Clinical Neurophysiology 120 (2009) 987–993

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

An initial transient-state and reliable measures of corticospinal excitability in TMS studies

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ARTICLE INFO

Article history:
Accepted 17 February 2009
Available online 8 April 2009

Keywords:
Transcranial magnetic stimulation
Human motor cortex
Cortical excitability
Muscle evoked potential
Navigated brain stimulation
Variability

ABSTRACT

Objective: The objective of this study was to determine if an initial transient state influences the acquisition of reliable estimates of corticospinal excitability in transcranial magnetic stimulation (TMS) studies. Whereas muscle evoked potential (MEP) amplitudes are an important index of cortical excitability, these are severely limited by sweep-to-sweep variability. Interesting in this context is the experimental observation that the first MEP amplitudes might be much larger than subsequent responses [Brasil-Neto JP, Cohen LG, Hallet M. Central fatigue as revealed by postexercise decrement of motor evoked potentials. Muscle Nerve 1994;17:713–9]. This led to the hypothesis that an initial transient-state of increased excitability affects MEP amplitude derived estimates of corticospinal excitability.
Methods: To address this issue we acquired repeated measures of single pulse MEP amplitudes over the primary motor cortex with and without navigated brain stimulation (NBS) and with various TMS-coils. Importantly, NBS allows for the sweep-to-sweep differentiation of physical and physiological variability.
Results: We found a significant decline in estimates of corticospinal excitability and a transition from log-Normal to Normal distributed state, after which reliable measures (British Standards Institute) could be acquired.
Conclusions: We argue that an initial transient state of physiological origin influences measures of corticospinal excitability.
Significance: This has important implications for investigations of cortical excitability. For example, it could reduce variability over studies and within small group comparisons.

1. Introduction

Muscle evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS) are well established electrophysiological parameters in clinical neurophysiology and research. They offer a unique non-invasive measure to characterize neurocortical function, for example in clinical settings and neuroplasticity. Whereas recordings of MEP onset latency are relatively stable, amplitude measures have a high variability (Kiers et al., 1993). This impedes the acquisition of reliable measures of corticospinal excitability (Wassermann, 2002; Awiszus and Feistner, 2007). In consequence, it has been argued that e.g. neither the motor threshold nor paired-pulse measures might be useful for comparisons in individual subjects or between groups with minor differences (Wassermann, 2002). Thus, a better understanding of the origin of this variability could be valuable.

It is a common observation that the first MEP amplitudes can be much larger than subsequent responses both in clinical as well as experimental settings in muscles at rest (Brasil-Neto et al., 1994). Be this the case, then the cause of this observation as well as its relationship to MEP amplitude size and distribution has not been systematically investigated. This could help explain MEP variability. Further, it might help clarify a controversy about MEP distribution (Kiers et al., 1993; Nielsen, 1996) that influences statistical testing (for discussion see e.g. Swayne et al., 2008).

Corticospinal excitability is known to be related to physiological parameters such as prestimulus muscle contraction (Kiers et al., 1993; Darling et al., 2006), arousal (Amassian et al., 1989), attention (Amassian et al., 1989; Mars et al., 2007), afferent feedback mechanisms (Nielsen, 1996) and spinal desynchronization (Magistris et al., 1999). Further support for the notion that these variations are of physiological origin is also found in the fact that MEP measures are correlated over siblings (Wassermann, 2002), independent muscles (Ellaway et al., 1998; Kiers et al., 1993) and sessions (Nielsen, 1996). Conversely, it is independent of cardiac

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1388-2457/$36.00
doi:10.1016/j.clinph.2009.02.164

and respiratory cycles (Amassian et al., 1989) and mental arithmetic (Kiers et al., 1993).

Corticospinal excitability is also related to physical parameters, such as coil orientation and optimal scalp location (Kiers et al., 1993; Devanne et al., 1997). On the other hand, physical and physiological variability have not previously been differentiated on a sweep-to-sweep basis. Navigated brain stimulation (NBS) with its optical tracking system can monitor individual physical parameters on a sweep-to-sweep basis with sub-millimeter precision. The parameters include: (i) coil location, (ii) coil orientation and (iii) coil tilt in reference to the scalp. As well as (iv) estimates of intracortical stimulus location and (v) intracortical stimulus strength. This allows for a precise differentiation of physical from physiological variability.

