Clinical Neurophysiology 130 (2019) 791–792

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Editorial

The new era of TMS-EEG: Moving towards the clinical practice

See Article, pages 802–844

After its introduction by the seminal works of Cracco et al. (1989) and Ilmoniemi et al. (1997), recording of TMS evoked brain responses by EEG is increasingly gaining consideration as a powerful tool to investigate key physiological aspects of neuronal activity in the human cortex.

While, in the past, this technique was extremely challenging and its use was constrained to a few experimental laboratories, the advent of novel advanced amplifiers with high sampling rates and the development of TMS-compatible EEG electrodes that minimized the TMS-induced artifacts has made the spread of this fascinating method possible for studying brain activity at numerous clinical research centers around the world.

In this issue of *Clinical Neurophysiology*, a panel of experts in the use of TMS-EEG provide an extensive overview on the recent advances, highlighting the clinical utility of TMS-EEG (Tremblay et al., 2019). In particular, TMS-EEG is viewed as a reliable method for studying neurophysiological markers of healthy brain function, and the potential diagnostic and prognostic utility in clinical populations is discussed.

TMS-EEG provides a unique opportunity to evaluate at the same time various neurophysiological processes, including cortical reactivity, local excitation and inhibition, oscillatory activity, effective connectivity and neural plasticity.

One of the main advantages of using TMS-EEG in clinical populations is the possibility to assess simultaneously different neurophysiological properties of the cortical area examined. For instance, the TMS-evoked potential (TEP), is a complex waveform time-locked to the TMS pulse that can be recorded starting from a few milliseconds after stimulation, and characterized by several peaks lasting up to 200 ms. TEPs waveforms are different when evoked over different areas, such as the primary motor cortex, the dorsolateral prefrontal cortex or the posterior parietal cortex, thus providing specific information on local neural activity. At the same time, TMS-induced effects may be evaluated on cortical oscillations, assessing ongoing changes of brain rhythms (Thut and Miniussi, 2009), likely involving synchronous thalamocortical circuits activated by TMS. In addition, the TMS pulse can probe the propagation of the cortical signal in time and space across interconnected brain regions (Bergmann et al., 2016). This permits investigation of brain networks involved in different cognitive processes and brain states, as well as the reorganization of networks in clinical populations. Indeed, when paired-pulse TMS is applied over non-motor areas, such as the dorsolateral prefrontal cortex, it is also possible to assess the integrity of local intracortical circuits, likely involving GABAergic activity (Farzan et al., 2010). Finally, it is possible to investigate plasticity within specific cortical circuits, for instance by applying repeatedly magnetic stimuli over two interconnected regions and measuring the after-effects of this paired associative stimulation (Koch et al., 2013; Casula et al., 2016).

Clearly, from the clinical point of view, such abundance of information can help to characterize the functional abnormalities of certain brain areas in a given pathology. Therefore, TMS-EEG can become useful for differential diagnosis, to predict the outcome and the progression of a particular disease and, eventually, to verify the response to drug treatment, or to neuromodulation protocols.

As a consequence, TMS–EEG has been recently tested in a wide spectrum of psychiatric and neurological disorders, including schizophrenia, major depression, bipolar disorder, addiction, autism, dementia, stroke, epilepsy, and disorders of consciousness (Tremblay et al., 2019).

For instance, in mood disorders, TMS–EEG neurophysiological measures have been used to predict remission following therapy (Sun et al., 2016) and to monitor the effects of non-pharmacological therapies such as ECT (Casarotto et al., 2013) and repetitive TMS (Pellicciari et al., 2017).

In patients with stroke, TMS–EEG has been put forward as a novel biomarker of response to therapy (Koch et al., 2018) and as a novel neurophysiological index of cortical reorganization after stroke (Pellicciari et al., 2018). Similarly, TMS–EEG has been identified as a reliable neurobiological marker in patients with disorders of consciousness (Casarotto et al., 2016). These are just a few examples of the growing interest in TMS-EEG in clinical practice.

