CHDR
Centre for Human Drug Research

Transcranial magnetic stimulation

Transcranial magnetic stimulation

CHDR is actively engaged in developing new biomarkers and optimising existing biomarkers to study compounds that penetrate the central nervous system (CNS). We have recently evaluated transcranial magnetic stimulation (TMS) coupled with electromyography (EMG) and electroencephalography (EEG) as a biomarker to study the clinical effects of drugs that are expected to affect cortical excitability. Both single-pulse and paired-pulse TMS stimulation protocols have been implemented at CHDR and can be customised according to study design.

A novel biomarker with great potential

TMS-EMG – TMS targeted at the motor cortex results in motor evoked potentials (MEPs) in a peripheral muscle, which can be measured with EMG. Single-pulse TMS-EMG has the potential to demonstrate corticospinal excitability, while paired-pulse TMS-EMG focuses on cortical excitability by investigating the relative contribution of inhibitory and excitatory networks.

TMS-EEG – TMS combined with EEG allows direct and non-invasive measurement of the cortical response to TMS stimulation, reflected in a TMS-evoked potential (TEP). TMS-EEG makes it possible to stimulate and evaluate responses of brain areas outside the commonly targeted motor cortex, with a spatial resolution of around 10 mm and millisecond temporal resolution.

Technical specifications

- MagPro R30 with MagOption stimulator (MagVenture GmbH, Hückelhoven, Germany)
- MCF-B65 butterfly coil (2x75mm) (MagVenture GmbH, Hückelhoven, Germany)
- 32-channel TMS compatible EEG system (EEG amplifier: TMSi, Oldenzaal, the Netherlands, EEG caps: ANT Neuro, Enschede, the Netherlands)
- Neurocenter software (Clinical Science Systems, Leiden, the Netherlands)

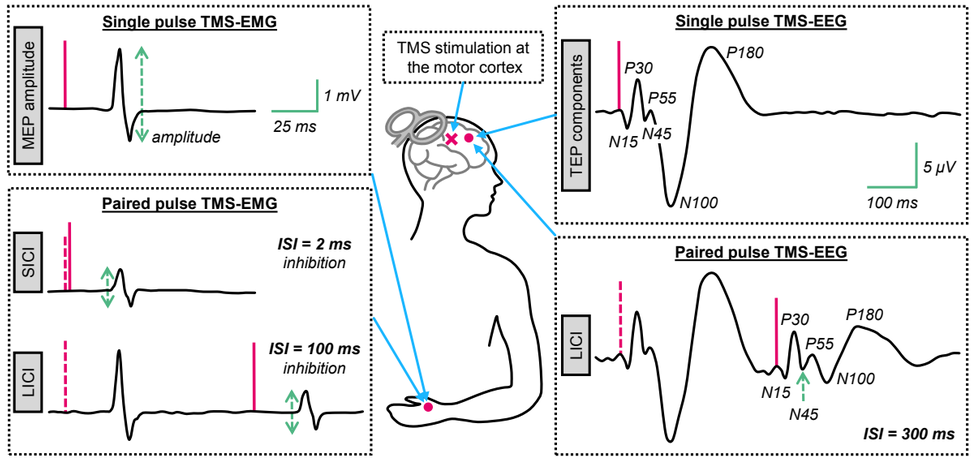

Figure 1: Outcome measures for TMS-EMG and TMS-EEG. Upper panels correspond to the single pulse TMS paradigm and the lower panels to the paired pulse TMS paradigm; pink solid lines = TMS pulse, pink dashed lines = conditioning TMS pulse. MEP = motor evoked potential, TEP = TMS evoked potential, SICI = short intracortical inhibition, LICI = long intracortical inhibition and ISI = interstimulus interval. Adapted from: de Goede A.A., ter Braack E.M. and van Putten M.J.A.M. (2016). Clinical Neurophysiology, 127(9):3140–3155.

Non-invasive, safe and painless assessments

Single and paired TMS pulses are applied using a coil positioned over the subject's head. TMS activates a brain area of only a few centimetres in diameter and reaches the superficial cortical layers (~2 cm from the skull).

Standardised, high-quality testing

Methodological rigour is ensured through the implementation of a standard operating procedure (SOP) which guides the performance of TMS-EMG and TMS-EEG assessments. Our highly-trained clinical and technical staff possess the latest expertise regarding factors that facilitate or limit the clinical applicability of TMS, including (sources of) intra-subject and inter-subject variability in excitability measures.

Our track record

Together with the Clinical Neurophysiology (CNPH) Group of the University of Twente – one of our closest collaborators in the field of cortical excitability testing – we have evaluated the effects of levetiracetam, valproic acid and lorazepam on cortical excitability in healthy volunteers. Our findings indicate that these drugs show significant effects on cortical excitability as measured by single-pulse and paired-pulse TMS-EMG and TMS-EEG. Find out more about this study in our poster presentation 'TMS-EMG and TMS-EEG as a biomarker for pharmacological effects on cortical excitability', which can be found at www.chdr.nl/library.

Future directions

At CHDR, we are driven to advance the front line of research. We welcome our clients to explore the possibilities of using TMS-EMG and TMS-EEG to study the clinical effects of CNS-active drugs that modulate cortical excitability. By supporting TMS-EMG and TMS-EEG in both sponsored and investigator-initiated clinical drug trials, we aim to actively expand knowledge in this area. We also strive for continuous improvements to our TMS methodology, by adding neuronavigation tools, optimising stimulation protocols and developing new methods of statistical analysis.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

To learn about CHDR's full range of services, contact us today.

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