SYNTACTIC IMPAIRMENT ACROSS THE ALS-FTD CONTINUUM: A GRADATION OF DIFFICULTY

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Characters in title:

Words in abstract:
Words in manuscript:
Tables:
Figures:

Statistical analysis was conducted by J.K. and M.H.

Search terms*:* ALS-FTD continuum; cognitive impairment; syntactic deficits

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ABSTRACT

Objective: To investigate, and establish the neural correlates of, syntactic deficits in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)-ALS, as compared to primary non-fluent aphasia (PNFA) and controls.

Method: Syntactic deficits were evaluated using a reduced version of the Test for Reception of Grammar (TROG) and voxel-based morphometry (VBM) analysis was conducted.

Results:

Conclusions:

INTRODUCTION

Since the realisation of clinical,[1–3] pathological,[4,5] and genetic[6–9] overlaps between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), studies have increasingly focussed on cognitive deficits in patients with ALS and ALS-FTD. Behavioural changes, similar to those identified in the behavioural variant of FTD,[1,10,11] and executive deficits have been well described,[12] although non-executive cognitive impairment, including language dysfunction, also occurs.[13,14]

Language impairment is one of the defining clinical features of FTD, and two distinct language phenotypes of the disease are recognised.[15] Semantic dementia (SD) is characterised by fluent speech, but often severely impaired word and object knowledge.[16] Anterior temporal atrophy (usually left > right) is almost pathognomonic of the disease. Alternatively, the progressive non-fluent aphasia (PNFA) phenotype is characterised by hesitant, non-fluent speech with variable combinations of phonological errors, apraxia of speech, and impaired production of grammar or syntax, as well as deficits in syntactic comprehension.[17] In PNFA, the pathology centres on the left peri-insular cortex.[18,19] These two phenotypes represent models of language dysfunction in neurodegenerative diseases of the frontal and temporal lobes. Importantly, neuropsychological tools such as the Test for the Reception of Grammar (TROG)[20] have been specifically applied to probe the characteristic deficits encountered in FTD language phenotypes.

Language impairment has been reported in ALS and ALS-FTD,[21] although without appropriate tools the presence of dysarthria may confound analysis of higher language in these disease groups. Pathological involvement of the left temporal lobe (including the temporal pole and the peri-insular region) and frontotemporal white matter connections,[22] have been reported in ALS and ALS-FTD.[23] As such, language dysfunction in ALS may not

be surprising; however, the frequency, profile, precise neuroanatomical correlates, and functional impact of language dysfunction are yet to be determined. Although a relationship between bulbar-onset ALS (bulbar-ALS) and language deficits has often been suggested, such a link has not been proven.

In recent work, we demonstrated that semantic deficits are common in ALS and ALS-FTD, and that such deficits became more pronounced across the ALS-FTD spectrum (Leslie et al, under review). As expected, semantic deficits were correlated with atrophy of the anterior temporal lobes. Separately, the left frontal inferior lobe has been associated with the processing of syntax in normal subjects,[24] although parts of the temporal lobes may also be involved.[25] Whether involvement of these regions in ALS results in clinically detectable syntactic deficits remains unclear.

In the present study we aimed to investigate syntactic comprehension in ALS and ALS-FTD, using PNFA as a disease model of how syntax may be impaired in the ALS-FTD disease spectrum. We hypothesised a gradation of syntactic impairment, such that ALS would demonstrate relatively mild deficits compared to controls, with more pronounced deficits in ALS-FTD, and severe impairment in PNFA. Secondly, we hypothesised that syntactic deficits would correlate with atrophy of left temporal lobe structures, including the left peri-insular cortex. Finally, we examined whether the presence of bulbar dysfunction correlated with performance on syntactic comprehension tasks.

METHODS

Participants

Patients were recruited from the multidisciplinary Motor Neurone Disease clinic at Prince of Wales Hospital and FRONTIER, an FTD specific research clinic based at Neuroscience

Research Australia. Controls were recruited from a database of healthy volunteers or were carers of patients. All controls performed normally on cognitive testing. Patients underwent detailed neurological and neuropsychological assessments, as well as magnetic resonance imaging (MRI) of the brain. Ethical approval was obtained from the South Eastern Sydney Local Health District and the University of New South Wales ethics committees. Informed consent was acquired in accordance with the Declaration of Helsinki.

