# Feasibility and future role of high-density TMS in ALS: a pilot study in healthy volunteers

Carobin A.[1], Bashford J.[1], Premoli I.[1], Santoro V.[1], Large C.[2], Richardson M.[1] and Shaw C.[1]
1Basic and Clinical Neuroscience, King's College London, London, 2 Autifony Therapeutics Limited, Stevenage Bioscience Catalyst, Stevenage, United Kingdom

## Background

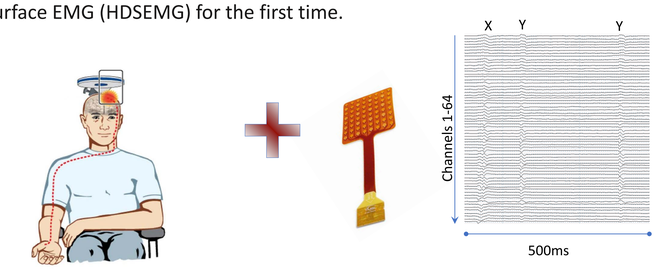
ALS is a neurodegenerative disorder that causes progressive paralysis and death on average within three years of symptom onset. The discovery of novel therapies is held back by the lack of early disease progression biomarkers.

**Transcranial magnetic stimulation (TMS)** combined with single-channel EMG has demonstrated that cortical-spinal hyperexcitability is an early pathogenic mechanisms preceding irreversible muscular atrophy in ALS.

Established TMS protocols such as SICI and ICF have shown potential as a non-invasive electro-diagnostic marker of ALS. However, how well these electro-diagnostic markers can track disease progression is less well understood and has led to some contrasting results

## Aim

This study aimed to validate the combination of TMS and high-density surface EMG (HDSEMG) for the first time.




Bashford et al., 2019

**TMS-EMG** uses an electro magnetic field to stimulate the primary motor cortex and measures the motor evoked potential (MEP) at the contralateral hand muscle.

**HDSEMG** employs a fixed array of 64 surface electrodes for quantitative recording of fasciculations potentials (see **X** an **Y**). These have been shown to represent spinal hyperexcitability in ALS patients.

## Hypothesis

High-density TMS (HD-TMS), compared to the conventional EMG recording, can provide an enriched dataset to characterize SICI and ICF with better spatial resolution into a 3D anatomical map of the FDI firing.

## Methods

- The magnitude of SICI and ICF was measured during simultaneous HDSEMG registration from the first dorsal interosseous (FDI) muscle of the dominant hand in 15 healthy volunteers (9 males, 6 females, mean age 69.3).
- Analysis was performed in MATLAB using customised scripts and and allowed the development of a new analytical pipeline for data visualization and analysis.

## Methods: the high-density TMS technique

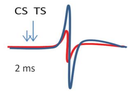

**1. Motor evoked potential (MEP)**

**RMT**= resting motor threshold as the minimum TMS intensity to elicit a minimal 50 uV MEP when FDI is relaxed.

**2. Short Intracortical Inhibition (SICI)**

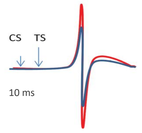
**CS**= subthreshold conditioning stimulus
**TS**=suprathreshold test stimulus

***Paired-pulse: CS (80%RMT), TS (120%RMT);***
***Single pulse : TS (unconditioned,120%RMT);***




a **reduction** in **the conditioned test MEP amplitude** (in red) when compared to **the unconditioned MEP response** (in blue) when ISI is 2 ms.

**2. Intracortical facilitation (ICF)**



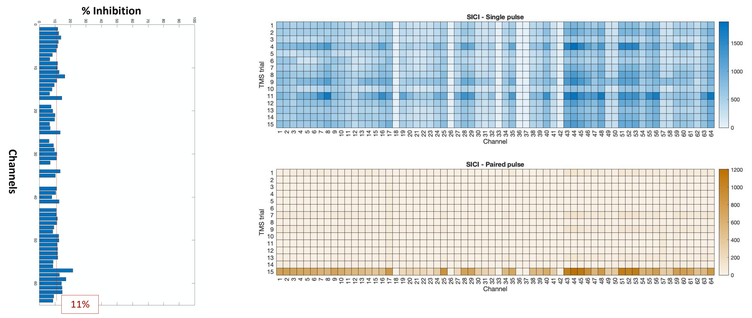

an **increase** in **the conditioned test MEP amplitude** (in red) when compared to **the unconditioned MEP response** (in blue) ISI is 10 ms.

