Assessing behavioural changes in ALS: cross-validation of ALS-specific measures

Article (Accepted Version)

Title: Assessing Behavioural Changes in ALS: Cross-Validation of ALS-specific Measures.

Running Head: Cross-Validation of the BBI against the ALS-FTD-Q

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Title: 72 characters (with spaces)

Running head: 49 characters (with spaces)

Abstract: 250 words

Introduction: 261 words

Discussion: 488 words

Body of the manuscript (not including abstract or references, figure legends, etc.): 2204 words

Tables: 3 Figures: 1 (Colour figures: 0) Supplementary Material: 0

References: 11

Abstract

Objective: The Beaumont Behavioural Inventory (BBI) is a behavioural proxy report for the assessment of behavioural changes in ALS. This tool has been validated against the FrSBe, a non-ALS specific behavioural assessment, and further comparison of the BBI against a disease-specific tool was considered. This study cross-validates the BBI against the ALS-FTD-Q.

Methods: 60 ALS patients, 8% also meeting criteria for FTD, were recruited. All patients were evaluated using the BBI and the ALS-FTD-Q, completed by a carer. Correlational analysis was performed to assess construct validity. Precision, sensitivity, specificity and overall accuracy of the BBI, when compared to the ALS-FTD-Q, were obtained.

Results: The mean score of the whole sample on the BBI was 11.45±13.06. ALS-FTD patients scored significantly higher than non-demented ALS patients (31.6±14.64, 9.62±11.38; $p<.0001$). A significant large positive correlation between the BBI and the ALS-FTD-Q was observed ($r=.807$, $p<.0001$), and no significant correlations between the BBI and other clinical/demographic characteristics, indicating good convergent and discriminant validity, respectively. 72% of overall concordance was observed. Precision, sensitivity and specificity for the classification of severely impaired patients were adequate. However, lower concordance in the classification of mild behavioural changes was observed, with higher sensitivity using the BBI, most likely secondary to BBI items which endorsed behavioural aspects not measured by the ALS-FTD-Q.

Discussion: Good construct validity has been further confirmed when the BBI is compared to an ALS-specific tool. Furthermore, the BBI is a more comprehensive behavioural assessment for ALS, as it measures the whole behavioural spectrum in this condition.

Keywords: ALS, Behaviour, Validation, BBI, ALS-FTD-Q

Introduction

The notion of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) as two extremes of the same disease continuum [1] has offered a better understanding of the clinical overlap between these conditions. Behaviour changes are a frequent and significant presentation in ALS, and behavioural assessments are fundamental in routine neuropsychological evaluations in this population. To this end, the Beaumont Behavioural Inventory (BBI) [2] was developed. The BBI is a 41-item, self-explanatory, proxy-report behavioural assessment, specifically developed for use in ALS patients as it considers the whole spectrum of behavioural changes that can occur in this condition. Moreover, the BBI accounts for the confounding effects of motor dysfunction on behaviour. The BBI has demonstrated high internal consistency (Cronbach's alpha=0.906) [3], and adequate convergent and discriminant validity (refer to [2] for tool development and validation details). The BBI cut-off scores (≥7 for mild behaviour changes, and ≥23 for severe behaviour changes) have high sensitivity and specificity, when validated against another behavioural tool, the Frontal System Behaviour Scale (FrSBe) [4]. Nonetheless, the use of the FrSBe as the gold standard to capture behavioural deficits in ALS raises concerns regarding the possibility of overestimating the presence of such deficits, as this tool does not correct for the effects of motor involvement in behaviour. Thus, there is a need to further compare the BBI against another ALS-specific tool that controls for such confounding effects.

Here we cross-validate the BBI against the ALS-FTD-Q [5], with the aim of comparing these two disease-specific measures and explore their ability to capture the entire spectrum of behavioural changes in ALS.

Methods

Participants and assessment procedures

Based on EMGO+ guidelines for the validation of measurement tools [6], 60 consecutive patients fulfilling El Escorial criteria [7] for the diagnosis of ALS and attending the MND National Clinic in Beaumont Hospital were recruited. Exclusion criteria included history of neurological, psychiatric or medical conditions other than ALS that can cause cognitive and behavioural changes. 5 participants (8%) from this cohort also met criteria for the diagnosis of behavioural variant FTD [8].

All patients meeting inclusion criteria were assessed in one of their clinic visits. Thus, the main carer accompanying the patient was asked to complete the BBI and the ALS-FTD-Q. Carers completing the forms included spouses (58%), children (30%), siblings (7%), and other (5%; granddaughter, friend and brother-in-law). The revised ALS functional rating scale (ALSFRS-R) [9] was also completed in a subset of patients (n=20) to assess disease severity. Demographic and clinical characteristics were acquired from the Irish ALS register [10].

