



Estimation of the resting motor threshold (RMT) in transcranial magnetic stimulation using relative-frequency and threshold-hunting methods in brain tumor patients

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Abstract

Background Application of transcranial magnetic stimulation is often based on the resting motor threshold. The aim of this study was to validate recent findings on the advantage of resting motor threshold estimation using adaptive threshold-hunting algorithms over the Rossini-Rothwell method in a clinical sample and healthy subjects.

Methods Resting motor thresholds in 115 patients with a brain tumor and 10 healthy subjects were assessed using the Rossini-Rothwell method and compared to an adaptive threshold-hunting algorithm. In healthy subjects, this measurement was repeated twice to capture test-retest reliability of both methods. Efficiency of both methods was assessed by comparing the number of pulses needed for resting motor threshold estimation.

Results There was no significant difference between the Rossini-Rothwell method and the adaptive threshold-hunting algorithm in patients and healthy controls with limits of agreement between ± 12 V/m. There was a strong intraclass correlation and both methods showed a good test-retest reliability. However, the adaptive threshold-hunting algorithm was significantly faster.

Conclusions The adaptive threshold-hunting algorithm was more efficient in assessing the resting motor threshold, while reaching comparable results as the Rossini-Rothwell method. Thus, our results support the advantage of adaptive threshold-hunting algorithms to determine the resting motor threshold also in a clinical sample.

Keywords Transcranial magnetic stimulation (TMS) · Resting motor threshold (RMT) · Rossini-Rothwell method · Adaptive threshold-hunting · Maximum likelihood algorithm

Introduction

Transcranial magnetic stimulation is a widely used method to non-invasively study the human brain and specifically, the motor system. In this context, the resting motor threshold (RMT) is used as an indicator of cortical excitability as well as the basis for determining the stimulation intensity for other

measurements. Thus, an accurate and efficient estimation of the RMT is crucial to assure reliability of a measurement and guarantee safety of the stimulation, for example, by applying lower doses or fewer TMS pulses to subjects [12].

The most commonly used estimation method is the Rossini-Rothwell method (R-R method) [13, 14], which, in its revised form, defines the RMT as the minimum stimulation intensity that elicits muscle responses > 50 μ V in at least 5 out of 10 trials. Despite the vast use of this method, there is a lacking standardization due to a missing specification of the exact RMT determination algorithm in the original publications [13, 14] and consequently continuous modification by researchers [2, 19]. Consequently, effects of hysteresis might influence RMT estimates and the extent of this influence might vary between studies and researchers [8]. Further, the R-R method does not take the probabilistic nature of the RMT into account and is hence more prone to variations and biases [6, 19]. In addition, it has been criticized to be mathematically unsafe, meaning that the probability of gaining an

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unacceptable estimate RMT is greater than the accepted α probability [3].

In contrast, adaptive threshold-hunting methods based on maximum likelihood estimation by sequential testing (ML-PEST) estimate the probability to evoke a muscle response at a given intensity, thus accounting for the probabilistic nature of the RMT [2, 6]. This method has been shown to yield comparable estimations as the R-R method, while using fewer pulses and thus being more efficient [1, 2, 16]. It is therefore recommended by the IFCN committee guidelines [6]. However, one critique for this method is the “black-box” design of the algorithm as well as the need for a separate software for the estimation [19].

A new variant of the maximum likelihood algorithm (nML algorithm) has been implemented in some TMS devices, thus making adaptive threshold-hunting algorithms more accessible for clinical settings. The nML algorithm is a modified version of the ML-PEST algorithm aiming to make the RMT assessment faster and less prone to participants’ anticipation of stimuli. However, the nML algorithm has only been tested in a small sample of healthy subjects so far [7]; thus, its reliability and comparability in a clinical setting remains to be established.

The aim of this study was to evaluate the nML algorithm in comparison with the R-R method, representing the current standard of RMT estimation, in terms of reliability and applicability in a clinical population. RMTs were assessed with both methods in an extensive sample of patients with brain tumors. Additionally, a healthy sample was recruited to determine robustness of each measure over time. We further aimed to show the advantage of the nML algorithm in terms of efficiency for the patient sample, thus highlighting its usefulness in clinical settings, where time for individual patients might be limited. Ultimately, this might help to overcome the skepticism of users towards automated estimation designs and show their usefulness also in clinical settings.