In summary, the general aim is to understand the baseline dynamics and to acquire reliable estimates of corticospinal excitability. The hypotheses are that (i) there is an initial transient-state of heightened excitability and (ii) this affects MEP amplitude derived estimates of baseline excitability. To address these questions we acquired repeated measures of single-pulse MEP amplitudes over the primary motor cortex with and without NBS and with various coils.

2. Materials and methods

2.1. Ethical approval and participants

Twenty healthy non-medicated TMS-naïve volunteers (5 female, 15 male; average age 26 ± 5 years) were recruited. Three of these subjects were discarded from the analysis. Of the remaining 17 subjects 1 subject was left-handed and 16 were right-handed. These subjects were randomly assigned to the NBS or non-NBS protocols. All subjects gave informed consent before participating in the experiment, which was approved by the local Ethics Committee (Charité Universitätsmedizin Berlin, Germany) and conformed to the standards set by the Declaration of Helsinki. Due to repeated sessions on individual subjects we acquired a total of 31 sessions from 17 subjects. Eighteen monophasic sessions were without NBS (non-NBS, or conventional). Thirteen sessions were with NBS, of which 6 were with a monophasic and 7 were with biphasic stimulation.

2.2. Data acquisition

2.2.1. Navigated brain stimulation

TMS was performed by an experienced experimenter with a Magstim 200 monopulse magnetic stimulator (Magstim Co., Whiteland, Dyfed, UK) or an Exima biphasic TMS (Nexstim, Helsinki, Finland) with a figure-of-eight coil (70/50 mm mean wing diameter, respectively). Both stimulators were guided by the personal computer based Exima software system (Nexstim, Helsinki, Finland). This system utilizes optical tracking to record the physical parameters with a precision of below 0.5 mm, as well as a spherical model (Sarvas, 1987; Tarkiainen et al., 2003), an individual structural MRI image, an individual X-ray derived coil model and the physical parameters to estimate the intracortical stimulation location and strength. These were superimposed in color-code on the subjects' structural Magnetic Resonance Image (GE 3T Signa LX, MPRAGE, 8 channel phased array, 1 mm^3 spatial resolution, NEX 3). In combination with an adaptive fixation system of the TMS-coil (MagicArm, Manfrotto Bassano Del Grappa, Italy) physical variations of the coil were kept below 2 mm. Thus, simultaneous pulse-by-pulse measurements of small variations of coil location, orientation and tilt as well as estimates of target site, location and electric field strength could be compared to MEP amplitude variations collected with electromyography (EMG, eXimia Nexstim, Helsinki, Finland).

2.2.2. Conventional stimulation

TMS was performed by an experienced experimenter with the Magstim 200 monopulse magnetic stimulator and a figure-of-eight coil.

2.2.3. Electrophysiological measures

The stimulation target i.e. the "hot-spot" was defined for both methods by maximal MEPs over the first dorsal interosseus (FDI) muscle for minimal suprathreshold stimulation larger than 50 μV, during systematic variation of coil location, orientation and tilt over intracortical anatomical landmarks of the dominant primary motor cortex. For NBS, the intracortical landmarks were defined by the "hand-knob" (Yousry et al., 1997). For conventional stimulation, the cranial landmarks were identified 5 cm lateral to the intersection line from the vertex to the external auditory meatus on the contralateral hemisphere to the dominant hand. The resting motor threshold (RMT) was defined statistically with 15 MEPs and an efficient maximum-likelihood algorithm (Awiszus and Feistner, 2007). Subsequent stimulation was at 110% RMT. The electromyographic data was sampled at 5 kHz, amplified and band-pass filtered (20 Hz–4 kHz) by CED 1902 amplifiers through a CED 1401 power laboratory interface using Spike 2 software (Cambridge Electronic Design, Cambridge, UK). The MEP was defined as the peak-to-peak amplitude of belly-tendon surface recordings from the FDI representation of the dominant hemisphere.

