites account for confounding factors—such as age, education, gender, and pre-morbid IQ—when classifying impairment, which can limit the interpretability of aggregated data. Cognitive performance may also be affected by mental health, yet the impact of depressive symptoms on ECAS scores is often overlooked, despite evidence of a negative correlation (14–17). Such symptoms can be mistaken for behavioral changes like apathy (18,19), emotional blunting, poor hygiene, and egocentrism (20). While the original ECAS cutoffs did not adjust for confounders (8), most subsequent norms account for age and education (10–12,21). However, methods vary: some countries use years of education, others use categories; age thresholds also differ (e.g. 65 in Ireland vs. 60 in Italy). These variations likely affect prevalence estimates and hinder cross-country comparisons.

In assessing behavioral change, the ECAS caregiver interview, Beaumont Behavioral Inventory (BBI) (22), Motor Neuron Disease Behavioral Scale (MiND-B) (23) the ALS Frontotemporal Dementia Questionnaire (ALS-FTD-Q) (24), and the Frontal Behavioral Inventory ALS Version (25) are most commonly cited in the literature (6). The method of classifying pwALS with behavioral change (ALSbi) or comorbid FTD (ALS-FTD) varies depending on the assessment tool used, with limited information on how comparable these classifications are across measures. For example, ALSbi can be classified with the endorsement of apathy and/or two non-overlapping behavioral symptoms on the ECAS caregiver interview, whilst the BBI requires scores above a threshold of 7 to be defined as ALSbi and scores above 22 indicating co-morbid FTD (22).

In rare, heterogenouse diseases such as ALS, it is essential to aggregate data to achieve the statistical power necessary to interrogate many research questions. We must therefore ensure standardization in terms of assessment practices and analysis

methods. Thus, the aim of this study was to document the cognitive and behavioral screening and assessment practices across PRECSISON-ALS sites, to identify differences in practices, and propose areas which can be harmonized to ultimately facilitate more robust cross-country comparisons.

Methods

Participants

Research sites within PRECISION-ALS comprise TRICALS sites (www.TRICALS.org), including Belgium (UZ Leuven, KU Leuven), France (University of Tours, CHU Bretonneau), Germany (University Medical Center Rostock), Ireland (Trinity College Dublin), Italy (University of Torino), Portugal (Lisbon Medical Academic Center-Faculty of Medicine, University of Lisbon), Spain (Bellvitge Hospital, University of Barcelona), Sweden (Karolinska Institutet and University Hospital), the Netherlands (University Medical Center Utrecht) and the United Kingdom (King's College London; University of Sheffield). A member of each PRECISION-ALS site was invited to take part in a semi-structured interview over videocall (between 16/04/2024 and 23/01/25), to survey their cognitive and behavioral assessment practices and protocols (see Supplemental Table 1 for responder details).

Materials

The semi-structured interview was designed to gather qualitative and quantitative data on the numerous factors relevant to cognitive and behavioral screening, and how they are interpreted to define impairment (see supplemental material for the questionnaire used to facilitate semi-structured interviews). This included questions on the types of cognitive and behavioral assessments employed, when in the disease course they are typically conducted and what normative data are used to define impairment. Furthermore, participants were asked whether pwALS undergo a full neuropsychological assessment, how often and when repeat assessments are carried out, and what mental health screeners are applied. Participant verbal responses were recorded on the questionnaire proforma, cross checked (EC & JDV) and stored in Excel files.

Procedure

Each PRECISION-ALS site was contacted via email, with information on the goal of the study, namely the documentation of cognitive and behavioral screening practices. Once participants agreed to the interview, a video call was arranged. A semi-structured interview was conducted with two interviewers (EC & JDV or JDV & EmD). The response rate was 100%, however one site declined a video call and provided responses to the questionnaire in a written manner.

Statistical analysis

Descriptive statistics were carried out to examine differences in protocols and practices across different PRECISION-ALS sites. The frequency of responses for each question was collated, and the percentage of respondents who indicated each possible response. All quantitative analyses were conducted using Excel.