This study is part of a broader population-based study of cognition in ALS, for which full approval from the Beaumont Hospital Ethics Committee was attained.

Statistical Analyses

The Bland-Altman measure of agreement was used to determine the appropriateness of sample size [11]. Assuming a sample size n=60, the formula for the confidence interval for the 95% limits of agreement was implemented: $CI = \pm 1.96\sqrt{\frac{3}{n}}s$. Assumption of normality of individual differences between ALS-FTD-Q and BBI was calculated using the formula: $\bar{d} \pm 1.96s$.

Descriptive statistics are presented in terms of means and standard deviations (sd) for quantitative data, and in number of cases (n) and percentage (%) for count data. All group

comparisons were performed using non-parametric methods (Independent Samples Mann-Whitney U Test), as assumption of normal distribution for all samples could not be assumed.

Correlational analysis was performed between the BBI and the ALS-FTD-Q to assess construct validity (convergent validity), and between the BBI and other clinical and demographic components (age, years of education, age at onset, age at diagnosis, diagnostic delay and ALSFRS-R) to assess discriminant validity.

Precision, sensitivity and specificity of the BBI in comparison to the ALS-FTD-Q were calculated. Accuracy or overall correctness was also obtained. To do so, the following formulae were applied:

- Precision or consistency between tests = True Positives / (True Positives + False Positives)
- Sensitivity or true-positives rate = True Positives / (True Positives + False Negatives)
- Specificity or true-negatives rate = True Negatives / (True Negatives + False Positives)
- Accuracy or correct classifications = True Positives / Total Observations

Behavioural changes on the BBI are assessed on a 3-point rating scale (0 - No Changes, 1 - Mild, 2 - Moderate, and 3 - Severe), and the score ranges from 0 to 123. On the other hand, the presence of behavioural changes on the ALS-FTD-Q is graded on a 4-point scale (0 - Completely disagree/Never, 1 - Largely disagree/Sometimes, 3 - Largely agree/Often, and 4 - Completely agree/Always), and the maximum score is 100. Thus, on both measures, the higher the score, the higher the presence of behavioural change. For the ALS-FTD-Q, the cut-off for mild disturbances is considered at ≥22, and for severe disturbances, at ≥29 [5]. The BBI cut-offs are ≥7 for mild changes, and ≥23 for severe changes [2].

IBM Statistical Package for the Social Sciences (SPSS) 22.0 was used for analyses.

Results

Sample size adequacy was assessed by calculating the limits of agreement, as per Bland and Altman [11]. A normal distribution within individual's measurements differences was assumed: $\bar{d} \pm 1.96s = -15.435\ and\ 17.565$ (see Figure 1). 95% limits of agreement using a sample size of 60 participants were as follows: $CI = \pm 1.96\sqrt{\frac{3}{60}}8.25 = -3.62\ and\ 3.62$. Thus, a sample size of 60 gives a CI of +-0.44*s, which is a low limit of agreement, robust enough to detect differences between measures.

