2019 Call for projects

NETWORK IMPAIRMENT IN ALS: QUANTIFYING THE UNQUANTIFIABLE

Acronym: NetworkALS

Principal Investigator: Orla HARDIMAN

Grant: 133 600€

Duration: three years

Summary of the research project

Clinically relevant extra-motor features, including changes in cognition and behaviour, are common in ALS but are not currently measured in clinical trials. Cognitive and behavioural changes are best understood in terms of disruptions in complex frontostriatal and frontotemporal networks, and are not amenable to investigation using in vitro (iPS) or rodent animal models.

Anatomical and functional interrogation of these network changes in human ALS using structural/function MRI and PET is limited by cost and tolerability, with poor correlation between structural change and findings on detailed neuropsychological profiling. By contrast, advances in neuroelectric signal analysis of high-density electroencephalography (HD-EEG) provide excellent temporal resolution of disrupted circuitry, and novel techniques in source analysis can localize neural activity within specific brain regions and circuits with a good spatial resolution.

We have demonstrated characteristic changes in neuroelectric signaling using source localised spontaneous EEG and event-related potentials (ERPs) in ALS. In resting state, fronto-parietal and fronto-temporal networks show consistent increased functional activity compared with healthy controls, and using attention switching paradigms, we have demonstrated reproducible evidence of increased activity in the left posterior parietal, central and dorsolateral prefrontal cortices, and reductions in activity in inferior frontal and left superior temporal gyri. These changes progress with disease, and correlate with structural degeneration (MRI), and with specific neuropsychological deficits. These data provide robust evidence that source-localised EEG can be used to quantify pathological changes in extra-motor networks in ALS.

Here we propose to use our previously established EEG resting-state and cognitive ERP measures of network activity to provide the first quantitative, data-driven suite of neuroelectric biomarkers for

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use in future trials. We will develop new measures of functional impairment in ALS derived from spectral power and connectivity changes, using dynamic analysis of resting-state EEG. Next, we will provide novel data-driven markers of cognitive and behavioural change suitable for use in clinical trials, using attention/inhibition-based tasks. We will provide longitudinal correlation of these measures with neuropsychology and imaging and provide reliable measures of network-based cognitive-behavioural impairment. On completion, this project will provide robust ***quantitative outcome measures of cognitive-behaviour impairment in ALS for use in future clinical trials.***

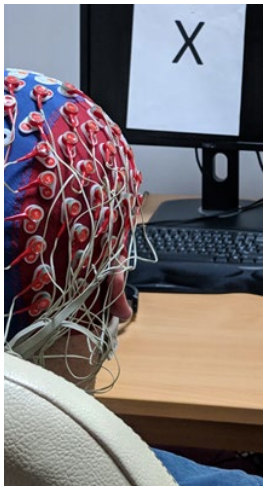

Fig.1. High Density electroencephalography (HD EEG) setup, including a cap and electrode sets, for recording the brain-s electrical activity.

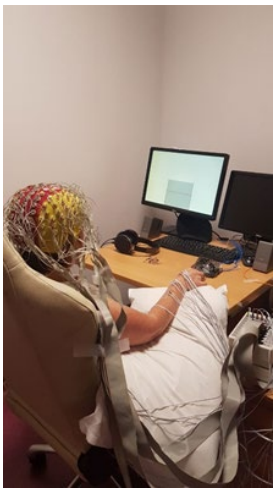

Fig.2. (right) An ALS patient taking part in an EEG recording session while engaging in the requested experimental task in a Clinical Research Facility, at St. James's Hospital in Dublin, Ireland.

The study is conducted by **Orla Hardiman** , Trinity College Dublin, the University of Dublin, Ireland

The researchers working on the project from left to right:
Mr Vladyslav Sirenko (Research Assistant), Ms Marjorie Metzger (PhD Student supported by The Thierry Latran Foundation), Professor Orla Hardiman (PI), Dr Bahman Nasseroleslami (Co-I), Dr Niall Pender (Co-I), Mr Mark Heverin (Research Manager)