Methods

Subjects

One-hundred fifteen patients (20–79 years, 52.4 ± 19 years, 43 females) with a motor-eloquent brain tumor that were routinely mapped with neuronavigated TMS before surgery were included in this study. Forty patients (34.8%) suffered from a paresis of the upper extremities and eighty-nine patients (77.4%) were treated with antiepileptic medication. The data from these patients was gathered at the Department for Neurosurgery at Charité between 2014 and 2017. Additionally, ten healthy subjects (21–45 years, 25.6 ± 6.8 years, 5 females) with no history of neurological or psychiatric illness were recruited for the study. Participants met

the inclusion criteria for receiving an MRI scan and the TMS and gave their written informed consent. The study was conducted in accordance with the Declaration of Helsinki and its later amendments and data collection and analysis was approved by the local ethics committee.

Study material

MRI

Participants brought their own structural MRI scan with them. Patients received a T1-weighted MRI scan including 3D gradient-echo sequence acquisition on a Siemens 1.5 or 3 Tesla MRI scanner (Siemens AG, Erlangen, Germany) as part of the clinical routine. These data sets were then used as subject-specific navigational datasets for the TMS.

Neuronavigated TMS

Neuronavigated TMS was applied using Nexstim NBS 4 and 5 stimulators (Nexstim, Helsinki, Finland) with a figure-of-eight coil (outer diameter = 70 mm), as specified previously [5, 10, 11]. Muscle evoked potentials were recorded from the first dorsal interosseous muscles of both hands with disposable silver-silver-chloride electrodes (Neuroline 720; Ambu, Ballerup, Denmark). A ground electrode was attached to the left palmar wrist. Muscle activity was monitored to assure relaxation of the muscle, with a maximum tolerated baseline activity of 10 μ V. The exact hotspot for stimulation as well as the optimal rotation was defined as the stimulation site, electric-field direction and angulation consistently eliciting the largest muscle evoked responses in the target muscle. The hotspot location as well as optimal rotation and tilting angle were then stored in the Nexstim system.

In the patient sample, the RMT was assessed once using the R-R method and the nML algorithm in variable order. In the healthy subjects, the RMT was determined first with the R-R method and then the nML algorithm. This procedure was repeated twice separated by a 15-min break in which subjects were instructed to sit relaxed. For analysis, the RMT was recorded as volts per meter (V/m) induced at the cortical level [9, 15].

R-R method

The RMT using the R-R method was defined as the minimum stimulation intensity necessary to elicit muscle evoked potentials with a peak-to-peak amplitude of $> 50 \mu$ V in the relaxed muscle in at least five out of ten consecutive trials [13, 14].

nML algorithm

For an automated determination of the RMT, the nML algorithm [7] as implemented in the TMS stimulator was used.

Briefly, the stimulator displays the stimulation intensity to be applied and the stimulation is manually started by the experimenter. Based on the recorded EMG response, the algorithm adapts the stimulation intensity of the next trial to elicit a muscle response $> 50 \mu\text{V}$ with 50% probability. This procedure is repeated until the final RMT is determined with a predefined accuracy of $\pm 2\text{--}3\%$ of the maximum stimulator output.

Data analysis

Data in patients was analyzed for the affected and non-affected hemisphere separately to capture potential influences due to the disease, while data in healthy subjects was analyzed irrespective of the stimulated hemisphere. Visual inspection of the patient RMT data revealed a normal distribution, while RMT data in the healthy subjects and number of pulses in the patient data violated this assumption. Subsequently, two-tailed paired-samples *t* tests were computed to assess differences in the patients RMT in each hemisphere between the R-R method and the nML algorithm. Cohen's *d* was used as a measure for the effect size. For the healthy subjects, differences between both methods for each timepoint and stability of the assessment for each method over time were assessed with two-sided paired Wilcoxon signed-rank tests. Rank biserial correlations were used as a measure of the effect size.

Additionally, intraclass correlation coefficients were computed to assess the amount of agreement between both methods or timepoints, as well as Pearson correlations. Bland-Altman plots and limits of agreement were determined to visualize potential differences between both methods further [4].

To determine if the R-R method needed more pulses for RMT estimation compared to the nML algorithm, one-sided Wilcoxon signed-rank tests were performed. Rank biserial correlations were used as a measure of effect size. *p* values < 0.05 were considered significant. Statistical analysis was performed in RStudio (R Version 3.5.1; Boston, USA).