FIGURE 1 HERE

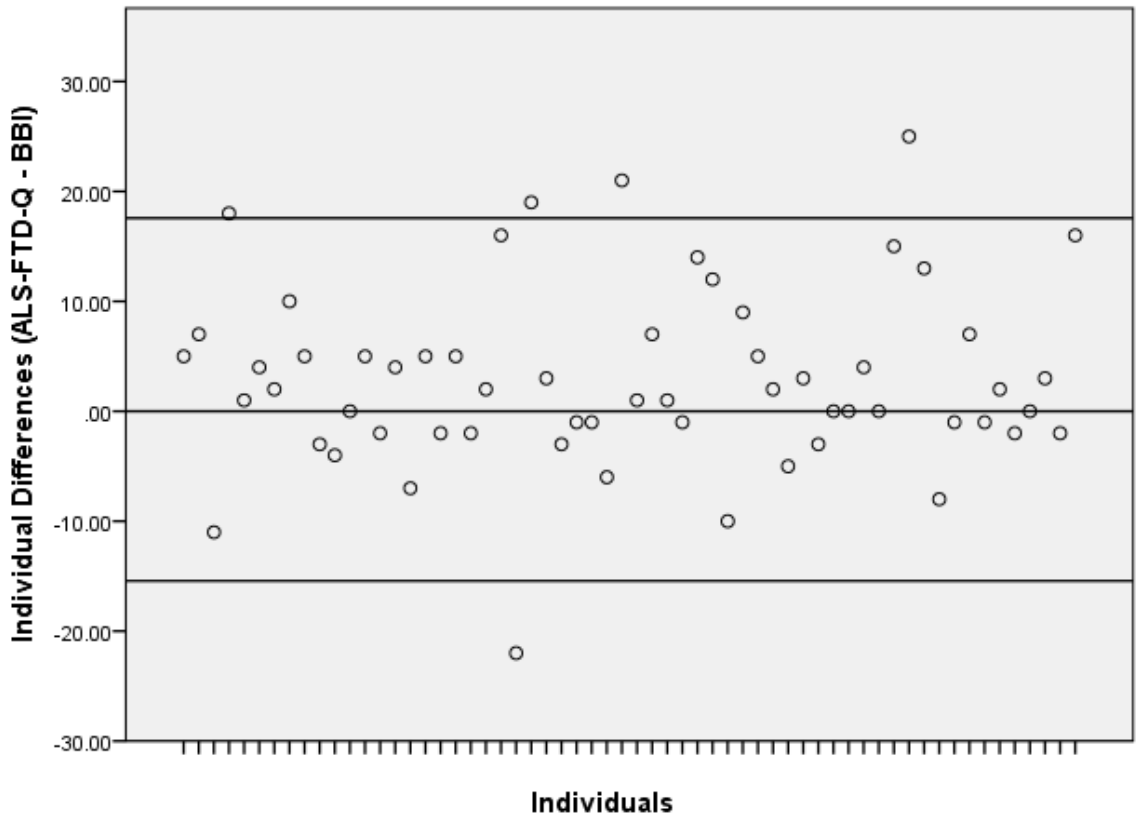

Figure 1. Bland-Altman Plot of within individual's measurements differences

Table 1 summarizes demographic and clinical characteristics of the sample.

[TABLE 1 HERE]

Table 1. Demographic and Clinical Characteristics of the Patient Sample				
		Patient Group n = 60	**ALS** n = 55	**ALS-FTD** n = 5
Gender n(%)	**Males**	42 (70%)	38 (69)	4 (80)
	Females	18 (30%)	17 (31)	1 (20)
Age mean(sd)		65.42 (9.72)	65.18 (9.85)	68.00 (8.69)
Years of Education mean(sd)		13.2 (3.42)	13.29 (3.5)	12.20 (2.39)
Age at Onset mean(sd)		63.42 (9.35)	63.30 (9.55)	64.80 (7.56)
Site of onset n(%)	**Spinal**	38 (64%)	34 (62)	4 (80)
	Bulbar	17 (28%)	16 (29)	1 (20)
	Thoracic/Respiratory	5 (8%)	5 (9)	0
Age at Diagnosis mean(sd)		64.68 (9.51)	64.42 (9.66)	67.60 (7.89)
Diagnosis Delay, in months mean(sd)		15.37 (11.69)	14.18 (10.20)	28.40 (19.49)
ALSFRS-R mean(sd)		n= 20	n = 17	n = 3
		33.4 (6.18)	32.18 (5.78)	40.33 (3.21)

Considering that the ALSFRS-R was available only for a proportion of the total sample, comparability of the subset of patients that had an ALSFRS-R (n=20) and the subset that had not (n=40) was examined. No significant differences between the two subsamples was observed in terms of demographic or clinic characteristics: (Age: ALS-FRS-R = 66.80±8.28, ⦸ALS-FRS-R = 64.73±10.39; p=.354. Education: ALSFRS-R = 13.03±3.61, ⦸ALS-FRS-R = 13.29±3.36; p=.950. Age at onset: ALSFRS-R = 64.53±7.88, ⦸ALS-FRS-R = 62.90±10.02; p=.431. Age at diagnosis: ALSFRS-R = 65.90±8.21, ⦸ALS-FRS-R = 64.07±10.14; p=.441. Diagnostic delay: ALSFRS-R = 20.40±15.28, ⦸ALS-FRS-R = 12.85±8.57; p=.104).

Regarding behavioural measures, the mean score for the BBI was 11.45±13.06, and 14.35±13.43 for the ALS-FTD-Q. When the sample was divided between patients meeting criteria for the diagnosis of ALS-FTD and ALS patients without dementia, ALS-FTD patients

scored significantly higher on both the BBI (ALS-FTD=31.6±14.64, ALS=9.62±11.38; p<.0001) and the ALS-FTD-Q (ALS-FTD=34.8±10.33, ALS=12.49±12.12; p=.002).

