Clinical Neurophysiology 128 (2017) 367–381

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

TMS combined with EEG in genetic generalized epilepsy: A phase II diagnostic accuracy study

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See Editorial, pages 365–366

ARTICLE INFO

Article history:
Accepted 12 November 2016
Available online 24 November 2016

Keywords:
Generalized epilepsy
TMS–EEG
Paired-pulse stimulation
Diagnostic accuracy
Sensitivity
Specificity

HIGHLIGHTS

- A paired-pulse TMS–EEG protocol with multi-level data analysis is presented.
- The accuracy of TMS–EEG for differentiating genetic generalized epilepsy (GGE) patients from controls is high.
- TMS–EEG differentiates responders from non-responders to antiepileptic drugs in GGE.

ABSTRACT

Objectives: (A) To develop a TMS–EEG stimulation and data analysis protocol in genetic generalized epilepsy (GGE). (B) To investigate the diagnostic accuracy of TMS–EEG in GGE.
Methods: Pilot experiments resulted in the development and optimization of a paired-pulse TMS–EEG protocol at rest, during hyperventilation (HV), and post-HV combined with multi-level data analysis. This protocol was applied in 11 controls (C) and 25 GGE patients (P), further dichotomized into responders to antiepileptic drugs (R, $n = 13$) and non-responders (n-R, $n = 12$).Features ($n = 57$) extracted from TMS–EEG responses after multi-level analysis were given to a feature selection scheme and a Bayesian classifier, and the accuracy of assigning participants into the classes P-C and R-nR was computed.
Results: On the basis of the optimal feature subset, the cross-validated accuracy of TMS–EEG for the classification P-C was 0.86 at rest, 0.81 during HV and 0.92 at post-HV, whereas for R-nR the corresponding figures are 0.80, 0.78 and 0.65, respectively. Applying a fusion approach on all conditions resulted in an accuracy of 0.84 for the classification P-C and 0.76 for the classification R-nR.

Abbreviations: TMS–EEG, TMS combined with EEG; GGE, genetic generalized epilepsies; AEDs, antiepileptic drugs; HV, hyperventilation; EDs, epileptiform discharges; TMS, Transcranial Magnetic Stimulation; TEPs, TMS-evoked potentials; SI, stimulus intensity; MSO, maximum stimulator output; LEThr, lower epileptogenic threshold; UEThr, upper epileptogenic threshold; ISI, inter-stimulus interval; MDS, multi-dimensional scaling.

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http://dx.doi.org/10.1016/j.clinph.2016.11.013

Conclusion: TMS–EEG can be used for diagnostic purposes and for assessing the response to antiepileptic drugs.
Significance: TMS–EEG holds significant diagnostic potential in GGE.

1. Introduction

Epilepsy, the propensity for recurrent, unprovoked epileptic seizures, is one of the commonest serious neurological disorders. It is estimated that approximately 65 million people worldwide suffer from this disease, experiencing significant negative consequences on their physical and mental health, education, ability to work and their overall quality of life (Moshé et al., 2015).

Scalp EEG is the principal laboratory diagnostic test for epilepsy, but suffers from significant limitations. First, it has a fairly low sensitivity, so that a significant proportion of patients (20–45%) remain undiagnosed, leading to delayed treatment (Pillai and Sperling, 2006). Second, it does not predict with sufficient precision who will suffer from recurrent seizures and it cannot be used efficiently as a biomarker for personalized patient management. This may result in unnecessary treatment of those who will remain seizure-free without medication, but also in withdrawal of treatment in those who are bound to suffer further seizures. Finally, EEG does not predict reliably the most effective and well-tolerated pharmaceutical or neuromodulatory interventions. It is clear that a novel biomarker with improved diagnostic and predictive yield, compared to scalp EEG alone, is highly desirable.

In recent years, Transcranial Magnetic Stimulation (TMS) emerged as a novel biomarker with numerous applications in the field of epilepsy (Kimiskidis et al., 2014). Pivotal studies in newly diagnosed and refractory epilepsy suggest that TMS provides evidence of cortical hyperexcitability in a syndrome-specific pattern and may serve as an early predictor of pharmacoresistance in individual patients (Badawy et al., 2007, 2010, 2013). On the other hand, there are limitations to the type of information that can be derived from these studies because they employ the method of TMS–EMG in which responses are recorded exclusively from muscles and stimulation is performed over the primary motor cortex. It is easily conceivable that for the investigation of a disease operating at the cortical level, such as epilepsy, recordings from the cerebral cortex and stimulation over the entire cortical mantle would be far more informative.

