Tensor electrical impedance myography identifies bulbar disease progression in amyotrophic lateral sclerosis

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Objective: Electrical impedance myography (EIM) is a promising biomarker for amyotrophic lateral sclerosis (ALS). A key issue is how best to utilise the complex high dimensional, multi-frequency data output by EIM to fully characterise the progression of disease.

Methods: Muscle volume conduction properties were obtained from EIM recordings of the tongue across three electrode configurations and 14 input frequencies (76 Hz–625 kHz). Analyses of individual frequencies, averaged EIM spectra and non-negative tensor factorisation were undertaken. Longitudinal data were collected from 28 patients and 17 healthy volunteers at 3-monthly intervals for a maximum of 9 months. EIM was evaluated against the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) bulbar sub-score, tongue strength and an overall bulbar disease burden score.

Results: Longitudinal changes to individual patient EIM spectra demonstrated complex shifts in the spectral shape. At a group level, a clear pattern emerged over time, characterised by an increase in centre frequency and general shift to the right of the spectral shape. Tensor factorisation reduced the spectral data from a total of 168 data points per participant per recording to a single value which we call tensor EIM (T-EIM). The absolute change in tensor EIM significantly increased within 3 months and continued to do so over the 9-month study duration. In a hypothetical clinical trial scenario tensor EIM required fewer participants (n = 64 at 50% treatment effect), than single frequency measures (n range 87–802) or ALSFRS-R bulbar sub-score (n = 298).

Conclusions: Changes to tongue EIM spectra over time in ALS are complex. Tensor EIM captured and quantified disease progression and was more sensitive to changes than single frequency EIM measures and other biomarkers of bulbar disease.

Significance: Objective biomarkers for the assessment of bulbar disease in ALS are lacking. Tensor EIM enhances the biomarker potential of EIM data and can improve bulbar symptom monitoring in clinical trials.

Keywords: Amyotrophic lateral sclerosis
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Abbreviations: ALS, Amyotrophic Lateral Sclerosis; ALS-FRS-R, ALS Functional Rating Scale-Revised; EIM, Electrical Impedance Myography; EMG, Electromyography; NTF, Non-negative Tensor Factorisation; PCA, Principal Component Analysis; AT-EIM, Change in Tensor EIM.

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1. Introduction

Electrical impedance myography (EIM) is a simple to use candidate biomarker for neuromuscular diseases. The pioneering work of Rutkove and colleagues has demonstrated its effectiveness across a range of disorders, including amyotrophic lateral sclerosis (ALS) (Rutkove and Sanchez, 2019; Mcilduff et al., 2017). Data are generated by the application alternating current (AC) and measurement of the resulting surface voltage (Rutkove and Sanchez, 2019). The frequency dependent effects of cell membrane capacitance and the resistive effects of the intra-/extracellular compartments mean that tissue is more fully characterised via a range of AC frequencies, an impedance spectrum (Holder, 2004).

A key question within EIM is how best to utilise the full spectrum of data. Most work has utilised a limited number of frequency outputs, even when a wide frequency spectrum has been collected (e.g., Mcilduff et al., 2017). More complete use of the frequency range has been attempted, either using reactance only measurements (Kapur et al., 2019), or a selection of different frequencies (Alix et al., 2020). In order to make use of the complete frequency spectrum we have recently developed an analysis technique which we term “tensor EIM”. The aim of the tensor EIM is to aggregate and simplify the large amount of EIM data, while minimising any loss of information. This is done using a mathematical procedure known as non-negative tensor factorisation, which has been applied to several areas of medicine (Escudero et al., 2015; Aram et al., 2015; Xie and Song, 2013). In EIM, where there can be both multiple input frequencies and multiple electrode arrangements, tensor EIM has the advantage of analysing all the information gained across all of these frequencies/configurations. Dominant patterns in the data are then identified and their importance quantified as a single ‘score’, which in previous work was able to correctly classify patients with ALS and correlated with disease severity (Schooling et al., 2021).

In ALS, quantitative measures of disease change over time are of increasing importance as several promising therapeutics reach clinical trials (Calabrese et al., 2021; Bald et al., 2021). While longitudinal EIM studies in ALS have used only a small amount of the available data, power analyses indicate that significant improvements in trial design can be achieved through limb EIM measurements (Rutkove et al., 2012; Shefner et al., 2018). Bulbar disease monitoring in trials is often limited (Yunusova et al., 2021) and the most commonly assessed muscle, the tongue, provides additional challenges relating to the complexity of the myo-architecture (Gaige et al., 2017). With fibres running in multiple orientations, multiple frequencies and electrode configurations may be required to sensitively detect disease, resulting in a large and complicated EIM dataset.