Group comparisons on behavioural measures between patients that had an ALSFRS-R (n=20) and patients for whom this was not available (n=40) were also performed. No significant difference was observed on the ALS-FTD-Q (ALS-FRS-R = 18.20±14.42, ∅ALS-FRS-R = 12.43±12.65; p=.074), although a significant difference was found on the BBI (ALSFRS-R = 16.25±14.29, ∅ALS-FRS-R = 9.05±11.88; p=.040). Considering that the majority of ALS-FTD participants are included in the group that had an ALS-FRS-R performed, and this is likely to have had an effect on these results, this analysis was carried out excluding all ALS-FTD cases. Results indicated that no significant difference existed on the BBI between patients who had ALSFRS-R and patients who did not (ALSFRS-R = 13.64±12.34, ∅ALS-FRS-R = 7.82±10.61; p=.076).

Regarding correlational analysis, a significant large positive correlation was observed between the BBI and the ALS-FTD-Q total scores (r=.807, p<.0001). No significant associations were observed between the BBI and most demographic and clinical measures: age (r=-.074, p=.576), education (r=-.077, p=.558), age at onset (r=-.100, p=.450), age at diagnosis (r=-.066, p=.615), and ALS-FRS-R (r=-.014, p=.954); or between most clinical/demographic characteristics and the ALS-FTD-Q: age (r=-.175, p=.181), education (r=-.153, p=.244), age at onset (r=-.216, p=.101), age at diagnosis (r=-.108, p=.169), ALS-FRS-R (r=-.049, p=.838). Nevertheless, a significant positive medium correlation was observed between diagnostic delay and the BBI (r=.405, p=.001), as well as between diagnostic delay and the ALS-FTD-Q (r=.319, p=.013). This relationship was further explored. Considering the longer diagnostic delay in the ALS-FTD group compared to the ALS group, ALS-FTD patients were removed from the analysis, and at that point the correlations did not reach statistical significance: BBI (r=.197, p=.149), ALS-FTD-Q (r=.221, p=.104).

Cross-tabulated data for the BBI and ALS-FTD-Q is presented in Table 2. Precision, sensitivity and specificity for each diagnostic category, as well as overall accuracy are presented in Table 3.

[TABLE 2 HERE]

[TABLE 3 HERE]

Table 2. BBI and ALS-FTD-Q cross-tabulations

		BBI			
		Normal	**Mild**	**Severe**	**Total**
ALS-FTD-Q	**Normal**	32	13	1	46
	Mild	0	3	3	6
	Severe	0	0	8	8
	Total	32	16	12	60

Table 3. Precision, sensitivity, specificity and accuracy of the BBI in comparison to the ALS-FTD-Q

	Normal	**Mild**	**Severe**
Precision	100	19	67
Sensitivity	70	50	100
Specificity	100	76	92
Overall Accuracy	72		

Further exploratory analysis was performed. In cases where the BBI seemed to overestimate the behavioural categorization when compared to the ALS-FTD-Q, items more frequently endorsed within this sub-cohort (n=17) were investigated. Items for which some degree of change was indicated by more than half of the subsample (>8 participants) were considered as frequently endorsed.

Two items from the BBI were endorsed by most caregivers in this subset of the sample: a social cognitive item (‘diminished social interest’) and an apathy item (‘loss of motivation for previous interests’). Within the behaviour category *Loss of sympathy or empathy* from the revised diagnostic criteria for bvFTD [8], the ALS-FTD-Q assesses the item ‘diminished

responsiveness to other people's needs and feelings', but it does not assess 'general decline in social engagement', which is indeed assessed by the BBI. In terms of apathy, the ALS-FTD-Q includes two items: 'less interest in surroundings' and 'display of more withdrawn behaviour'. The BBI, on the other hand, includes an apathy item which is more specific to loss of interest in previous rewarding activities. To assess reliability of apathy measurement within the two scales, correlational analysis was performed between the apathy items on the ALS-FTD-Q and the highly endorsed apathy item on the BBI ('loss of interest in previous interests'). Spearman's rank correlation coefficients were calculated, and no significant findings were observed: 'less interest in surroundings' (rho=.252; p+=.330); 'display of more withdrawn behaviour' (rho=.285; p=.267).

Other behavioural aspects that were frequently endorsed (by 7/8 participants) by this subcohort of patients who were classified as abnormal on the BBI but as normal on the ALS-FTD-Q (n=17), included 'distractibility', 'inappropriate emotional display', 'increased sensitivity to sensations such as touch, noise, heat, cold, taste or pain', and 'increased occurrence of grammatical mistakes'. Although decreased concentration and impaired emotional stability are assessed by the ALS-FTD-Q, this does not assess altered responses to sensory stimuli or cognitive changes related to language.