2.3. Experimental implementation

The subjects were seated in a comfortable reclining chair. They were instructed to relax and visually fixate on a fixation cross. Surface EMG-electrodes were attached to the dominant FDI. For NBS, the individual head and structural MRI were co-registered via scalp landmarks (<3 mm root mean square). The hot-spot and RMT were identified as described above. Subsequently, subjects received 100 single TMS pulses applied to the FDI hot-spot with an interstimulus interval of 3 s. One subject received only 92 stimuli due to coil heating.

2.4. Data analysis

2.4.1. Signal processing and statistics

Signal processing was carried out with the software package MATLAB 7.0 (Mathworks, Gatwick, USA). The MEP amplitudes were defined by peak-to-peak measurements. The consecutive mean (CM) and consecutive standard deviation (CSTD) were quantified as the iterative mean over consecutive measures. Thus, the first CM value is identical to the mean of the first MEP amplitude; the 20th CM is the mean of the first twenty MEP amplitudes. Thus, the 10th and 20th value depict the mean that would have been estimated if 10 or 20 MEPs had been acquired, respectively. The CSTD-M parameter combines both parameters by CSTD minus CM. Correlation coefficient analysis tested for linear dependency between each of the physical parameter and MEP-amplitudes on a vector by vector basis. Tests of Normal distribution utilized the Lilliefor modification of the Kolmogorov-Smirnov test ("lillietest", Conover, 1980) on data normalized in terms of percent maximum MEP-amplitude. A steady-state was understood to be attained when it was clear that a recently observed behavior of a system would be maintained into the future, i.e. when the probabilities that various different states will be repeated remains constant. The state between steady-states was defined as a transient-state. Statistical tests in the steady-state were parametric, tests in the

transient-state or on the transition between states were non-parametric. The window size for sliding mean and median measures was 10 events.

Consecutive measures, tests for normal distribution and reliable definition of transition points were applied to group data. To validate group results, we also investigated these analyses on a subject-by-subject basis. To account for systematic effects, we applied analyses to: (a) all sessions, (b) NBS sessions acquired with biphasic and monophasic, (c) NBS sessions acquired only with a biphasic stimulator, and (d) conventional monophasic sessions acquired without NBS.

2.4.2. Consecutive measures of transition

Cut-off values between two different cortical states were investigated in *z*-transformed linearly detrended data. Consecutive measures of *z*-transformed data must terminate with a mean of 0 and a standard deviation of 1. A mean of 0 and a standard deviation of 1 can be seen as the equivalent of a steady-state; in this case our cut-off was a value of 0 or 1 with a 5% error. For example, the *z*-transformed MEP amplitudes in a steady-state will fluctuate around zero. Conversely, if the first three MEP responses were larger than the session mean, then subsequent values will deviate below and only gradually return to the 0 mean baseline. For single subject analyses, in line with the best fit on the group data, a third-degree polynomial fit was utilized for cut-off identification.

2.4.3. Repeatability measures of transition

Since the data beyond the 20th event followed Normal distribution, well defined conservative measures of repeatability (RPT, Bland and Altman, 1986) could be utilized in a post-hoc analysis. The mean and two standard deviations of the mean difference between MEP-amplitudes were defined in the Normally distributed data. The transition point was found when events became reliably repeatable, i.e., when 95% of the subsequent events were within two standard deviations.

3. Results

3.1. Physical parameters in NBS

Three subjects were discarded from further analysis. Two of these subjects had a translational displacement of the coil on the scalp away from the hot-spot that was larger than 2 mm (2.63 and 4.39 mm). Their mean MEPs were 0.19 and 0.15 mV, respectively. A third subject's mean deviation was < 2 mm, but post-hoc analysis due to a mean MEP of 0.15 showed a strategically unfavorable translational displacement from the precentral to the postcentral gyrus. The group average dislocation was 1 ± 0.48 mm. Physical variations of coil orientation and coil tilt never exceeded 0.1°. A cross correlation analysis between all the individual physical parameters and the sweep-to-sweep MEP amplitude showed no correlation ($r < 0.1$) for any of the parameters.

