ALS-Electrode: Novel Neuro-electrical Biomarkers of Heterogeneous Network Degeneration in Amyotrophic Lateral Sclerosis for Quantifying the Progression and Outcome in Clinical Trials

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neuromuscular disorders
Study type	Observational non invasive

Summary

ID

NL-OMON52587

Source
ToetsingOnline

Brief title
ALS-Electrode

Condition

- Neuromuscular disorders

Synonym
motor neuron disease, muscle disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ALS Stichting Nederland

Intervention

Keyword: ALS, EEG, EMG, MND

Outcome measures

Primary outcome

Primary Final Endpoints:

Discovered ALS biomarker(s) for reliable and early detection, as well as distinction between different ALS subphenotypes and healthy people based on differences in ERPs identified using EEG/EMG experiments with subsequent source localisation.

Secondary outcome

Secondary study outcomes:

• EEG and EMG (anonymised) data sets, for wider research purposes

• Assessing the difference in terms of cortical network dysfunction in the cognitive domains between different ALS sub-phenotypes and healthy controls

• Cross validation between obtained task-based (ERP) and resting-state alternations in both motor and cognitive networks.

• Research Publications

Study description

Background summary

Amyotrophic Laterals Sclerosis (ALS) or Motor Neuron Disease (MND) is a

terminal neurodegenerative disease, leading to progressive loss of motor function. Treatment of ALS remains an unresolved challenge despite intensive research into diagnosis, prognosis and therapy. New therapeutics and the quality of care after diagnosis can be enhanced by early, more personalised diagnosis at individual patient level, enabling tailored care and individualised treatment. To personalise the diagnosis, there is a need for reliable quantitative biomarkers, for early detection of disease onset and to distinguish the different subtypes of the disease with different symptoms and progression rates.
In the motor domain, several biomarkers have been investigated for use in ALS, e.g. motor unit number index (MUNIX), magnetic resonance imaging (MRI), electromyography (EMG) and electroencephalography (EEG). However, the diagnostic utility of these techniques, especially the inexpensive non-invasive recordings of electrical activity (EEG/EMG) is limited: the biomarkers are not strongly linked to the neurophysiological mechanisms affected in ALS. Therefore, it is of interest to distinguish and dissociate the electrophysiological signatures that reflect sensorimotor network communication patterns pertaining to each sub-system in function and dysfunction, which in turn can act as biomarkers. This aim can be achieved with simultaneous EMG/EEG recordings.
In the cognitive domain, it has been shown that ALS patients may present with frontotemporal dementia (FTD) (13%), significant cognitive impairment (30%), and behavioural changes (~50%) that map onto network disruption in orbitofrontal, frontotemporal, and fronto-striatal neural pathways. From a pathobiological perspective, there is an overlap between ALS and neuropsychiatric conditions in population-based studies (~30% of ALS kindreds have family history of conditions such as schizophrenia) and genomic studies (4% polygenic overlap between ALS and schizophrenia).
Taken together, this gives a compelling argument in favour of studying the heterogeneity within ALS in the context of a wider disturbance of different neural networks, rather than at the level of individual (motor or non-motor) networks.

Study objective

Our objectives are to simultaneously record high-density EEG and EMG, and to use source analysis to assess the activity and communication in motor and non-motor (underlying cognition) neural networks during rest and during cognitive and motor tasks. These objectives will be achieved by conducting the resting-state (no task) and task-based event-related potential (ERP) paradigms; e.g. mismatch negativity (MMN), sustained attention to response task (SART) and Stroop test. Source localisation methods will be applied on the collected EEG/EMG data, as well as unsupervised clustering of the measures of network function.

The key objectives of our project ALS-Electrode are:

1. To cross-sectionally and longitudinally define the disrupted resting-state networks (in-cluding the communication between the primary motor cortices and between the frontal-parietal networks), using EEG source and connectivity analysis; and to identify the motor and cognitive nature of the impairments by correlates to neuropsychological batteries, motor performance measures and structural MRI.