## Results

Heatmap of peak-to-peak amplitude in μV split in single pulse trials (blue) and double pulse trials (orange)

Topological heatmap display for the peak-to-peak amplitude in the grid for each TMS trial.

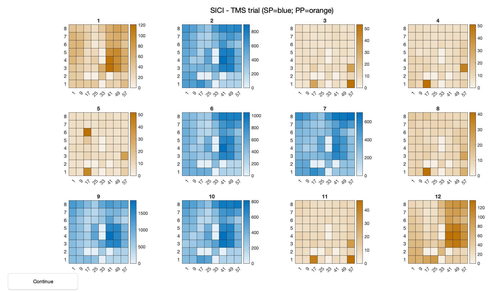
### Example data output for SICI for one participant



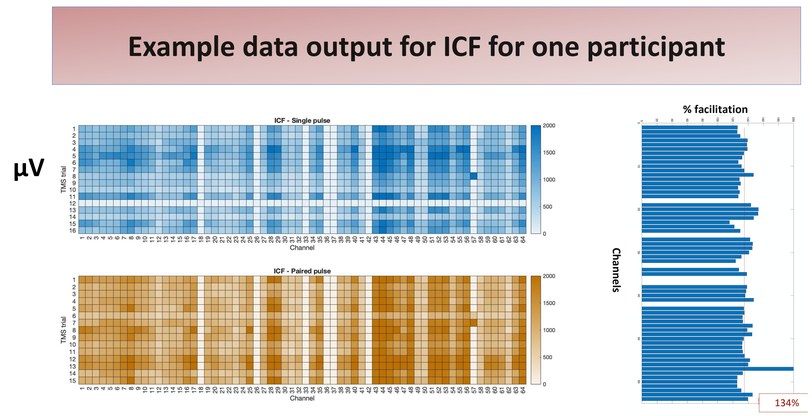

**89% inhibition** of mean MEP amplitude in double pulse trials

**% Inhibition** = Amplitude Conditioned TS (uV)/ Amplitude Unconditioned TS (uV) *100.
n=15 trials

**Topographical distribution of inhibition across the FDI muscle**



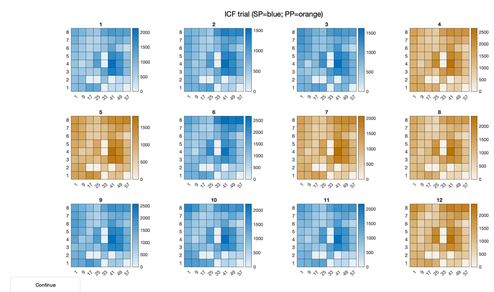

### Example data output for ICF for one participant




**34% facilitation** of mean MEP amplitude in double pulse trials

**% Facilitation** = Amplitude Conditioned TS (uV)/ Amplitude Unconditioned TS (uV) *100.
n=15 trials

**Topographical distribution of facilitation across the FDI muscle**




## Conclusions

- ❑ Preliminary data indicated high data quality and methodological validity of our novel electrophysiological approach
- ❑ The application of these findings to the ALS population has the potential to improve our understanding of the topographical distribution of disinhibition or excess facilitation that has been postulated to underlie cortical hyperexcitability in ALS. Precisely determining how excitability abnormalities evolve and spread over time may help the progression of a detailed anatomical map of disease trajectory in ALS..

**References**
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Rogasch et al., Schizophr Bull. 2014 40(3):685-96.

For information contact anna.1.carobin@kcl.ac.uk