3.2. Data distribution and transition points

3.2.1. Data distribution

The group consecutive mean over all subjects showed a strong exponential decline (see Fig. 1a). This decline was log-Normal distributed (lillietest, $p < 0.0001$). Subsequently, the data was Normally distributed (lillietest, $p = 0.069$ [>20th event], 0.042 [>21st event], 0.025 [>22nd event].

3.2.2. Transition points

Transition points in group average data were found after 14, 18 and 19 events for CSTD-M, RPT and CM, respectively. Session-by-session analyses showed transition points at 20 (+1/−1),[1] 19 (+2/−5) and 20 (+1/−2) events for CSTD-M, RPT and CM, respectively. The results from the session-by-session analyses are depicted as horizontal box plots superimposed on group results (Fig. 1b and c). This allows for a direct comparison between single subject median-derived and group mean-derived results. Discarding the transient-state events led to a significant change in estimates of corticospinal excitability in group measures as well as in 27 of 31 sessions (Wilcoxon rank sum test, $p < 0.01$). The mean MEP amplitude in the steady-state was 660 ±430 μV for non-NBS and 530 ± 160 μV for NBS sessions.

3.3. Data stratification

The data was stratified for stimulation with NBS, with and without a biphasic stimulator and conventional stimulation (see Fig. 2). Single subject transition points for non-NBS data were 20 (+1/−2), 20 (+0.5/−1), 20 (+2/−5), for NBS data 20 (+0.5/−2), 21 (+0.5/−1), 18 (+2/−4), and for NBS biphasic data 20 (+0/−2), 21 (+1/−1), 17.5 (+2.5/−3). There was no statistical difference between methods (ANOVA, F 0.53, df 2, $p > 0.59$), indicating that the initial transient-state is not due to stimulator type or navigated versus non-navigated stimulation. A second control compared consecutive means with simple and sliding mean measures (see Fig. 3). Single subject transition points for simple and sliding mean measures in NBS data were 14 (+2.75/−4) and 13 (+5.5/−5.75), which was significantly less than for consecutive measures (ANOVA, F 4.48, df 2, $p < 0.05$). The group data distribution has log-Normal before and Normal distribution after the transition points (lillietest, $p < 0.05$).

4. Discussion

With repeated TMS probes, NBS and consecutive measures of mean MEPs, we find a log-Normally distributed initial-transient-state of corticospinal excitability that is clearly distinguishable from a normally distributed steady-state. We argue that these states are of physiological origin and discuss possible implications of MEP distribution and MEP amplitude estimates for future studies of corticospinal excitability.

4.1. Physiological and physical correlates of an initial-transient-state

In all but three of the subjects, physical variations were kept below 2 mm root-mean-square (RMS) with NBS and a stabilized adaptive mounting system. Further, the cross correlation of physical and physiological parameters had a maximum value of 0.1 in any given subject for any given parameter. These results show that the initial transient-state is not due to physical parameters. This is in line with and extends on previous research that "clamped" the stimulator to the head and found that physical variations do not affect MEP amplitude variability (Ellaway et al., 1998). Furthermore, we did not find that the use of NBS or different coil types affected these parameters.

If the initial-state is not due to physical parameters, then what is the physiological correlate? Here, on account of the temporal dynamics, a transient cortical or contextual effect seems most likely. This notion is also supported by the fact that the initial transient state was found after multiple stimuli applied to map the motor cortex and define the FDI-hotspot. Amongst others, stimulus expectancy, motor imagery, motor preparation, attention and negative emotional context are known to facilitate corticospinal excitability (Fadiga et al., 1995; Oliveri et al., 2003; Amassian et al., 1989; Rossi and Rossini, 2004; Mars et al., 2007). Yet, these

[1] The numbers in brackets depict the upper and lower quartile.