2. To identify biomarkers of disruption in non-motor networks associated with functional neuropsychological tasks using evoked response potentials (ERPs). This analysis in-cludes behavioural performance measures such as Mismatch Negativity (MMN), SART, Stroop and oddball tasks, as well as the accompanying source-localised EEG activity and connectivity that interrogate cognitive networks (involving frontal dysfunction), against experiment control conditions (practice and motor effects) and age/gender-matched controls.

3. To identify biomarkers of disruption in motor networks using source-resolved cortico-muscular communication. The source-space signatures of cortico-muscular communication *image* and quantify the disruption of broader cortical projections to the spinal cord during active motor tasks.

In doing so, our aim is to advance understanding of ALS pathology and identify novel, inexpensively measured biomarkers that can distinguish these neurodegenerations and their sub-phenotypes from healthy individuals. Such biomarkers have applications in disease prognostics and measurement of therapeutic activity of neurotherapeutic candidates. Successful discrimination of the electrophysiological signatures can be used to diagnose ALS which may be also useful in terms of better patient care and the development of novel neuro-motor rehabilitation.

Study design

Observational study, cross-sectional and longitudinal design.

Study burden and risks

Serious risks with low probability: Similar to any recording, there is a remote risk of electric shock, device malfunction, etc. The device is a CE (Conformité European) certified regarding the electromagnetic compatibility and electrical safety for research purposes. The recording system is powered from a battery and connected to a computer using optical technology (hence, electrically isolated from the power grid); Consequently, the risks associated to such incidences are very low, similar to many day-to-day situations.
Transient benign risks with low probability: The risks of the procedures executed during the experiment set-up and recording are low. The subjects may show allergic reactions to the recording gels (though this is an exclusion criteria) that can be managed by medications. This is expected to be extremely

rare, if not beyond the bounds of possibility.
Probable discomforts: The experiments may be boring or tiring for some patients as it requires remaining in sitting position for more than an hour. People may need to wash their hair after the experiment. The removal of medicine tapes on hand and forearm may be painful or uncomfortable for some patients. The experimenter will use maximum care to minimise such discomforts by allowing limited mobility to the patient between the recording sessions.
Other Risks: Other risks of participating in the experiment are considered to be minimal and not greater than the normal life of the participant.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Belong to one cohort of interest

a. ALS patients: definite, probable, probable-laboratory supported or possible ALS according to the revised El Escorial criteria (Brooks et al., 2000)
b. PMA/PLS patients: patients with clinical diagnosis of PMA or PLS, after excluding other diseases.
c. Asymptomatic carriers: Carriers of ALS-related gene mutations with no neurological symptoms associated with ALS
d. Healthy controls: age- and gender-matched to patient groups, intact physical ability to take part in the experiment
2. Age 18-80 years (inclusive)
3. Capable of thoroughly understanding the study information given; has signed the informed consent.

Exclusion criteria

Exclusion criteria for all participants:
• Pregnancy
• History of major head trauma
• Any medical condition associated with neuropathy (e.g. diabetes), transient ischemic attack, stroke, epilepsy, seizure disorder, brain tumours and other comorbidities (e.g. human immunodeficiency virus)
• Alcohol dependence syndrome, current use of neuroleptic medications or high dose psychoactive medication
• History of reaction or allergy to recording environments, equipment and the recording gels
• Tracheostomy, tracheostomal ventilation of any type or frequent need for (non)-invasive ventilation

Further exclusion criteria for patients:
• Insufficient dominant hand function to perform button pressing (SART/Stroop) and/or motor tasks
Further exclusion criteria for healthy controls and asymptomatic carriers:
History of neuromuscular, neurological or active psychiatric disease.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-01-2020
Enrollment:	330
Type:	Actual

Medical products/devices used

Generic name:	EEG;EMG
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	12-09-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL70373.041.19