Results

All subjects tolerated the stimulation well and their data was included in the analysis. The results of the patient sample are summarized in Fig. 1. The RMT measured with the R-R method ($67 \pm 21 \text{ V/m}$) and the nML algorithm ($66 \pm 21 \text{ V/m}$) in the affected hemisphere is shown in Fig. 1a and was not significantly different ($t(114) = 1.55$, $p = 0.125$, $d = 0.144$). Further, both measures showed a strong positive Pearson correlation ($r = 0.964$, $p < 0.001$; Fig. 1c) and high agreement in the intraclass correlation coefficient ($\text{ICC} = 0.964$, $p < 0.001$), highlighting their similarity in RMT estimation. Figure 1e shows a Bland-Altman Plot for the individual RMT estimates

of the R-R method and nML algorithm to visualize their agreement. The plot displays limits of agreement of -10.1 to 11.7 V/m with a mean difference between both methods of $0.8 \pm 5.6 \text{ V/m}$, which can be argued to reflect good agreement. However, the R-R method (33 ± 14 pulses) used significantly more pulses ($Z = -9.04$, $p < 0.001$, Effect size $r = -0.6$) than the nML algorithm (15 ± 4 pulses) to determine the RMT. Figure 1b shows the RMT in the unaffected hemisphere obtained with the R-R method ($68 \pm 16 \text{ V/m}$) and the nML algorithm ($66 \pm 16 \text{ V/m}$), which reflected a significant difference ($t(114) = 3.54$, $p < 0.001$). However, the effect size of this difference was only moderate ($d = 0.33$). Additionally, a strong positive Pearson correlation ($r = 0.953$, $p < 0.001$; Fig. 1d) and high agreement in the intraclass correlation coefficient ($\text{ICC} = 0.948$, $p < 0.001$) was observed, pointing to similarities of RMT estimation in both methods. Figure 1f shows a Bland-Altman Plot for the individual RMT estimates of the R-R method and nML algorithm with limits of agreement of -7.9 to 11.1 V/m and a mean difference between both methods of $1.6 \pm 4.9 \text{ V/m}$. This, again, reflects a good agreement between both methods. When comparing the number of pulses needed for the R-R method (30 ± 13 pulses) and the nML algorithm (15 ± 3 pulses), the R-R method again used significantly more pulses ($Z = -9.18$, $p < 0.001$, effect size $r = -0.61$).

The results of the healthy sample are presented in Figs. 2, 3, and 4. The RMT estimated with the R-R method ($58.8 \pm 13.9 \text{ V/m}$) and the nML algorithm ($59.6 \pm 13.9 \text{ V/m}$) at timepoint 1 did not significantly differ ($Z = -0.97$, $p = 0.554$, effect size $r = -0.15$). Also at timepoint 2, the RMT estimated with the R-R method ($59.6 \pm 13.7 \text{ V/m}$) and the nML algorithm ($58.7 \pm 15.2 \text{ V/m}$) did not significantly differ ($Z = -0.47$, $p = 0.635$, effect size $r = -0.08$; Fig. 2). Further, a strong positive Spearman correlation between the RMT estimated with both methods was observed at timepoint 1 ($\rho = 0.956$, $p < 0.001$; Fig. 3a) and timepoint 2 ($\rho = 0.951$, $p < 0.001$; Fig. 3b). This agreement between the methods is also supported by a high intraclass correlation coefficient at timepoint 1 ($\text{ICC} = 0.954$, $p < 0.001$) and timepoint 2 ($\text{ICC} = 0.93$, $p < 0.001$). Figure 3c shows a Bland-Altman Plot for the individual RMT estimates of both methods at timepoint 1 with limits of agreement of -9.2 to 7.4 V/m and a mean difference between both methods of $-0.9 \pm 4.2 \text{ V/m}$. Figure 3d shows the same relationship for timepoint 2 with limits of agreement of -9.9 to 11.6 V/m and a mean difference between both methods of $0.9 \pm 5.5 \text{ V/m}$. For both timepoints, this can be regarded as good agreement.