Adding to this complexity are the contrasting effects muscle changes in ALS would be expected to have an impedance spectrum, as denervation is followed by reinnervation, which is then punctuated with further episodes of denervation and ultimately reinnervation failure. In preclinical studies utilising sciatic nerve ligation, changes to impedance spectra in the acute setting were both short lived and different to those observed in a chronic setting (Carlson, 2014; Ahad et al., 2010). Later work with the SOD1G93A mouse model demonstrated resistance decreased in the presymptomatic stage and then increased in the symptomatic stage (Li et al., 2016).

On the basis of such observations, we hypothesised that in ALS the longitudinal changes in EIM spectra from individual patients would be complex, owing to the competing effects of acute and chronic denervation/reinnervation. To investigate this, we employed multi-directional tongue EIM recordings and captured the dominant spectral patterns with tensor EIM. By utilising data from a range of frequencies (i.e. the impedance spectrum) we demonstrate a more sensitive detection of disease-related impedance changes.

2. Methods

2.1. Data collection

Patients meeting any of the three levels of the Awaji-Shima criteria for ALS were recruited through the specialist motor neurone disease clinic at the Royal Hallamshire Hospital, Sheffield, UK (De Carvalho et al., 2008). Longitudinal EIM tongue measurements were made in 28 ALS patients (11, male, 17 female), with a mean age of 60 years (range 30–77). At baseline visit patients had a mean disease duration of 49 months (range: 5–204) and mean bulbar symptom duration of 30 months (range: 0–204). Measurements were made at baseline, 3, 6 and 9 months, with some attrition in patient numbers seen over time (Table 1). Additionally, 20 healthy control subjects (9 male, 11 female; mean age 51 years, range 22–82) were studied at baseline and 6 months.

EIM recordings were recorded utilising three 3-dimensional electrode configurations in which current and voltage sense electrodes were on opposite surfaces of the tongue (Fig. 1a). Measurements were made on both the central and lateral portions of the tongue blade (Fig. 1b), which have previously shown to be sensitive and specific for disease detection (Schooling et al., 2020). The spectra were recorded at 14 frequency values starting at 76 Hz and doubling each step up to 625 kHz. The impedance values were calibrated to give volume conducted potential (VCP) values, as proposed by (Sanchez et al., 2021). For these the cell constant of each electrode configuration was used to calibrate the impedance. The volume independent impedivity values obtained provide a standardised measure of the passive electrical properties of tissue, with the advantage that data from different electrode configurations can be directly compared and combined (Luo et al., 2021; Sanchez et al., 2021).

In addition to EIM data, the amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) bulbar sub-score was completed at each visit and a thorough clinical bulbar examination performed. Clinical signs of disease (wasting, weakness and fasciculations) were quantified by a simple scoring system (Table 2). Tongue strength recordings were also undertaken using the Quantitative Muscle Testing system (Averil Medical), coupled to the Iowa Oral Performance Instrument (Shellikeri et al., 2015). A comprehensive bulbar disease burden score was calculated by combining the ALSFRS-R, tongue strength and clinical examination signs into a score out of 36, with a lower value representing more severe disease (Schooling et al., 2021). The rate of symptom change was calculated for each patient as the change in bulbar disease burden score divided by the number of months for which the change was measured.

Details on the collection of Electromyography (EMG) data are outlined in Supplementary Methods S1.

2.2. Tensor EIM method

Each participant at each visit generated 168 data values (see Fig. 1c). These complex data were simplified in two steps. First, from a range of frequencies (i.e. the impedance spectrum) we demonstrate a more sensitive detection of disease-related impedance changes.

| Visit       | Patients | Healthy |
|-------------|----------|---------|
| Baseline    | 28       | 20      |
| 3 Months    | 26       |         |
| 6 Months    | 20       | 20      |
| 9 Months    | 14       |         |
non-negative tensor factorisation was performed, where the high dimensional data were represented by contributions from dominant spectral shapes. For the interested reader, the mathematical outline is included in Supplementary Methods S2. This algorithm combines the contribution of each spectral shape into a single tensor EIM score, which was then used to monitor disease changes.