Discussion

The BBI, an ALS-specific behavioural scale, has been further validated against another disease-specific behavioural instrument, the ALS-FTD-Q. BBI scores highly correlated with ALS-FTD-Q scores, but were independent of other clinical and demographic measures such as age, years of education, age at onset, age at diagnosis and ALSFRS-R. Thus, the current cross-validation of the BBI has confirmed adequate convergent and discriminant validity.

Nonetheless, when performing correlational analysis, a significant positive medium correlation between the degree of behavioural change on both the BBI and the ALS-FTD-Q, and diagnostic delay was observed. A possible explanation for this observation is that three out of the five ALS-FTD patients in this sample experienced cognitive/behavioural changes before or at the same time as the motor symptoms, which would have prompted a diagnosis of FTD, and delayed the diagnosis of ALS. This proposition was supported by the longer diagnostic delay of the ALS-FTD group, compared to the ALS group. So, with this hypothesis in mind, correlational analysis was repeated excluding the ALS-FTD sub-cohort, and no significant correlations between behavioural changes and diagnostic delay were further observed.

The original BBI validation established a cut-off of ≥7 for mild behavioural changes (88% sensitivity and 79% specificity), and ≥23 for severe behavioural changes (90% sensitivity and 96% specificity). Considering these cut-offs, 47% of the ALS sample presented with behavioural changes. When compared to the ALS-FTD-Q, classification assessment indicated that a cut-off of ≥23 on the BBI is adequate for the diagnosis of severe behavioural changes (Precision=67; Sensitivity=100; Specificity=92). A cut-off of ≥7 showed limited accurateness in diagnosing mild behavioural changes (Precision=19). However, further investigation of items endorsed by 'over categorized' participants on the BBI showed that most of these items assess behavioural aspects not measured by the ALS-FTD-Q. Among them, a general decline in social engagement, a loss of interest in previously rewarding interests, higher sensitivity to sensory stimuli, and the presence of more grammatical mistakes outstand. Thus, significant behavioural aspects in ALS such as diminished social interest or an altered response to sensory stimuli are not measured by the ALS-FTD-Q. Moreover, the ALS-FTD-Q incorporates cognitive items that focus solely on executive function, and do not take language changes into account. Finally, although the ALS-FTD-Q measures apathy, correlations between apathy items on the ALS-FTD-Q and the BBI were not significant, indicating that such items assess

different aspects of apathy, and the BBI item 'loss of motivation for previous interests' seems to be more sensitive to capture changes.

In conclusion, cross-validation of the BBI against the ALS-FTD-Q has shown that the BBI is more sensitive to mild behavioural changes in ALS, as it assesses the entire behavioural spectrum observed in this condition. These data confirm that the BBI is a robust and psychometrically sound tool for the assessment of behavioural changes in ALS. Further cross-sectional and longitudinal population-based studies with large incident samples are needed to confirm the prevalence of behavioural changes in ALS using this new behavioural measure.

Author Contributions

MPG contributed to the process of data collection, data entry, analysed the data and wrote the manuscript; EC contributed to the process of data entry, data analysis and revised the intellectual content of the manuscript; SOC contributed to the process of data collection, and revised the intellectual content of the manuscript; ME and TB revised the intellectual content of the manuscript; MH administered the management aspects and revised the intellectual content of the manuscript; NP supervised the neuropsychological aspects of the study and revised the manuscript from a neuropsychological perspective; and OH supervised all clinical aspects of the study in all stages of development and revised the manuscript from a clinical perspective.

Acknowledgements

This research has received funding from the Health Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 259867, ALSA (the ALS Association), HRB (the Health Research Board, grant H01300), Joint Programme in Neurodegeneration (JPND), The

Irish Institute of Clinical Neuroscience (grant 12549.201616) and Research Motor Neuron (previously named Motor Neuron Disease Research Foundation).

Conflicts of Interest

Ms. Marta Pinto-Grau, Mr Emmet Costello, Ms Sarah O'Connor, Dr Marwa Elamin, Dr Tom Burke, Mr Mark Heverin, and Prof. Niall Pender have nothing to disclose.

Prof. Orla Hardiman has received fees for consultation work from Biogen Idec, Cytokinetics and Novartis. She serves as Editor-in-Chief of Amyotrophic Lateral Sclerosis. The authors report no conflict of interests.

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