Neuroelectric Biomarkers of Network Dysfunction in Amyotrophic Lateral Sclerosis

Bahman Nasseroleslami (1*), Stefan Dukic (1, 2), Roisin Mc Mackin (1), Amina Coffey (1), Teresa Buxo (1), Antonio Fasano (1), Rangariroyashe Chipika (1), Marta Pinto-Grau (1), Tom Burke (1), Emmet Costello (1), Christina Schuster (1), Michael Broderick (1), Kieran Mohr (1), Brighid Gavin (1), Parameswaran M. Iyer (1), Mark Heverin (1), Niall Pender (1, 7), Peter Bede (1), Muthuraman Muthuraman (3), Edmund C. Lalor (4, 5), Madeleine Lowey (6), Richard Carson (5), Orla Hardiman (1, 5, 7)

1. Academic Unit of Neurology, Trinity College Dublin, the University of Dublin, Dunlin, Ireland.
2. Department of Neurology, Brain Centre Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands.
3. Biomedical Statistics and Multimodal Signal Processing Unit, Department of Neurology, Johannes-Gutenberg-University Hospital, Mainz, Germany.
4. Trinity Centre for Bioengineering, Trinity College Dublin, the University of Dublin, Dublin, Ireland.
5. Trinity College Institute of Neuroscience, Trinity College Dublin, the University of Dublin, Dublin, Ireland.
6. School of Electrical and Electronic Engineering, University College Dublin, Dublin, Ireland.
7. Beaumont Hospital, Dublin, Ireland.

The quantification of phenotypes, progression and outcome in ALS trials remains a challenge, due to major shortcomings of the existing biomarkers: focus on focal structural degeneration rather than functional changes in motor/cognitive networks (emerging from the pathobiology), invasiveness and cost. We have developed high density EEG measures to quantify the functional neuroelectric activity in specific brain networks that are engaged during resting-state and cognitive/motor tasks.

Crossectional and longitudinal "resting-state" EEG showed characteristic patterns of increased connectivity. When we source-localised the activity to the underlying brain source, we observed a frequency-specific pattern of change in spectral power, synchrony and co-modulation. We found increased average co-modulation of neural oscillations with other brain regions in the central and posterior regions of the brain (δ-, θ- and γl-band) and frontal regions (δ- and γl-band). Furthermore, the average synchrony to other brain regions was decreased in the temporal and frontal lobes (δ-, θ- and α-band) and in the motor cortex (β-band), with decreased region-to-region connectivity in frontal (δ-band) and motor (β-band) network.

An auditory mismatch negativity "cognitive task", further revealed the network dysfunction: increased activity in the left posterior parietal, central and dorsolateral prefrontal cortices and a decrease in the inferior frontal and left superior temporal gyri.

The cortico-muscular (EEG-EMG) coherence during isometric pincher grip "motor tasks" interrogated the motor networks: The PLS and Post-Polio Syndrome patients showed α-, β- and γ-band increases over frontal, parietal, and ipsilateral motor regions, while the abnormal coherence patterns in the ALS was widespread.

The correlations of the EEG changes with structural degeneration (MRI) and functional scores, revealed the motor/cognitive and direct/compensatory nature of these network impairments. The afforded discriminatory powers (AUC=0.79), exceeded the levels in (f)MRI studies. The EEG measures had minimal overlap with the traditional phenotypes (site of onset and genotype), but rather formed new clusters of patients suggesting the discovery of new network-based phenotypes.

Our findings demonstrate that the quantitative EEG measure of neural activity and connectivity elucidate the network pathology in ALS and can serve as prognostic biomarkers and outcome measures for clinical trials.