To first evaluate the group trend with time, a four-dimensional factorisation was employed (dimensions: 28 spectral features; 6 measurement types; each participant; 2 timepoints, baseline and 6 months). This was repeated for the ALS patient group and healthy volunteers and the average spectral pattern at each time point was calculated. Additionally, a comprehensive measure of individual participant’s spectral signature at each visit was calculated through a three-dimensional factorisation (dimensions: 28 spectral features; 6 measurement types; each participant measurement visit) followed by principal component analysis, to return the tensor EIM score. Absolute longitudinal change of the tensor EIM was analysed with a linear-mixed model using a compound symmetry covariance matrix, fitted using Restricted Maximum Likelihood. Assessment of change was through the mixed model and using Mann-Whitney U tests in comparison to the healthy controls.

2.3. Sample size estimation

Estimating sample size requirements in hypothetical clinical trials have been utilised to assess the potential contribution of EIM to such studies (Rutkove et al., 2012; Shefner et al., 2018). The variation in the slopes of change of each metric was quantified using the effect size:

\[
\text{Effect size} = \frac{\text{mean slope}}{\text{STD}}
\]  

For metrics with healthy control comparisons this is modified to:

Table 2

| Clinical Sign     | Description and corresponding score |
|-------------------|-------------------------------------|
| Tongue wasting    | None: 0 | Minimal: 1 | Moderate: 2 | Severe: 3 |
| Tongue weakness   | None: 0 | Movement inside and outside mouth: 1 | Movement only inside mouth: 2 | Paresis: 3 |
| Fasciculations    | Absent: 0 | Present: 1 | | |

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Effect size = \frac{\text{mean slope}}{\text{STD} + \varepsilon} \quad (2)

where $\varepsilon$ is the average slope of the healthy controls; this provides the statistical noise within the data and helps avoid an over-estimate of the effect size. The sample size was estimated for a hypothetical clinical trial at 80% power and 5% significance level. This was calculated at 50% and 20% treatment effects.

3. Results

3.1. Exploring disease related tongue EIM changes at the level of the whole spectrum

On average the ALS patient group demonstrated a spectral shift to the right over time. By contrast, healthy participant spectra were stable (Fig. 2a). Of note, the shift in the ALS patient EIM spectra is in keeping with that associated with worsening disease severity (Schooling et al., 2021; Li et al., 2016; Li et al., 2012) (Appendix Figure A2).

However, when inspecting the raw spectra of individual patients, the change over time was often more complex. Some patients demonstrated consistent movement of the spectra to the right, while for others we observed transient shifts to the left, followed by spectral movement to the right (Fig. 2b). Out of the 28 patients, 13 had a consistent shift to the right, while 15 patients had spectra which demonstrated movement to the left on at least one occasion.

3.2. Longitudinal tensor EIM

In order to capture the effects of disease as completely as possible we utilised spectra from all recording locations and all electrode configurations via tensor EIM. The change in the tensor EIM metric ($\Delta T$-EIM) was then used to quantify the direction of spectral change. Histograms of the change from baseline for all patients are shown at 3 months ($n = 26$), 6 months ($n = 20$) and 9 months ($n = 14$) (Fig. 3a). These reveal that, to begin with, spectra shifted in equal proportions in both directions. As time progressed, more spectra shifted in the positive direction (Fig. 3b), which corresponds to the overall spectral shape shift to the right.

While the numerous spectra for each patient can be reduced to the single $\Delta T$-EIM value, the algorithm can also extract the dominant spectral patterns within the data (Fig. 3c). When $\Delta T$-EIM is positive, the contribution from the spectral shape shown in red increases, while that in blue decreases (resulting in an overall spectral shift to the right). By contrast, when $\Delta T$-EIM is negative, the contribution from the spectral shape shown in blue increases, and that in red decreases (encompassing an overall spectral shift to the left). The tensor EIM patterns were subsequently parameterised through simple circuit modelling to offer insight into the potential cellular changes underpinning these spectral shapes (Supplemental Methods S3, Appendix Figure A1).

To assess the sensitivity of tensor EIM for monitoring disease progression, the absolute value of $\Delta T$-EIM was used in order to resolve the bidirectional change in spectral shape. Longitudinal linear mixed modelling demonstrated a significant change of tensor EIM with time (Fig. 4a). The measures of tongue strength,
ALSFRS-R bulbar subscore and the overall bulbar disease burden score demonstrated more limited change (Fig. 4b-d).

3.3. Clinical trial design

To illustrate the potential of tensor EIM for the detection of bulbar disease, a hypothetical clinical trial sample size was calculated (Table 3). Tensor EIM required the smallest sample size in comparison to other measures of symptoms. Trial size required when using raw data with a single frequency, as typically employed in EIM studies on ALS (Rutkove et al., 2012; Shefner et al., 2018), has a large variation depending on the frequency and electrode configuration selected but the best performing single frequency did not surpass the performance of tensor EIM.