The advent of TMS combined with EEG (TMS–EEG) opened up new avenues for the investigation of epilepsy allowing, for the first time in a noninvasive manner, the recording and mapping of neuronal responses induced by TMS at the cortical level, as well as the investigation and modulation of brain connectivity (Ilmoniemi and Kičić, 2010). Recent studies suggest that TMS may result in the induction (Valentin et al., 2008; Kimiskidis et al., 2013, 2015), but also modulation of ictal and interictal epileptiform discharges (EDs) and therefore has significant diagnostic, prognostic and possibly therapeutic potential (Rotenberg, 2010;Kimiskidis, 2016).

Although TMS–EEG is a highly promising method in the field of epilepsy (Rotenberg, 2010), its clinical and research potential remain underutilized. There is a single diagnostic study of TMS–EEG in patients with focal epilepsy (Valentin et al., 2008), concluding that this novel method can reliably identify the epileptogenic zone and may significantly improve the diagnostic approach to epilepsy. No study has investigated the diagnostic potential of TMS–EEG in genetic generalized epilepsies (GGE) so far.

The present paper describes an exploratory TMS–EEG study in GGE with the following objectives. (A) To develop and optimize a TMS–EEG brain stimulation and data analysis protocol in patients with GGE. (B) To investigate the diagnostic accuracy of TMS–EEG in patients with GGE.

2. Methods

2.1. Study design

The study was designed as a phase II diagnostic accuracy study (Gluud and Gluud, 2005; Sackett and Haynes, 2002) aiming: (a) to compare TMS–EEG findings in patients with known disease (GGE) and healthy controls (cross-sectional phase IIa study), and (b) to investigate whether TMS–EEG results in the patient group are related to response to antiepileptic drug (AEDs) treatment (delayed type cross-sectional phase IIb study (Knottnerus and Muris, 2003)). To the latter end, the patient group was dichotomized into a *responder to AEDs subgroup* (patients remaining seizure-free for at least 12 months post-TMS–EEG examination), and a *non-responder to AEDs subgroup* (patients experiencing non-provoked seizures during the post-examination follow-up period) and TMS–EEG findings were compared between the two subgroups (STARD diagram provided in Fig 1).

The reference standard was the diagnosis of two experienced epileptologists who, on the basis of clinical and laboratory data, reached consensus regarding the assignment of a subject in the patient or healthy control group (phase IIa study) and the designation of responder/non-responder status in the patient group (phase IIb study). It should be noted that the epileptologists determining subject status were not involved in the execution of the index test or data analysis. Routine scalp EEG was not employed by itself as a reference standard, due to well-established limitations regarding sensitivity (Krumholz et al., 2007; Valentin et al., 2008).

Sample size calculations were based on the only currently available evidence regarding the diagnostic accuracy of TMS–EEG (Valentin et al., 2008). On the basis of these data, it was estimated that a sample size of 23 patients and 11 controls would provide a sensitivity of 0.91 (minimum sensitivity of 0.65 and minimum specificity of 0.65), with an alpha = 0.05 and beta = 0.10.

2.2. Subjects

Study participants gave written informed consent for the procedures, which were approved by an institutional review board, and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

The study population included a cohort of 25 patients with GGE (11 females; median age 28 years, range 18–43), slightly exceeding the estimated sample size so as to account for lost-to-follow up cases, as well as an age-matched group of 11 healthy controls (6 females, median age 26 years, range 19–47).

The patient group comprised consecutive adult patients with GGE screened and referred from a tertiary Outpatient Epilepsy clinic of a University Hospital on the basis of the following *inclusion criteria*: (a) they passed the TASS questionnaire (Keel et al., 2001), save for the epilepsy related questions, and (b) they had both clinical and EEG features consistent with GGE. All patients had suffered at least two generalized seizures and were started on AEDs prior to study enrollment. *Exclusion criteria* included the presence of CNS disorders other than epilepsy on history or examination, comorbid conditions, EEG evidence of focal abnormalities, slow spike and wave discharges or triphasic patterns, use of centrally acting drugs other than AEDs and history of current or past alcohol or recre-