Results

Practices of cognitive and/or behavioral screening

Of the eleven PRECISION-ALS sites interviewed, ten implement routine cognitive and/or behavioral screening at least once for each individual with ALS, either for clinical or research purposes (with the exception of Tours, where ECAS is used for a subset of pwALS for research purposes). All sites which do carry out routine cognitive and behavioral screening use the ECAS screening tool to assess cognition. The ECAS caregiver interview is used in eight out of ten sites to assess behavioral change (Dublin and Rostock the exception, with Dublin using the BBI and Dimensional Apathy Scale (DAS) (26) and Rostock using the Frontal Systems Behavior Scale (FrSBe) (27)). In eight out of ten sites, aside from Stockholm and London, a psychologist was involved in the ECAS assessments (Supplemental Table 2). Two sites (Dublin and Sheffield) carry out online assessments for a subset of pwALS (~10–15% of assessments).

All sites indicated that they classify pwALS as either impaired or unimpaired based on cognitive and behavioral screening, with four centers applying the revised Strong criteria (2). The normative data used, the time between assessment and diagnosis, and the factors from which cutoffs are stratified by, varied substantially across sites (see Table 1). Eight sites use local (i.e. national) normative data, while three centers utilize norms from another country. One center utilizes norms from a neighboring site which speaks the same language (Leuven adopting norms from the Netherlands) and two centers utilize the original ECAS cutoff norms. Seven out of eleven centers utilize the original ECAS table to calculate verbal fluency scores.

Seven sites stratify their abnormality cutoffs based on age and education, one based on age and gender, while four do not take any factors into account. Stratification boundaries for age and education differ considerably across sites, with age being dichotomized at 50, 60, 65. or 75 years of

Table 1. Baseline cognitive and behavioral clinical screening practices across PRECISION-ALS sites.

PRECISION-ALS site (n)	Norms used to classify impairment	Time of first assessment since diagnosis	Factors cut- offs are adjusted for	How factors are stratified
Dublin ($n=120$)	Irish Norms	Day of diagnosis	Age	<65, ≥65 years
			Education	<12, ≥12 years
Utrecht ($n=425$)	Dutch norms[a]	Day of diagnosis	Age	<65, 65–75, >75 years
			Education	Low, High (Verhage Education Scale)
Leuven ($n=125$)	Dutch norms[b]	0–4 months	Age	Continuous (not stratified)
			Education	Low, High (ISCED)
Stockholm ($n=40$)	Swedish norms	0–4 months	None	NA
London ($n=200$)	UK norms	0–8 months	None	NA
Sheffield ($n=100$)	UK norms	0–8 months	None	NA
Tours ($n=90$)	UK norms	Not specified	None	NA
Turin ($n=180$)	Italian norms	0–4 months	Age	≤60, >60 years
			Education	<14, ≥14 years
Barcelona ($n=80$)	Irish norms	0–4 months	Age	<65, ≥65 years
			Education	<12, ≥12 years
Lisbon ($n=70$)	Portuguese norms	0–4 months	Age	≤50, >50 years
			Education	≤12, >12 years
Rostock ($n=40$)	German norms	0–6 months	Age	≤60, >60 years
			Education	≤12, >12 years

n = Number of newly diagnosed pwALS seen each year.
[a]Dutch norms used in Utrecht are unpublished.
[b]Dutch norms used in Leuven are those presented by Bakker et al. (12).
ISCED = International Standard Classification of Education.

