Final Report

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Title of Project: ALS progression: multimodal approach to assessing cortical dysfunction which may underlie pathogenesis

Summary: In the present project 41 ALS patients have been studied for brain function changes associated with ALS using the novel technique of brain excitability measurement. In addition, patients have undergone clinical and cognitive profiling and a proportion of them studied earlier in the year have recently completed the first progress study at six months. This data will be presented at the MND/ALS Symposium in December 2019. A subset of 16 ALS patients have undergone structural and functional MRI. Data from MRI is currently being analysed and numbers over 20 will be required to achieve robustness of result which should be complete before the end of this year. The third modality of studying brain changes in ALS called TMS EEG has been undertaken in 10 subjects and data is currently being analysed. By the end of this year a subset of 15 ALS patients will have undergone all three modalities of assessment at one time point and will be followed up for a period of 24 months in order to understand the changes in the brain that occur and progress with ALS disease progression.

Hypothesis vs Findings:

Aims

1. To determine if evolution of cortical dysfunction in ALS progresses to brain regions under the control of corticofugal projections.
1. To determine if hyperexcitability of descending corticofugal fibers precedes LMN dysfunction in ALS.
2. To determine whether pattern and rate of disease spread in ALS is mediated by cortical influences (i.e. corticofugal fiber hyperexcitability and neocortical spread).

Cortical hyperexcitability has been shown to predominate in the onset or dominant hemisphere in patient with ALS. Completion of the MRI connectome analysis and TMS EEG study will provide information on cortical changes in other brain regions apart from the motor cortex and reveal if there is a sequential progression of cortical dysfunction in the two cortical hemispheres or progression is simultaneous with unilateral preference. This will be correlated with clinical score of muscle weakness, functional loss in motor, bulbar and respiratory domains and cognitive dysfunction in patients to know if cortical dysfunction precedes clinical manifestations of motor neuron disease. More information on neocortical spread can only be compiled after

TMS EEG and MRI data collection is completed over a 24-month period in at least a subset of patients.

Unanswered Questions
The patterns or spread of dysfunction within non motor areas of the neocortex is still awaited.

What these research outcomes mean
Cortical hyperexcitability in ALS does have laterality and dominates in the onset hemisphere or the dominant hemisphere in global or bulbar disease. More knowledge of neocortical spread of dysfunction in ALS and the patterns or lack thereof of spread between the cortical hemispheres will require completion of 24 months of data collection.

Abstract for presentation at the MND/ALS Symposium 2019

Cortical hyperexcitability and cognitive dysfunction in ALS

Background: Amyotrophic lateral sclerosis (ALS) is a multisystem disorder and ALS-specific cognitive changes have been extensively investigated. Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was recently developed and showed that cognitive deficits were more frequent in more advanced stage of ALS. Meanwhile, threshold tracking transcranial magnetic stimulation (TMS) technique demonstrated that hyperexcitability of motor cortex was reliable diagnostic marker of ALS from the early stage.

Objective: To elucidate the relationship between cortical hyperexcitability and cognitive dysfunction in ALS.

Methods: 32 patients with ALS were recruited from the MND clinic at Westmead Hospital. Besides neurological assessment, the degree of upper motor neuron (UMN) involvement was graded using UMN score and neuropsychological status was assessed by ECAS. Functional disability and pseudobulbar affective lability were also assessed with ALSFRS-R and pseudobulbar affect score (PAS), respectively. Cortical function was assessed on both sides using the threshold tracking TMS technique and compared to non-ALS neuromuscular controls.

Results: Cognitive dysfunction, as reflected by ECAS total score, was evident in 41% of ALS patients. Interestingly, executive dysfunction was noted in 22% of patients, while abnormalities in the ECAS language scores were evident in 47%, verbal fluency scores 28% and ALS-specific scores in 31% of ALS patients. Separately, there was a significant reduction of mean short-interval intracortical inhibition (SICI) [$P_{DOMINANT\ CORTEX} < 0.05$; $P_{NON\text{-}DOMINANT\ CORTEX} < 0.05$] and short-interval intracortical facilitation (SICF) [$P_{DOMINANT\ CORTEX} < 0.05$; $P_{NON\text{-}DOMINANT\ CORTEX} < 0.05$] in ALS patients which was accompanied by a reduction in cortical silent

period duration (P< 0.05), all indicative of cortical hyperexcitability. Multiple linear regression disclosed a significant correlation between ECAS $_{executive}$ scores and cortical silent period duration (B= -0.48, P<0.01) and disease duration (B= -0.63, P<0.01). There was no significant correlation between SICI/SICF and cognitive abnormalities.

Discussion: The present study has established that features of cortical hyperexcitability that are mediated by dysfunction of long latency $GABA_B$ circuits, precede the development of executive cognitive dysfunction. In contrast, cortical circuits mediating short latency inhibition (via $GABA_A$ receptors, as reflected by SICI) and facilitation (SICF) appear not to be related to biomarkers of cognitive dysfunction. Therapeutic agents aimed at modulating the long latency inhibitory circuits could prove therapeutically useful for executive cognitive dysfunction in ALS.