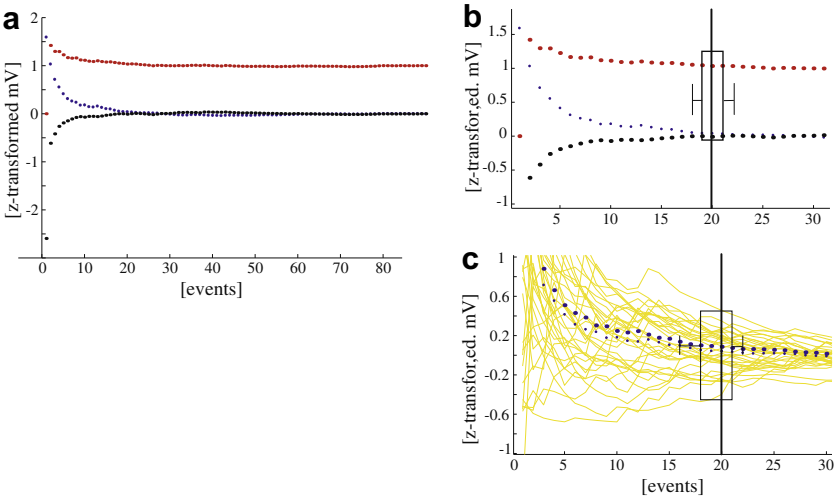

Fig. 1. Estimates of corticospinal excitability depend on the number of stimuli. The transition between a log-Normal distributed transient-initial-state and a steady-state can be defined in *z*-transformed data in terms of CM and CSTD-M. The abscissa is given in terms of stimulus number and the ordinate in terms of *z*-transformed peak-to-peak amplitude in mV. In 1b and 1c the vertical black line is the median, the box sides depict the 25th percentile and the black lines the 75th percentile of the transition points found on a session-by-session analysis. The triangle depicts the transition point found for the respective method in group data. (a) Red dots represent the consecutive standard deviation, blue dots the CM and black dots the CSTD-M. (b) The CSTD-M transition point found in session-by-session analysis superimposed on group data results. (c) The CM transition point found in session-by-session analysis superimposed on group data results. Yellow lines depict the *z*-transformed consecutive mean for each individual subject. The large blue dots depict the standard error, the small dots the group consecutive mean values.