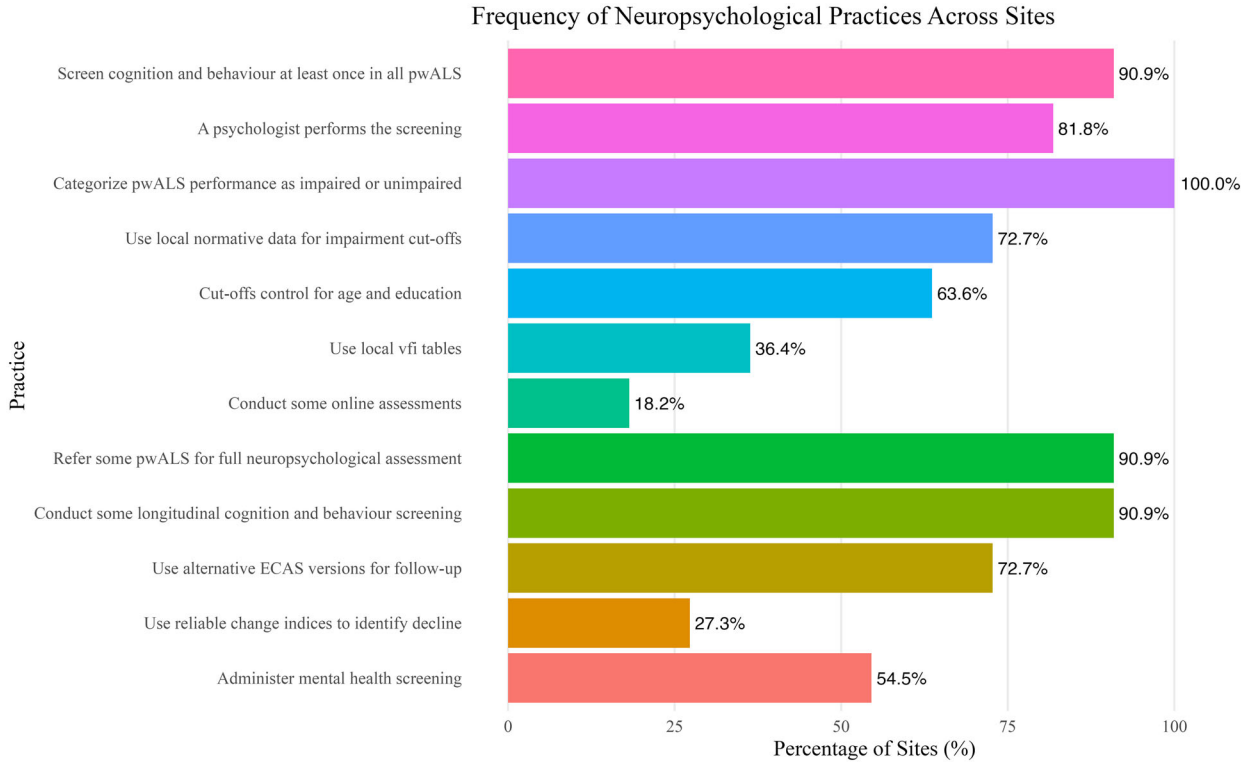

Figure 1. The frequency of which each neuropsychological assessment practice is applied.

age across different countries, while education is dichotomized at 12 or 14 years of education, or as low or high educational attainment based on International Standard Classification of Education (ISCED). See Figure 1 for an overview of key neuropsychological screening practices and how frequently they are applied across sites.

At ten PRECISION-ALS sites, some pwALS are referred for full neuropsychological assessment. Referrals are most often based on clinical

judgment (eight sites), abnormal ECAS scores (five sites), behavioral questionnaire results (three sites), or caregiver concerns (three sites), while two centers assess all pwALS routinely (Supplemental Table 2). Two sites report minimal referrals due to limited resources, and another two cited it was not deemed essential. In seven sites, a consistent test battery is used (Supplemental Table 3). Referral practices vary: research settings typically use standardized assessments, whereas clinical settings often rely on shorter, tailored batteries.

All centers typically evaluated language abilities, executive functioning, social cognition, (visual) memory, attention and visuospatial and constructional abilities. A small number of tests are used across multiple centers, such as the Digit Span test (which is used in all but one center), and the Boston Naming Test (BNT) and Stroop test that are included in the test batteries of three different centers. Many assessments are used only in individual centers, such as the use of the Mehrfachwahl–Wortschatz-Test Version B (MWT-B) to assess premorbid verbal IQ in Rostock, or the Bergen left right orientation task to evaluate body representation in Utrecht. This diversity in test selection may be due to test availability in specific languages or as a results of tailored approaches to cognitive assessment, to meet each center's distinct research or clinical objectives/priorities.

All PRECISION-ALS sites conduct caregiver interviews to assess behavioral changes in pwALS. However, the use of additional behavioral questionnaires varies: three sites use the DAS or BBI, two use the ALS-FTD-Q, and others use the MiND-B, Frontal Assessment Battery (FAB) (28), DAPHNE (29), or FrSBe (see Table 2). Depression and anxiety measures are used in seven and five of the eleven sites, respectively. The Hospital Anxiety and Depression Scale (HADS) is the most common (40%), followed by the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI) and the ALS Depression Inventory (ADI-12) (used in two centers each), and the Clinical Outcomes in Routine Evaluation 10 (CORE-10) (one center). The General Anxiety Disorder-7 (GAD-7) is used in two centers to assess anxiety symptoms.

Table 2. Mental health and behavioral screening practices across PRECISION-ALS sites.