Despite this general enthusiasm, there are still several question marks that remain without a clear answer. Although artifact correction has been implemented, there is still uncertainty on the actual physiological value of the early components of TEP. Moreover, there are relevant confounding factors due to the fact that each TMS pulse produces a loud clicking noise (100–120 dB) that generates an auditory-evoked potential, potentially contaminating the underlying TMS-evoked activity. In addition, the TMS pulse can induce unwanted somatosensory-evoked potentials (Conde et al., 2018) that could contribute to the signal. Post-processing of the EEG signal is also an important step in the data analysis that is

https://doi.org/10.1016/j.clinph.2019.02.004

potentially biased by the lack of a gold standard approach. Artifacts can be removed using the application of blind source separation tools, such as independent component analysis (ICA) or principal components analysis (PCA). Open-source analysis approaches for TMS–EEG processing have been recently developed in the attempt to standardize TMS–EEG analysis procedures, but still need to be implemented and validated (Rogasch et al., 2017). Ultimately, in the near future TMS-EEG measurements would need to be validated across different centers in order to define the clinical reliability of these novel TMS–EEG neurophysiological markers of brain dysfunction.

The great gold rush has started, but we are just at the beginning of the TMS-EEG era in clinical practice.

Conflict of interest

I have no conflict of interest related to the present work.

References

Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: current approaches and future perspectives. Neuroimage 2016;140:4–19.

Casarotto S, Canali P, Rosanova M, Pigorini A, Fecchio M, Mariotti M, et al. Assessing the effects of electroconvulsive therapy on cortical excitability by means of transcranial magnetic stimulation and electroencephalography. Brain Topogr 2013;26:326–37.

Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol 2016;80:718–29.

Casula EP, Pellicciari MC, Picazio S, Caltagirone C, Koch G. Spike-timing-dependent plasticity in the human dorso-lateral prefrontal cortex. Neuroimage 2016;143:204–13.

Conde V, Tomasevic L, Akopian I, Stanek K, Guilherme B. The non-transcranial TMS-evoked potential is an inherent source of ambiguity in TMS-EEG studies. Neuroimage 2018;185:1–35.

Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB. Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr Clin Neurophysiol 1989;74:417–24.

Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, Daskalakis ZJ. Reliability of long interval cortical inhibition in healthy human subjects: a TMS-EEG study. J Neurophysiol 2010;104:1339–46.

Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 1997;8:3537–40.

Koch G, Ponzo V, Di Lorenzo F, Caltagirone C, Veniero D. Hebbian and anti-hebbian spike-timing-dependent plasticity of human cortico-cortical connections. J Neurosci 2013;33:9725–33.

Koch G, Bonnì S, Casula EP, Iosa M, Paolucci S, Pellicciari MC, et al. Effect of cerebellar stimulation on gait and balance recovery in patients with hemiparetic stroke: a randomized clinical trial. JAMA Neurol 2018. https://doi.org/10.1001/jamaneurol.2018.3639.

Pellicciari MC, Ponzo V, Caltagirone C, Koch G. Restored asymmetry of prefrontal cortical oscillatory activity after bilateral theta burst stimulation treatment in a patient with major depressive disorder: a TMS-EEG study. Brain Stimul 2017;10:147–9.

Pellicciari MC, Bonnì S, Ponzo V, Cinnera AM, Mancini M, Casula EP, et al. Dynamic reorganization of TMS-evoked activity in subcortical stroke patients. Neuroimage 2018;175:365–78.

Rogasch NC, Sullivan C, Thomson RH, Rose NS, Bailey NW, Fitzgerald PB, et al. Analysing concurrent transcranial magnetic stimulation and electroencephalographic data: a review and introduction to the open-source TESA software. Neuroimage 2017;147:934–51.

Sun Y, Farzan F, Mulsant BH, Rajji TK, Fitzgerald PB, Barr MS, et al. Indicators for remission of suicidal ideation following magnetic seizure therapy in patients with treatment-resistant depression. JAMA Psychiatry 2016;73:337–45.

Thut G, Miniussi C. New insights into rhythmic brain activity from TMS–EEG studies. Trends Cogn Sci 2009;13:182–9.

Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. Clin Neurophysiol 2019;130:802–44.

Giacomo Koch *

Non Invasive Brain Stimulation Unit/Department of Behavioral and Clinical Neurology, Santa Lucia Foundation IRCCS, Rome, Italy

Stroke Unit, Department of Neuroscience, Tor Vergata Policlinic, Rome, Italy

* *Address: Non Invasive Brain Stimulation Unit, Neurologia Clinica e Comportamentale, IRCCS Fondazione S. Lucia, Via Ardeatina, 306, 00179 Rome, Italy.*

E-mail address: g.koch@hsantalucia.it

Accepted 6 February 2019

Available online 20 February 2019