Diagnosis and group classification

The diagnosis of ALS, ALS-FTD, and PNFA, were made with reference to relevant diagnostic criteria. Briefly, ALS was diagnosed in the presence of progressive upper and lower motor neuron dysfunction in three or more non-contiguous regions.[26,27] ALS-FTD patients satisfied the diagnostic criteria for ALS, but also exhibited behavioural and/or cognitive dysfunction in keeping with concomitant FTD.[12] Patients with PNFA exhibited non-fluent speech combined with variable motor speech apraxia, agrammatism, or impaired syntactic comprehension, despite spared single-word comprehension and object knowledge.[28] When necessary, alternative diagnoses were excluded on the basis of blood tests for immune-mediated or inflammatory disorders, cerebrospinal fluid examinations, imaging of the spine, and electromyographic studies. Patients with a history of prior mental illness, significant head injury, movement disorder, or drug and alcohol abuse were excluded. In addition, ALS patients with a forced vital capacity (FVC) below 70% or evidence of nocturnal hypoventilation were excluded.

Motor assessment

Motor functional ability in the ALS and ALS-FTD groups was evaluated using the ALS functional rating scale revised (ALSFRS-R).[29] The ALSFRS-R is a 12-item questionnaire that grades ability on everyday performance on everyday tasks such as speech, swallowing,

handwriting, cutting food, and walking. Each item is scored on a 5-point scale (0-4; maximum score 48), with a lower score representing greater motor impairment. Raw scores were used to generate bulbar, fine motor, gross motor, and respiratory subscores.

Cognitive screening

Cognitive screening was performed using the Addenbrooke's Cognitive Examination - Revised (ACE-R).[30] The ACE-R is a brief cognitive screening tool that assesses five cognitive domains, including: attention (18 points), memory (26 points), verbal fluency (14 points), language (26 points) and visuospatial ability (16 points). A total score below 88/100 detects dementia with a sensitivity of 94% and specificity of 89%.[30] Raw ACE-R scores were converted to percentages, to account for items omitted due to motor deficits.

Syntactic Comprehension

The Test for the Reception of Grammar (TROG)[20] was used to assess syntactic comprehension. The TROG is a sentence-picture matching task that examines interpretation of different syntactic structures consisting of single nouns, verbs and adjectives, combined in various ways.[20] The test includes 20 four-sentence blocks and increases in difficulty as it proceeds. To account for fatigue in ALS and ALS-FTD patients, the TROG was modified to include two, rather than four, sentences in each of the 20 blocks. Patients were randomly assigned either the first and third, or second and fourth, sentences of the original TROG blocks. The 20 blocks were subdivided into 4 sections (1-4; range 0-10 for each), with each section ascending in syntactic difficulty. Total Blocks Correct (range: 0-20) and errors in each block section were compared across groups. In addition, individual patient performance was defined as "Impaired" if they scored more than 1.5 standard deviations below the control mean of Total Blocks Correct.

Behavioural Statistical Analyses

Demographics, motor function, cognitive ability, and performance on the TROG were compared across the ALS, ALS-FTD, PNFA, and control groups. Subsequently, patients with ALS and ALS-FTD were re-classified according to the mode of presentation in order to investigate the relationship between bulbar impairment and impaired syntactic comprehension. Specifically, patients were grouped in limb- and bulbar-onset groups, as well as a cognitive/mixed group, and performance on the TROG was compared between groups.

All analyses were conducted using IBM Statistics Software version 20. Normal distribution of continuous variables was examined via Kolmogorov-Smirnoff tests. Overall group effect was examined via independent samples *t*-tests or one-way analyses of variance (ANOVA) with Tukey post-hoc comparisons for parametric data, and Kruskal-Wallis with post-hoc Mann-Whitney U Tests for nonparametric data. Between-group differences in categorical variables were assessed with Chi-square tests. To correct for multiple comparisons, significance level was $p < .01$.

