TMS as a pharmacodynamic readout for testing novel CNS therapeutics.

What is TMS?
Transcranial Magnetic Stimulation (TMS) is a non-invasive brain stimulation technique which in combination with electromyography (EMG) and electroencephalography (EEG) enables the assessment of human brain excitability in health and disease.

The observation of TMS-electrodiagnostic markers (TMS-EDM) before and after the administration of drugs with well-known mechanisms of action contributed to the development of markers of cortical inhibitory and excitatory processes. For this reason, TMS-EDM started to be used in early stage clinical trials of new therapeutics to obtain pharmacodynamic read-outs.

TMS-EDM offers new avenues of investigation providing

(i) in-vivo markers for pharmacological activity;
(ii) in-vivo markers for specific biological processes (i.e., GABAergic inhibition, voltage-gated channel ligand activity, NMDA receptor activity).

It offers a better signal to noise ratio compared to EEG resting state recordings and thanks to a 'perturbation and measure approach' it does not require subject involvement in a specific task.

Aim and Technological Description
We use TMS technology to provide pharmacodynamic endpoints of newly developed drugs acting in the human brain. Neurophysiological responses elicited by TMS stimulation of the motor cortex can be measured with:

- EMG applied at the contralateral hand muscle. The main parameter for single-pulse TMS-EMG is the resting motor threshold (RMT) which reflects cortico-spinal excitability. RMT is the minimum stimulation intensity required to elicit a small motor evoked potential (amplitude of 50V).
- EEG sensors applied over the volunteer's head. The main parameters are the TMS-evoked EEG potentials (TEPs) which are a reliable and reproducible alternating sequence of positive (P) and negative (N) peaks at 25 (P25), 45 (N45),100 (N100) and 180 (P180) ms after stimulation. Measurement of TEPs amplitude allows a direct investigation of cortical excitability and connectivity in a highly time-resolved fashion.

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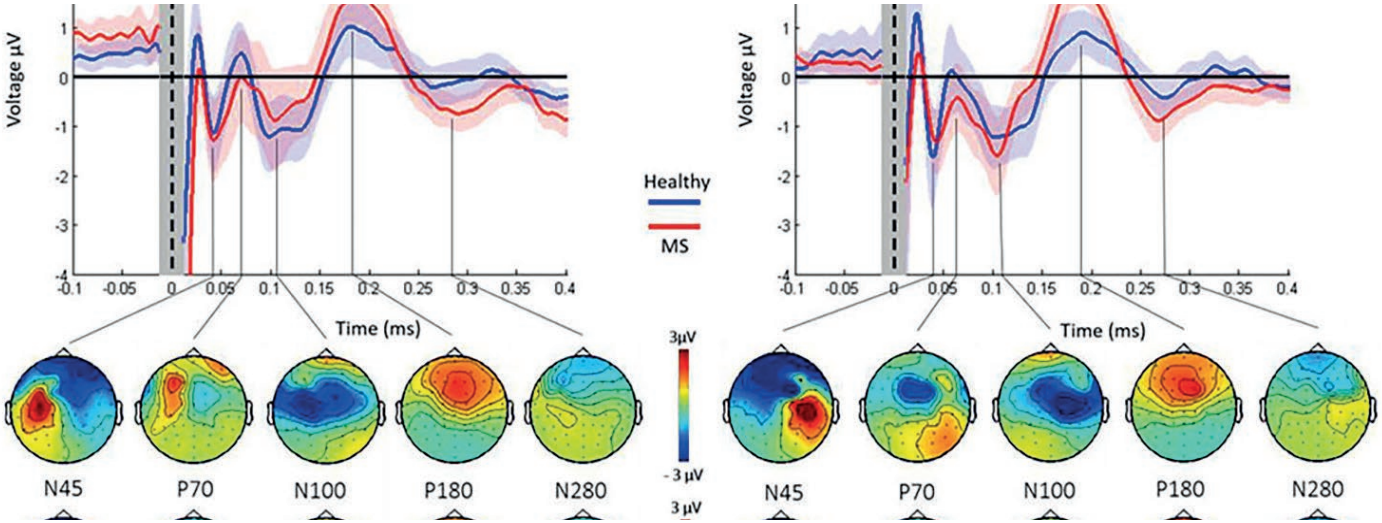

Background
Pharmacology has greatly contributed to the development of TMS by helping identify the underlying mechanisms of:

- Single-pulse TMS-EMG The RMT is a parameter associated to neural membrane excitability and represents a key EMG output related to AED activity. Several AEDs acting on voltage-gated channels enhance RMT values.
- Paired-pulse TMS-EMG protocols consist of a conditioning stimulus (CS) which precedes a test stimulus (TS). According to the inter-stimulus interval and the stimulation intensity specific inhibitory and excitatory intracortical circuits can be tested. The modulation of GABAergic compounds and NMDA antagonist helped revealing specific neurophysiological fingerprints.
- TMS-EEG TEPs can measure inhibitory processes mediated by GABAergic neurotransmission. Single oral doses of alprazolam and diazepam increased the negative component at 45 ms post TMS (N45) and decreased the negative potential at 100 ms after the pulse (N100). Baclofen, a GABAB receptor agonist, increased the N100 amplitude. A novel competitive selective antagonist of the extrasynaptic 5-GABAAR decreased the N45 amplitude.

TEPs can reveal specific fingerprint for antiepileptic drug (AEDs) activity. Lamotrigine and levetiracetam, two of the most prescribed AEDs showed an increased N45 and a suppressed P180. Carbamazepine decreased the P25 and P180 TEP components, and brivaracetam the N100 amplitude in the non-stimulated hemisphere.

TMS-EMG/EEG outputs provide early pharmacodynamic read-out measuring impact on corticospinal and cortical excitability. They crucially help shaping future development plans of new therapeutics.

This technology can be applied in the context of several neurological and neuropsychiatric conditions (i.e. epilepsy, ALS, Parkinson's disease, MS, autism and schizophrenia).

The Science Behind uniquely is able to offer services to support clinical trials during volunteer screening and trial. These include Psychological evaluation; EEG monitoring, data acquisition, data review and reporting; EMG response data acquisition, data review and reporting; Study design; Equipment (hire or purchase) – EEG, EMG, TMS and tES and Technician hire.

We work together as part of your clinical trial team adhering to Good Clinical Practice guidelines.

As a trial or research group, you can access our services on a study-by-study basis without the need to make significant capital investment in technology and expertise. Giving you the freedom to enhance your service offer or build elements into your study as and when you need to.

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