4. Discussion

Herein we have presented evidence that a new analysis framework called tensor EIM is able to capture ALS-related changes within the highly complex ultrastructure of the tongue muscle. Development of biomarkers for bulbar disease in ALS is an area of unmet need and these results indicate that high dimensional EIM data can be utilised to provide a disease sensitive characterisation.

Most EIM technology captures information at a range of frequencies but the majority of studies to date have only made use of one or two frequencies (Rutkove et al., 2014; Shefner et al., 2018). The increasing use of multiple electrode configurations adds further information about the state of the underlying muscle but also increases the amount of data collected (Luo et al., 2021). This generates a large (or ‘high dimensional’) dataset. While a more complete tissue characterisation is intuitively preferable, large datasets carry with them difficulties, such as the so-called ‘curse of dimensionality’. With this, a large number of observations not only risks reducing the generalisation of the results to other patients (overfitting) but also makes finding important patterns in the data more difficult (Kisil et al., 2018). By finding dominant spectra in a large EIM dataset, the tensor approach shows promise as a tool to maximise the potential of EIM as a biomarker for ALS and related conditions.

When assessing longitudinal EIM data at the level of the whole spectrum, we observed a complex and varied pattern of changes. The overall spectral shift to the right (or increase in centre frequency) over time is consistent with the progressive changes reported in mouse models of ALS (Li et al., 2016; Li et al., 2012), as well as in tongue and limb recordings from human patients (Mcilduff et al., 2017; Pacheck et al., 2016; Jafarpoor et al., 2011). We also observed transient spectral shifts in the opposite direction, in keeping with earlier work in animal models demonstrating that acute denervation can transiently shift impedance spectra in this fashion (Westgaard, 1975).

We have demonstrated for the first time in human ALS patients that the direction of spectral shift is complex and varied but we can only speculate as to what underpins this. Acute denervation results...
in extracellular oedema (Kamath et al., 2008) (Carlson, 2014), which would act to reduce extracellular resistance and in turn shift spectral profiles to the left. Histological studies of muscle in ALS report myocyte hypertrophy (Jensen et al., 2016), which could, at least in theory, increase capacitance and also cause this spectral change. In contrast, authors of previous studies have attributed EIM changes in chronic settings to progressive myofibre atrophy (acting to reduce the overall tissue capacitance) and extracellular space remodelling (which would increase extracellular resistance). Our circuit modelling based on dominant spectral patterns found changes in extracellular resistance and membrane capacitance, which is in agreement with these suggestions (Appendix Figure A1). We thus tentatively hypothesise that the transient shift of spectra to the left relates to crescendos of denervation, while movement right represents the progression of chronic denervation-related changes. A preliminary stratification of EIM spectra by EMG findings potentially matches with these (Appendix Figure A3), but tongue EMG is fraught with technical difficulties. Further work relating EIM spectral patterns to EMG findings in other muscles may provide a better platform for testing our hypothesis.

An objective biomarker of bulbar disease would enhance ALS clinical trial design (Yunusova et al., 2019). The ability of tensor EIM (Electrical Impedance Myography); the median and range values for single frequency raw EIM data; bulbar disease burden score; ALSFRS-R (ALS Functional Rating Scale–Revised); and tongue strength.

Table 3
Effect size and hypothetical clinical trial sample size estimation with 80% power and 0.05 significance level at 50% and 20% treatment effects. Calculated for tensor EIM (Electrical Impedance Myography); the median and range values for single frequency raw EIM data; bulbar disease burden score; ALSFRS-R (ALS Functional Rating Scale–Revised); and tongue strength.

|                          | Effect Size | Sample size at 50% treatment effect | Sample size at 20% treatment effect |
|--------------------------|-------------|-------------------------------------|------------------------------------|
| Tensor EIM               | 0.99        | 64                                  | 401                                |
| Median single frequency  | 0.48        | 274                                 | 1715                               |
| Range single frequency   | 0.28–0.85   | 87–802                              | 545–5014                           |
| Bulbar Disease Burden    | 0.84        | 89                                  | 558                                |
| Score                    |             |                                     |                                    |
| ALSFRS-R Bulbar Sub-Score| 0.46        | 298                                 | 1860                               |
| Sub-Score                | 0.37        | 461                                 | 2881                               |

5. Conclusion

Tensor EIM appears to be capable of capturing the complex spectral fingerprint of ALS disease progression in the tongue. Spec-
tral change is described by a single tensor EIM metric, which can provide a simple measure for longitudinal studies. This approach enhances the potential of EIM as biomarker in ALS and could improve the monitoring of disease progression in clinical trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.04.015.

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