Voxel-based Morphometry (VBM)

A 3T Phillips MRI scanner with standard quadrature head coil (eight channels) was used to obtain imaging data. The 3D T1-weighted images were acquired using the following sequences: coronal orientation, matrix 256x256, 200 slices, 1x1 mm^2 in-plane resolution, slice thickness 1mm, echo time/repetition time=2.6/5.8 msec, flip angle $\alpha=19°$.

MRI data was analysed using FSLVBM, a voxel-based morphometry (VBM) analysis using the FSL FMRIB software package (http:// www.fmrib.ox.ac.uk/fsl/fslvbm/index.html). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool from brain-extracted images (BET), using a fractional intensity threshold of 0.26.[31] Upon visual inspection of each scan, if non-brain matter (e.g., skull, optic nerve, dura mater) was included

or brain matter falsely excluded, then the BET algorithm for that scan was repeated with a modified fractional intensity threshold, to give smaller or larger brain border estimates.

MRI data was analysed using FSLVBM, a voxel-based morphometry (VBM) analysis using the FSL software package (http:// www.fmrib.ox.ac.uk/fsl/fslvbm/index.html). First, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool from brain-extracted images. The resulting grey matter partial volumes were aligned to the Montreal Neurological Institute standard space (MNI152) using nonlinear registration approach via FNIRT, which uses a b-spline representation of the registration warp field. A study-specific template was created and the native images were re-registered nonlinearly. Modulation of the registered partial volume maps was carried out by dividing them by the Jacobian of the warp field. The modulated, segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

Next, a voxel-wise general linear model was applied and permutation-based nonparametric testing with 5000 permutations per contrast was used to form clusters with the Threshold-Free Cluster Enhancement method, tested for significance at $p < .05$ and corrected for multiple comparisons. Age and disease duration were included as nuisance variables, and a cluster-extent threshold of 50 contiguous voxels was used. Finally, to investigate correlations between regions of grey matter atrophy and performance on TROG total blocks correct, patient groups were combined with Controls, consistent with previous methodology.[32,33] A covariate only statistical model with a [1] *t*-contrast was used.

RESULTS

Demographics

In total, 85 participants were included in the study; 20 ALS, 15 ALS-FTD, 27 PNFA, and 23

Controls. The demographics of participants are presented in Table 1. All groups were matched for education (p=.142), and patient groups were matched for disease duration (p=.941; Table 1). Male gender was more common in the ALS group than either PNFA (p=.003) or Control (p=.003) groups. The ALS group was also significantly younger than the PNFA group (p=.002). To determine whether age impact syntactic performance, a bivariate correlation for age, and a chi-square for sex, were conducted with total correct for the TROG in the control group, revealing no effect (both p values > .252), suggesting that these variables are unlikely to influence syntactic performance in a healthy adult population.

Clinical features

There was no significant difference in motor impairment between the ALS and FTD-ALS groups, as measured by the ALSFRS-R total (p=1.00). There was a significant (p<.001) difference in cognitive performance between groups, reflected in the ACE-R total. Post-hoc tests revealed that FTD-ALS and PNFA patients were significantly impaired compared to controls (both p<.001) and there was a trend (p=.024) for impaired performance in the ALS group, which did not survive correction for multiple comparisons (*See Methods*). FTD-ALS and PNFA patients demonstrated a similar level of overall cognitive impairment (p=.121).

Syntactic Comprehension

FTD-ALS and PNFA patient groups were impaired on Total Blocks Correct, relative to ALS and Controls (all p vales < .001). Surprisingly, FTD-ALS patients performed disproportionately worse than PNFA patients (p=.007), but ALS patients did not differ from Controls (p=.792). Overall, 25% of ALS (p=.011), 81.5% of ALS-FTD (p<.001), and 86.7% of PNFA (p<.001) patients were impaired on the TROG compared to controls (Figure 1).

FTD-ALS and PNFA patients exhibited significantly more errors across Sections 1, 2, 3, and 4 of the TROG (all p values <.001), while ALS patients performed commensurate with

Controls (all *p* values >.022, Figure 2). Compared to ALS, FTD-ALS patients were significantly ($p<.001$) impaired on more difficult sections (i.e. Sections 2, 3, 4), and there was a trend for impairment on Section 1 ($p=.011$). PNFA patients demonstrated a similar pattern of performance, with significantly more errors in Sections 2, 3, and 4 (all *p* values <.001), and a trend for more errors in Section 1 ($p=.020$), compared to ALS. When compared to FTD-ALS patients, PNFA patients exhibited a similar level of errors at Section 1 ($p=.168$), but as test difficulty increased, the difference between the two groups became significant (Section 4: $p=.001$).