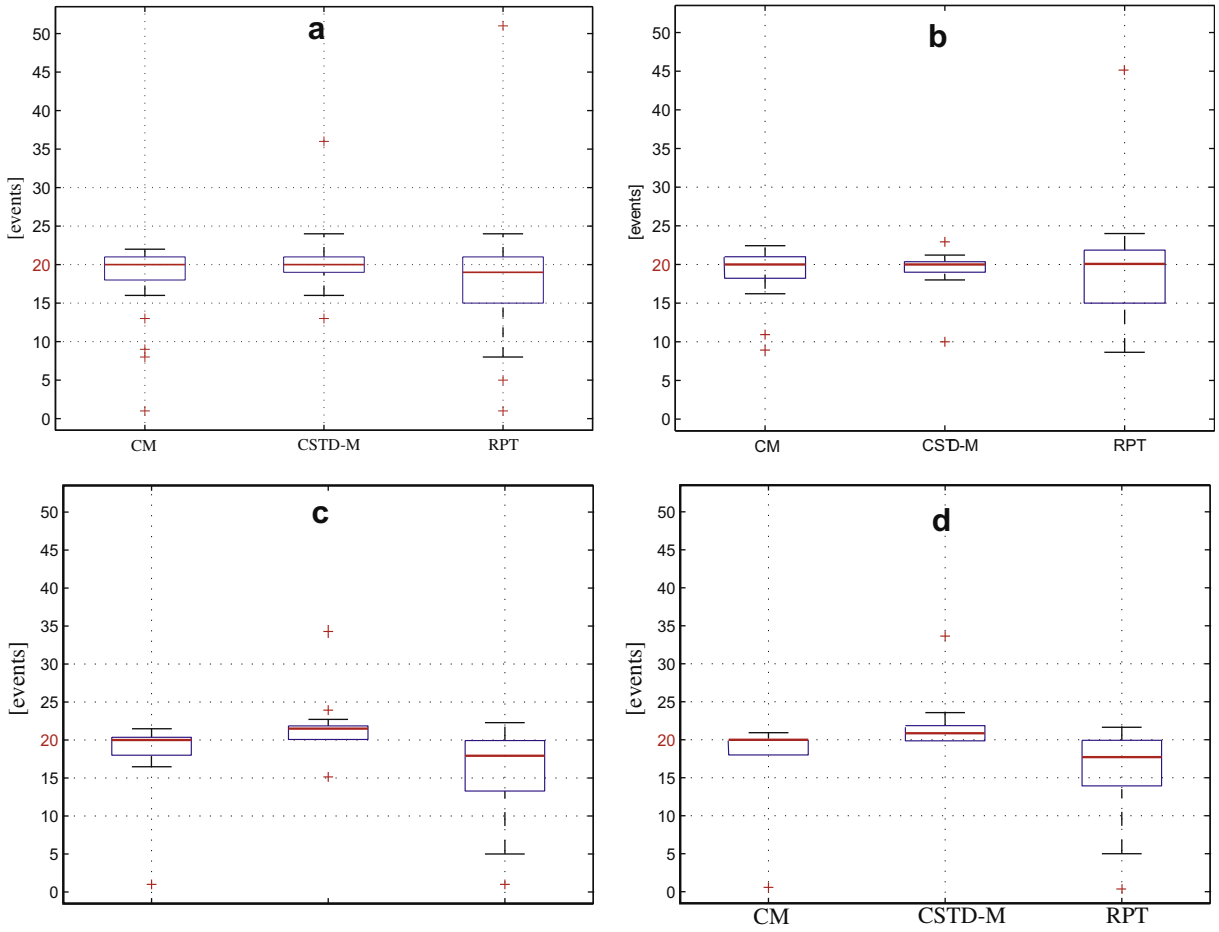

Fig. 2. Comparison of methods utilized to identify the transition between initial and steady-state. The three box plots depict CM, CSTD-M and RPT transition point measures derived from session-by-session analysis. The red line is the median, the box depicts the lower and upper 25th percentiles, the black lines the 75th percentiles, the red crosses are the outliers. The abscissa displays the number of events, the ordinate the number of events until state transition. (a) All data. (b) Data from non-NBS sessions. (c) Data from NBS sessions. (d) Data from NBS sessions with biphasic stimulation.

