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A new neurometric dissection of the area-under-curve-associated jiggle of the motor evoked potential induced by transcranial magnetic stimulation

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HIGHLIGHTS

- The literature on the area under curve method is contradictory.
- The variability of the motor evoked potential is beyond pathological conditions.
- Novel indicators will improve the analysis of the area under curve of neural signals.

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ABSTRACT

Objective: The jiggle of the motor evoked potential (MEP) induced by transcranial magnetic stimulation (TMS) depends on a number of factors including the assessment of this stochastic signal by the method known as area under curve (AUC). We aim to ascertain the MEP findings assessed by the AUC method obtained from individuals affected by lesions at different levels of the neuroaxis.
Methods: We systematically search and critically appraise the scientific reports publishing on the MEP obtained from individuals with hypo- or hyperkinetic disorders of the neural system, and dissect the neurophysical assessment of the obtained data. To accomplish this, we used the instruments named to as *U-Pen Instrument for Neurometric Evaluation Uncommonly and Rarely Obtained from NeuroSignals 1.0* (UPINEURON 1.0), and the *Quality of Assessment Statistics Index* (*QuASI*).
Results: The MEP differences found by the classical peak-to-peak method decreased or disappeared when the AUC was used. The opposite was also true (Kappa = < 0.00). The internal consistency of the UPINEURON was 0.88. The mean of the UPINEURON 1.0 indicator was 34.8 (range = 16–50), and the mean of the *QuASI* scores was 56.5 (range 30–80). Spearman correlation between UPINEURON 1.0 and *QuASI* was 0.513.
Conclusions: The MEP jiggle found in individuals with disordered neural function is not a "minor" factor; it is beyond the underlying neural condition, sample size, type of coils, and number of trials, among other variables. The use of the novel indicators introduced in this investigation will help to improve the analysis of the AUC of neural signals. They may also lead to the reconsideration of current practices.
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1. Introduction

Muscle responses generated by painless transcranial magnetic stimulation (TMS) are referred to as motor evoked potentials (MEPs). The latency and amplitude of the recorded MEP are the parameters most commonly investigated [1]. The latency of a neural response is the

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time elapsing between onset of the stimulus and the initial deflection from baseline [2]. The latency of the MEP largely depends on the state of the conducting neural fibers [1]. The amplitude of a neural response can be assessed from the most negative peak to the most positive peak of the recorded response. Such approach is referred to as the peak-to-peak (PTP) method. The amplitude of the MEP reflects the activity of both upper and lower motor neuron and the integrity of the neural pathways from the brain to the muscles [1,3]. The amplitude of the recorded signal is a function of the frequency and temporal coherence of the neural activity that controls that specific muscle [3]. Despite the usefulness of the abovementioned parameters in studying the function and dysfunction of the neural pathways at rest and during activity [4–8], the variability of the MEP elicited by TMS or the "M-jiggle" [9–11], defined as the variation of the size of the evoked potential from one stimulus to the next, has precluded its wider use in diverse settings.

The M-jiggle depends on a number of factors such as age, gross anatomy, genetic factors, personality, peripheral and central deafferentation, gender, and menstrual cycle [1,10–13], among others. Type and orientation of the coil, stimuli strength, bioelectronics of the magnetic pulse, number of stimuli, neural threshold, and level of muscle activation influence the MEP responses as well [1,14–17].

Another factor not properly addressed yet in the study of the M-jiggle concerns the assessment of this evoked stochastic signal by the method known as area under curve (AUC), which unveils key aspects of the neural activity. In mathematical terms, the AUC is defined as the limit and summation of the net area between a function and the *X*-axis [18]. From a neurobiological point of view, the AUC of the neural responses generated within the motor system is a function of the total motoneuron activity over a particular temporal domain [3]. However, in most cases the area of the MEP is measured without a clear rationale, in a rather arbitrary way, and with an incomplete mathematical analysis. For example, the assessment of the AUC of the MEP from the disordered neural transmission has not considered the amount of energy contained within the MEP signal itself [19,20]. In other cases, the AUC of the MEP has been measured "including small intervals before and after the MEP," without explaining what the "small intervals" meant; further, it was stated that such criteria "does not affect essentially the values of its area" [21].