PRECISION-ALS site	Mental health measures	Behavioral questionnaires
Dublin	None	BBI
		DAS
Utrecht	HADS	ECAS
		ALS-FTD-Q
Leuven	PHQ	ECAS
	BDI	BBI
	GAD-7	ALS-FTD-Q
	HADS	MBI-C
		DAS
Stockholm	HADS	ECAS
	ADI-12	DAS
London	None	ECAS
Sheffield	PHQ	ECAS
	CORE-10	DAS
	GAD-7	MiND-B
Tours	None	ECAS
		DAPHNE
Turin	HADS	ECAS
		BBI
		FAB
		FBI
		FrSBe
Barcelona	None	ECAS
Lisbon	None	ECAS
Rostock	BDI	FrSBe
	ADI-12	

Abbreviations: ADI-12: ALS Depression Inventory; ALS-FTD-Q: Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire; BBI: Beaumont Behavioral Inventory; BDI: Beck Depression Inventory; CORE-10 = Clinical Outcomes in Routine Evaluation 10; DAS: Dimensional Apathy Scale; ECAS: Edinburgh Cognitive and Behavioral ALS Screen; GAD-7: General Anxiety Disorder-7; HADS: Hospital Anxiety and Depression Scale; MBI-C: Mild Behavioral Impairment Checklist, MiND-B: Motor Neuron Disease Behavioral Instrument; PHQ: Patient Health Questionnaire; FrSBe: Frontal Systems Behavior Scale.

Practices of longitudinal follow-up in cognitive and/or behavioral screening

Ten PRECISION-ALS sites perform longitudinal follow-up assessment of cognitive or behavioral symptoms. Seven out of ten sites adhere stringently to a schedule for follow-up assessments (e.g. assessment every 4 or 6 months). However, the time interval between repeat assessments varies from three months to one year (see Table 3).

In four centers, longitudinal cognitive and behavioral assessment is offered to all pwALS. In the six remaining PRECISION-ALS sites, repeat assessments are only offered to a subset of pwALS, based upon clinical indication. We observed a notable divergence in which subgroups are followed up. In Dublin, pwALS are less likely to undergo repeat assessments when classified as abnormal on ECAS, as the potential impairment has been flagged, while in Tours, these pwALS were prioritized for repeat assessments, to track further decline. In Rostock, all pwALS are considered for repeat full neuropsychological assessments regardless of baseline impairment or not.

Eight centers accounted for practice effects in pwALS by using at least two alternative ECAS versions (73%). In two out of seven sites, the healthy normative sample that abnormality cutoffs are derived from completed ECAS A-B-C sequentially, enabling those centers to better account for practise effects. Two of the centers that do not

Table 3. Longitudinal cognitive and/or behavioral screening practices across PRECISION-ALS sites.

PRECISION-ALS site (n)	Longitudinal cognitive assessment	Longitudinal behavioral assessment	Typical assessment interval	Sequence of ECAS versions	No. of follow-up assessments
Dublin ($n=400$)	x	x	4–8 months	A-B-C-A …	1–4
Utrecht ($n=1750$)	x	x	4–6 months	A-B-C-A …	>1
Leuven ($n=250$)	x	x	6–12 months	A-B-A …	1–4
Stockholm ($n=115$)	x	x	6 months	A-B-C-A …	>1
London ($n=400$)	x	x	4 months	A-B-C-A …	1
Sheffield ($n=300$)	x	–	Depending on need	A-B-A …	1
Tours ($n=280$)	–	x	n/a	–	n/a
Turin ($n=210$)	x	x	8–12 months	A-A …	1–4
Barcelona ($n=265$)	x	x	4–6 months	A-B-C-A …	Not specified
Lisbon ($n=200$)	x	x	6 months	A-A/B …	1–4
Rostock ($n=60$)	x	x	12 months	A-A	1–2

n = Number of pwALS followed up annually.

utilize alternative versions of the ECAS aim to minimize practice effects by leaving a longer interval (> 6 months) between assessments. Three centers also calculate clinically meaningful change, by means of reliable change indices (30,31) (one center) or mixed effects models (two centers).

Discussion

The findings of this study indicate that at least one cognitive and behavioral screening assessment of pwALS is standard practise across the vast majority of PRECISION-ALS sites, with all using the ECAS to assess cognition. In the majority of sites a psychologist or neuropsychologist conducts or oversees the screening process. This is essential to ensuring good data quality and correct interpretation. As indicated by the literature, the methods used by each site to classify pwALS as impaired or unimpaired vary considerably, with most using local normative data stratified by age and education. As shown by McMillan et al. (13), the use of local normative data has a notable impact on the proportion of people who are categorized as impaired and should be recommended where available.