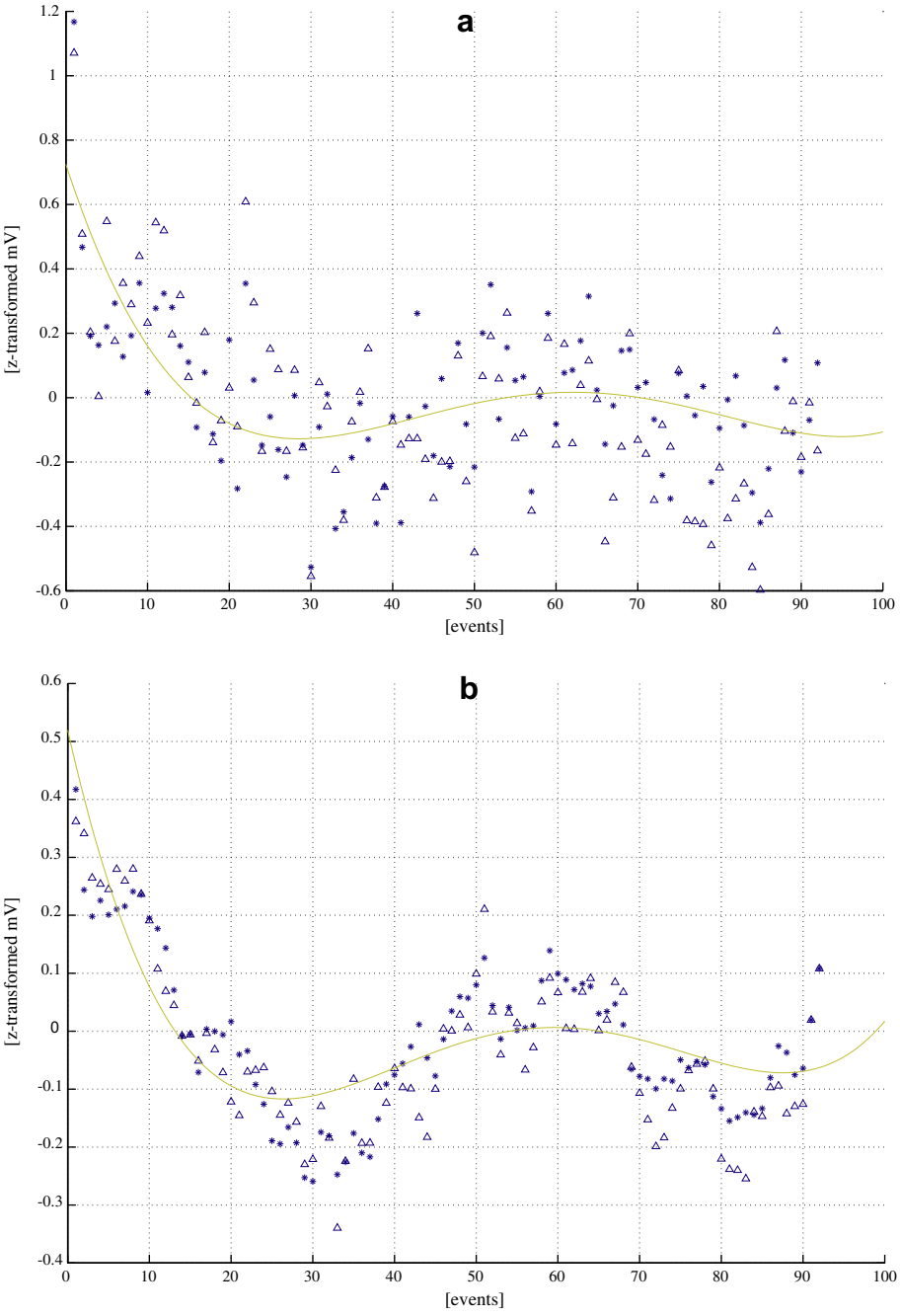

Fig. 3. Alternative methods to identify the duration of a transition state. Triangles depict median and circles mean estimates for (a) the average normalized single interindividual MEP amplitude or (b) values derived from a sliding window analysis. The fitted curve is the best fit to both median and mean values (4th degree polynomial fit).

investigations follow various experimental designs both with and without multiple randomized trials, vary in the number of TMS-probes applied, offer possibly conflicting results (Kiers et al., 1993; Mars et al., 2007) and were not designed to identify the origin of an initial transient state of heightened excitability.

4.2. MEP amplitudes

MEP variability has limited usefulness in single subjects or groups with minor differences (Magistris et al., 1999; Wassermann, 2002). It has been suggested that MEP amplitudes (Nielsen, 1996) as well as RMT and some dual-pulse protocols (Wassermann, 2002) are log-Normal distributed. Interestingly, the present results fit well with the previous findings of log-Normal distribution of MEP amplitudes in consideration of the acknowledged 12 event limitation in the study by Nielsen and colleagues. Here we show that the dynamics of MEP amplitudes follow a specific log-Normal temporal rule over as many as 20 stimuli. In contradistinction the subsequent steady-state data is normally distributed.

On a single-subject basis the differentiation between an "initial transient-state" and a "steady-state" can be difficult. In the present investigation we suggest three possible algorithms with highly consistent results on both group as well as single subject data. The major difference among the algorithms is found in the prerequisite of Normal distribution: (i) Consecutive measures are indifferent to distribution functions, but they are susceptible to outliers. Outliers

will protract transition identification and lead to conservative definitions of state transition. (ii) The measure of repeatability is less conservative, but it is not applicable to data with non-Normal distribution. (iii) Under the prerequisite of Normal distribution classic statistical measures of repeatability (British Standards Institute, Bland and Altman, 1986) can be applied to identify the transition between the two states. The results from all three methods were consistent over group as well as single subject analyses. We generally suggest that the first 20 MEPs should be excluded from further analysis, i.e. further analysis should utilize reliable measures beyond e.g. the 20th event. Conversely, post-hoc analyses of Normal distribution and measures of reliability on a session by session basis might allow for the inclusion of some of the previously excluded MEPs (see Fig. 2a, third box-plot outliers).