Bulbar dysfunction and syntactic comprehension

In order to investigate the relationship between bulbar dysfunction and impaired syntactic comprehension, ALS and ALS-FTD patients were grouped according to the main symptom at onset (limb, bulbar, cognitive/mixed, *See Methods*). Classified in this manner, 14 (40%) patients presented with bulbar-onset disease and another 14 (40%) presented with limb-onset disease, while 7 (20%) patients initially presented with a cognitive/mixed syndrome. There was a significant ($p<.01$) group wise difference in the frequency of deficits in syntactic comprehension, reflected in impaired performance on the TROG. Specifically, all 7 patients who presented with a cognitive or mixed syndrome demonstrated impairment, compared to only 7 (50%) of bulbar-onset and 4 (28.6%) of limb-onset cases. The proportion of bulbar-onset patients with impaired performance on the TROG did not differ from that of limb-onset cases ($p=.246$). Separately, there was no correlation between the bulbar subscore of the ALSFRS-R and the TROG total score (p=.619). In contrast, there was a highly significant ($p<.001$) and ($r=.798$) powerful correlation between the TROG total score and the ACE-R.

DISCUSSION

In the present study, we demonstrated that impaired syntactic comprehension is a feature of

ALS, especially in patients with ALS-FTD. In fact, patients with ALS-FTD were as impaired as patients with PNFA on syntactic comprehension. For the first time, the present study has demonstrated that syntactic comprehension deficits in ALS and ALS-FTD are associated with atrophy in the ..……. Finally, we demonstrated that bulbar involvement does not appear to influence the rate of syntactic comprehension deficits, which may be more closely linked to overall cognitive impairment.

Several caveats should be kept in mind when interpreting this work. First, our groups differed in distribution of sex, …. Discuss in terms of disease stages and characteristics of each patient group (likely to be diagnosed earlier

Only a few previous studies have examined syntactic comprehension using specific tasks such as the TROG. One study reported impaired performance in 2 of 3 ALS patients.[36] A further study demonstrated deficits in syntactic comprehension in 5 of 6 patients who presented with an aphasic syndrome in the context of ALS.[37] Impaired performance on the TROG was reported in 35% of ALS patients in one study,[38] whereas as many as 72% of non-demented ALS patients were reported to be impaired on a Japanese test of syntactic comprehension.[39] Unlike the present study, previous studies have been small, or have not distinguished cases of ALS from those with ALS-FTD. The influence of bulbar dysfunction on syntactic comprehension has not previously been examined.

In the present study, 25% of non-demented ALS patients demonstrated deficits in syntactic comprehension, and the rate rose to 81.5% of patients with ALS-FTD, rivalling the rate in patients with PNFA. The

Previous studies have implicated syntactic dysfunction in ALS and FTDALS (?),using the TROG.[40]

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FIGURE CAPTIONS

Figure 1. **Overall Impairment for patient groups.**

Calculated based on 1.5 standard deviations below the Control mean for performance on Total Blocks Correct. *significantly more impaired relative to ALS.

Figure 2. **Total mean errors by section for ALS, FTDALS, PNFA, and Control groups.**

Section 1, 2, and 3 Errors available for 19 ALS, 13 FTDALS. Main effect for each section $p<.001$. Section 4 Errors available for 19 ALS, 13 FTDALS, 25 PNFA patients. Group differences (sig at $p<.01$). Section 1: FTDALS, PNFA > Controls; FTDALS > ALS (trend: $p=.011$). Section 2: FTDALS, PNFA> Controls, ALS; FTDALS > PNFA (trend: $p=.010$). Section 3: FTDALS, PNFA > Controls, ALS; FTDALS>PNFA (trend: $p=.010$). Section 4: FTDALS, PNFA > Controls, ALS; FTDALS > PNFA.