While positive that many sites stratify normative data by age and education, the thresholds used vary, limiting cross-country comparability. To address this, PRECISION-ALS sites plan to adopt shared methodologies and confounders—particularly age and education. However, these must reflect population differences in demographics and cultural norms. Quantile regression may be better suited for non-parametric subdomains (e.g. visuospatial scores) and individual ECAS subtasks (e.g. naming and comprehension) (13). Broad adoption of regression methods will require larger normative samples, consistent statistical approaches, and the development of a user-friendly tool (e.g. a webpage or app) to support clinical use.

The use of alternative ECAS versions is encouraging, with 70% of sites using versions B or C for longitudinal follow-up. Minimum intervals between assessments varied widely across PRECISION-ALS sites, which may impact how well longitudinal data can be aggregated or compared across countries. We also observed variation in which pwALS are prioritized for follow-up, highlighting the importance of documenting protocols and the need for a standardized approach. Understanding these differences is crucial for interpreting the effectiveness and applicability of screening instruments across diverse settings.

Future comparability can be improved by ensuring all centers use alternative versions if available, and by harmonizing the indication and interval between assessments. Utilizing four- to six-month intervals would require the least change, as this is already the most frequent. However, such intervals are somewhat arbitrary. Further research is needed to determine the optimal interval based on sensitivity to cognitive/behavioral decline. Given ALS's variable progression, it may be more appropriate to repeat screening based on rate of functional decline—fast progressors followed up sooner, slow progressors less frequently. While a standardized interval may aid research, clinicians may wish to tailor frequency based on individual need.

Consideration of clinically meaningful cognitive decline was notably underutilized, with only three centers using measures such as reliable change indices (RCI). Such measures are particularly important in detecting decline of clinical significance, accounting for practise effects, and detecting impairments in pwALS with high baseline performance, where decline might be very clinically meaningful, but missed by normative data (See Crockford et al. (32) and Costello et al. (33) for examples of how to calculate RCI scores for the ECAS (32,33). Further work is needed to facilitate the adoption of clinically meaningful change scores in a consistent manner across sites.

A standardized longitudinal protocol is also of major importance to clinical trials. Historically most trials have omitted the administration of the ECAS and/or behavioral assessments (34). In some cases, the ECAS is used as a secondary outcome and could be utilized better, with trials not using alternative versions and/or giving insufficient time between assessments to limit practise effects (34). The ECAS is frequently misused as a screening tool when determining trial eligibility, and is not used where it would have been informative, for example, detecting side effects or additional benefits for candidate drugs on cognition. This reflects a lack of an established standardized methodology within the field, limiting our ability to measure cognitive decline consistently. Furthermore, in trials where cognition is assessed behavioral changes and/or neuropsychiatric symptoms are overlooked, despite their relatively large prevalence in pwALS, and their considerable impact on survival (35), quality of life (36) and caregiver burden (37).

The widespread use of the ECAS caregiver interview supports collaborative behavioral screening across sites, enabling stronger multi-center studies. However, consistent application and interpretation are needed. Some behavioral components, such as pathological laughing and crying and emotional lability, are not assessed in the ECAS caregiver interview. More comprehensive scales, such as the BBI and ALSFTD-Q should be applied across Precision sites to address these gaps. Furthermore, given that apathy is the most prevalent behavioral symptoms, more sites could consider a more comprehensive scale, suach as the DAS.

Over half of PRECISION-ALS sites assess mental health, with HADS being most common. The link between neuropsychiatric symptoms and cognitive or behavioral changes in ALS is complex; for example, McHutchison et al. found that a family history of neuropsychiatric disorders is associated with poorer visuospatial performance (15). Although often overlooked in clinical trials (34), assessing neuropsychiatric and cognitive impairment is important for both research and care. Clear guidelines are needed to distinguish disease-specific cognitive changes from those related to depression (38), and to identify the most appropriate mental health measures, especially given the overlap between depressive and ALS-related physical symptoms (39). If the same ALS-adapted measures of mental health (e.g. ALS Depression Inventory (ADI-12) (40) or HADS for Motor Neuron Disease (HADS-MND (41)) can be collected across all sites, future studies can better control for these confounds in their statistical analysis.