It should be noted that randomized conditions with multiple probes might be relatively immune to effects derived from an initial transient-state of corticospinal excitability. Further, experimental designs might compare MEPs between tasks or possibly cerebral hemispheres. In contradistinction, in this study and in line with baseline estimates of corticospinal excitability and physiological studies, we conducted the MEP measurements at rest over the FDI-hotspot. Finally, alternative approaches might utilize sliding mean or median measures or the average *z*-transformed mean or median estimate over all subjects (see Fig. 3). We chose a consecutive measure as it depicts the estimate as a function of events. Thus, it supplies both a specific transition event as a function of acquired events and also often allows for the simple comparison with estimates from previous or future studies. The weakness with this choice is the possibility of overestimation, e.g. the extended duration of an initial transient state possibly due only to two or three events. In comparison, sliding measures or estimates over all subjects are less or not susceptible to this overestimation. In contrast to consecutive measures, data-set variability or window size can bias these measures. In the present investigation simple and sliding measures suggest an initial transient state with significantly shorter duration of on average 12 to 13 events, yet with higher estimate variability. The relevance of these estimates is supported by the finding of log-Normal and Normal distribution before and after 12 or 13 events in group data, respectively. On the other hand reliable measures could not be found in 13 of the subjects for simple mean and in 6 of the subjects for sliding mean measures. This can be explained by the generic variability of these measures and supports the notion of estimating a measure with multiple probes. In consideration of these factors, simple and sliding measures might offer a valid alternative to identify the initial transition state prior to reliability analyses. The prerequisite for reliability analyses is the definition of permissible estimate variability, e.g. by two standard deviations of mean MEP amplitude estimates over 100 single events, or possibly theoretically.

4.3. Methodological considerations

Typical measures of the corticospinal state are the triple stimulation technique (Magistris et al., 1998), input-output curves (Devanne et al., 1997), mean MEPs (Fitzgerald et al., 2007), motor thresholds (Awiszus and Feistner, 2007), and measures of inhibition or facilitation (Kujirai et al., 1993; Ilic et al., 2002; Ferbert et al., 1992). These methods commonly utilize 10–20 stimuli per condition, possibly multiple times in randomized order (see e.g. Ilic et al., 2002). These measures have been found to correlate with both physiological and clinical measurements (see Talelli et al., 2006, for review). In the current study we argue that a conservative estimate would discard initial-transient state saturation stimuli. The results are in line with previous findings of log-Normal distribution and might explain the intra- and intersubject differences found when defining cortical states (Wassermann, 2002; Talelli et al., 2006) and statistical comparisons (see e.g., Swayne et al., 2008 for discussion). Although not formally investigated, our results also suggest a 27% reduction of MEP amplitude variance for data acquired with NBS as compared to non-NBS studies. On the other hand, interindividual comparisons on subjects receiving both treatments with comparable stimulation strength would be preferable.

5. Conclusions

We found a log-Normal distributed initial-transient-state preceding a steady-state of corticospinal excitability. These states are of physiological origin, i.e. not due to physical mechanisms. Estimates of corticospinal excitability as well as probabilistic statistics are affected by these states. Conservative estimates might need to discard about 20 first saturation trials from analyses. This should reduce the variability in future studies of corticospinal excitability. Correction for baseline dynamics could open important perspectives for the clinical acquisition of measures of cortical excitability, for example in epilepsy, unconscious states or post-lesional neuroplasticity.

Acknowledgements

We are grateful to Dr. L. Brumbaugh-Walter (University of Washington, St. Louis, Missouri, USA) for editing the manuscript.

Supported by the Bernstein Center for Computational Neuroscience Berlin (BCCN) and DFG Grant IR 48/1-1.

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