These aforementioned shortcomings have resulted in contradictory and, at times, disparate conclusions. Such flaws have fueled the claims that the AUC does not accurately reflect the net motor output from brain to anterior horn cells somatotopically organized in the spinal cord [22–24] and have fed the concept that the "MEP amplitude and to lesser extent area, do not accurately reflect the net motor output" [24,25]. Having said this, Bühler et al. [26] considered that "… in practice, measurement of MEP area may be misleading, because it poorly reflects the integrity of the corticospinal path," while Kiers et al. [23] stated that the significance of changes in MEP area should be regarded with caution, in clinical and practical grounds, at least until better approaches consistently demonstrate its practical and reliable usefulness.

With this view, we hypothesize that the analysis of the MEP data published in peer-review journals, obtained from individuals having unbalanced neural activity, will uncover elements that may have precluded the use of the AUC as a reliable measure of the function of the human motor system. Owing the heterogeneity of the study populations, study designs, assessment of the AUC, and statistical tests, pooled analysis precluded us performing meta-analysis and the like. Thus, we systematically search and critically appraise the scientific reports publishing on the MEP values assessed by the AUC method obtained from deranged motor systems in the light of the following three main aims. First, to ascertain the MEP findings assessed by the AUC method obtained from individuals affected by lesions at different levels of the neuroaxis. To accomplish this aim, synthesis, analysis, and consistency of the reported studies were carried out. Second, to investigate the assessment, quantification, analysis, and interpretation done on the AUC of the MEP signals. To accomplish this aim we introduce a novel scale named as the *U-Pen Instrument for Neurometric Evaluation Uncommonly and Rarely Obtained from NeuroSignals 1.0* (UPINEURON 1.0). This scale was constructed following relevant methodological details reported in the publications done during the past on validated variables used to measure neural signals. Third, since statistical procedures are a key step to accurately report the obtained data, we also aim to analyze the adequateness of the statistical reasoning and data presented by the selected studies. To accomplish this aim we created the *Quality of Assessment Statistics Index* (*QuASI*) score, following validated criteria defined for the appropriateness of the use of descriptive or inferential methods, among other characteristics, and applied it to the statistical information provided in the reports. The results of this study will provide the foundations to define future research that may disentangle the variability of the AUC found in the assessment of the neural activity recorded in health or disease, and may lead to reconsideration of current practices.

2. Material and methods

2.1. Study selection

Several steps were taken to obtain all possible data relevant to the assessment of the MEP by the AUC method in subjects with neural disorders and their control groups. First, we performed an exhaustive computerized search in the PubMed/Medline database for articles reporting findings on neural disorders that were published from January 1985 until June 2013. Second, we used combinations of the following terms identified from each article: "TMS" AND "transcranial magnetic stimulation" AND "MEP" AND "motor evoked potential" AND "single pulse" AND "paired-pulse" AND "pyramidal tract" AND "corticospinal pathway" AND "AUC" AND "area under curve." We tried to be as sensitive as possible within the bounds of feasibility because of the difficulties in finding the appropriate keywords and the different types of assessment of the MEP. Third, reference lists were also searched by hand, and the relevant articles were identified and reviewed. Fourth, when the same groups of subjects were tested and the data obtained were published in separate papers, we contacted the corresponding author of those papers by e-mail to clarify the total number of people investigated (e.g., Vacherot et al., personal communication). No language restrictions were applied.

2.1.1. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) Studies had to describe the method employed to apply single or paired-pulse TMS, 2) the site of stimulation in the scalp had to be in the brain motor cortex, 3) the recording of the muscle responses had to be informed, 4) the AUC had to be reported in the section of methods and/or use AUC data in the section of results, 5) the neural responses obtained when subjects were tested while their target muscles were relaxed and/or under voluntary contraction were appraised, and 6) statistical analysis had to be reported.

Papers that published findings obtained by using the AUC of sigmoid curves constructed with MEP values, measurement of neural responses by parameters other than those investigated here (e.g., silent period), or data obtained with the triple stimulation technique that looks for compensating motoneuron desynchronization and MEP phase cancelation [26] were not included in this investigation. Animal studies, abstracts, editorials and review articles were not searched.

2.1.2. Study acceptance, data extraction and synthesis

Study acceptance and data extraction were completed by FEL-S and checked by CVR-S; disagreements were resolved through discussion or referral to JSL-A, DSL-A, RS and DGP. The following information was identified from each article: year of publication, name of the journal, IF of the journal where the research was published, name of the authors, country where the study was done, type of study, name of the neural

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