A key finding of our study is the discrepancy in referral practices for full neuropsychological assessment between research and clinical settings. This likely reflects differing priorities: research emphasizes consistent data collection for valid outcomes, while clinical settings focus on immediate care and resource limitations, leading to more selective referrals. These differences highlight the need for consensus on managing cognitive and behavioral changes in pwALS and clear indicators for in-depth screening. Our findings also reveal barriers to harmonization, including the lack of local ECAS norms (30%) and limited resources for comprehensive assessments (50%). Greater use on online assessments can help address some challenges, providing greater scalability, and better access for pwALS with limited mobility. However, it may also contribute to greater variability between in-person and online assessment, and is less suitable for more certain plwALS. Consideration of these issues reinforces the value of collaboration among neuropsychologists across research sites.

Future initiatives will convene academic and clinical experts in the field, to harmonize neuropsychological assessments in ALS in Europe, following the example of the strategic biomarker roadmap (42). A robust, harmonized neuropsychological dataset will be developed across ALS research sites, with the potential to vastly improve our understanding of the cognitive and behavioral component of the disease, and facilitate robust multimodal studies using clinical, health service, imaging, biomarkers and omics data (see Box 1). Furthermore, this will inform clinical practice on the best practice approach for robust neuropsychological screening throughout the disease process, providing pwALS and their families with reliable and up-to-date information on their cognitive and behavioral symptoms.

Box 1. Steps towards harmonisation of cognitive and behavioural screening.

- Bring together academic and clinical experts at international symposia to develop consensus on assessment and analysis protocols.
- Pool neuropsychological data from control participants and individuals with ALS across all PRECISION-ALS sites.
- Compare statistical approaches to defining cognitive impairment (e.g., regression-based methods vs. 2SD cut-offs).
- Analyse longitudinal cognitive data to determine the most effective protocol for tracking change over time.
- Apply a harmonised methodology to define cognitive impairment, generating country-specific abnormality cut-offs using a standardised approach.

Limitations and strengths

As our results are limited to the PRECISION-ALS sites, they may not fully reflect the practices observed across all European ALS centers that belong to the European Network to Cure ALS (ENCALS), or other research centers globally. However, we anticipate that this work will facilitate harmonization efforts in neuropsychological research in ALS. As normative data collection is ongoing in many sites (Rostock, Portugal and Utrecht in particular), some of the information is expected to change in the near future. A strength of this study was that the semi-structured interview design allowed for a deep description of assessment practices. Whilst a harmonized approach is desirable for data sharing, applying a common screening tool leaves all sites exposed to the weaknesses of such tools, for example, visuospatial and social cognition subscores of the ECAS are prone to ceiling effects and reduced sensitivity.

Conclusions

This study outlines the numerous discrepancies in how cognitive and behavioral impairment is assessed and interpreted across PRECISION-ALS sites. In order to facilitate aggregated datasets, and improve cross-country collaborative projects, harmonized protocols are recommended. Further work will be required to establish an agreed protocol, based on empirical analysis, and through agreement from each center. An established, standardized protocol will facilitate more statistically powered analyses, informing clinical practice and clinical trials.

Declaration of interest

E.C., J.D.V., E.B., E.M., E.MD., C.P., F.H., and M.H. have no conflicts of interest to declare. N.P. serves as the associate editor of the International Journal of Neuroscience and has received speaker honoraria from Novartis. O.H. has received speaking honoraria from Janssen Cilag, Biogen Idec, Sanofi Aventis, Novartis and MerckSerono. She has been a member of advisory panels for Biogen Idec, Allergen, Ono Pharmaceuticals, Novartis, Cytokinetics and Sanofi Aventis. She serves as the editor-in-chief of the journal Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. SA serves as the associate editor for the journal Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. PVD has served in advisory boards for Biogen, CSL Behring, Alexion Pharmaceuticals, Ferrer, QurAlis, Cytokinetics, argenx, UCB, Muna Therapeutics, Alector, Augustine Therapeutics, VectorY, Zambon, Amylyx, Novartis, Prilenia, Verge Genomics, Sapreme Technologies, Trace Neuroscience, NRG Therapeutics (paid to institution). PVD has received speaker fees from Biogen and Amylyx (paid to institution). PVD is supported by the E. von Behring Chair for Neuromuscular and Neurodegenerative Disorders (paid to institution). JF has consulted for SOBI and NHTA, and is the co-chair of the International Network for ALS Research and Care (INARC, non-for-profit organization).

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

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