Regarding the stability of the estimated RMT, both the R-R method ($Z = -1.04$, $p = 0.297$, effect size $r = -0.16$) and the nML algorithm ($Z = -0.64$, $p = 0.519$, effect size $r = -0.1$) estimates did not significantly differ over time (Fig. 2). There was a strong positive Spearman correlation between the RMT at both timepoints for the R-R method ($\rho =$

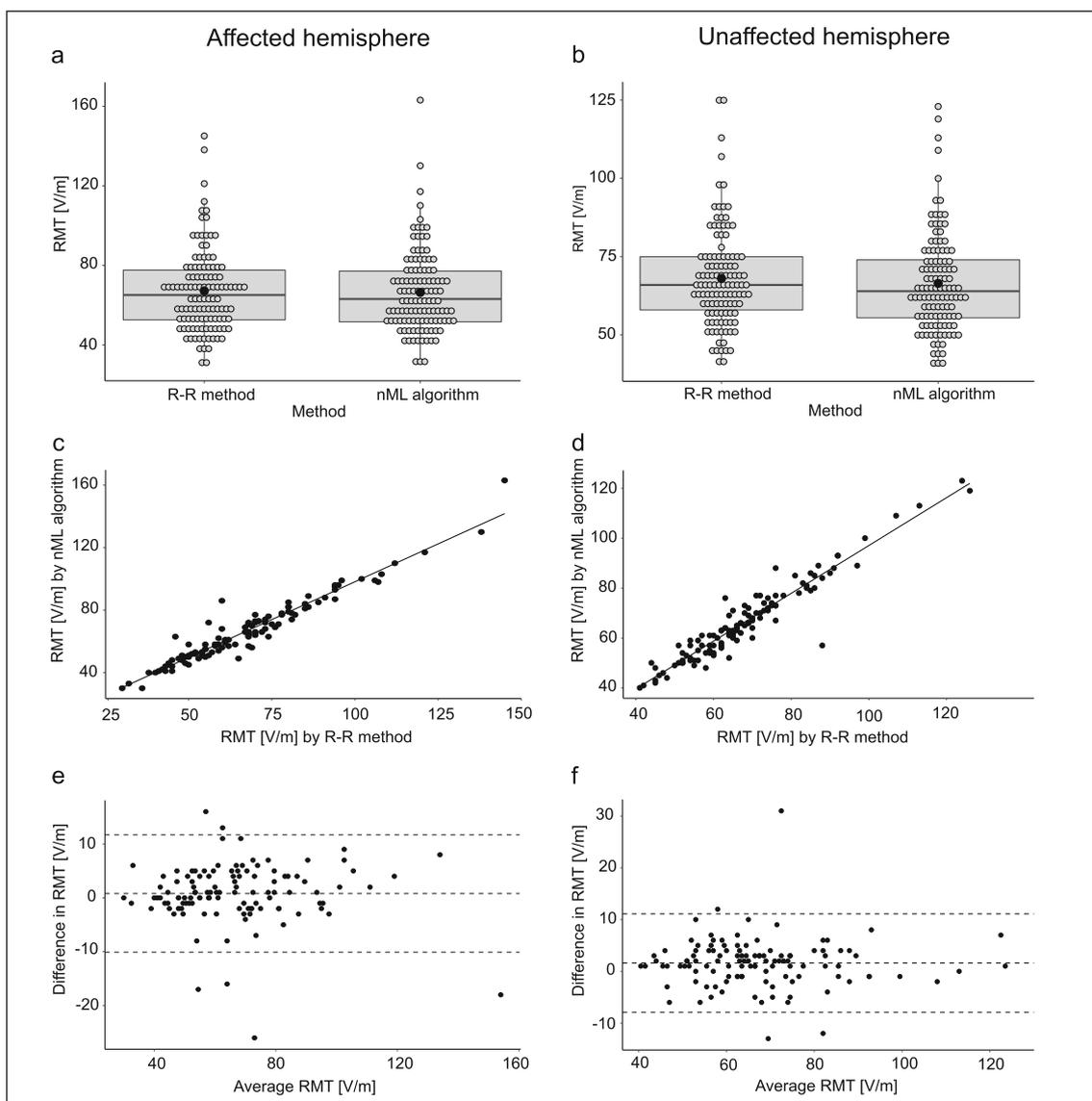


Fig. 1 Comparison of R-R method and nML algorithm in patients. **a** RMT estimates in the affected hemisphere obtained with the R-R method and nML algorithm. The black dot corresponds to the respective group average; smaller gray dots represent individual participant values. **b** RMT estimates in the unaffected hemisphere obtained with the R-R method and nML algorithm. **c** Scatterplot with regression line showing a high correlation between the RMT estimated by the R-R method and nML

algorithm in the affected hemisphere. **d** Scatterplot with regression line showing a high correlation between the RMT estimated by the R-R method and nML algorithm in the unaffected hemisphere. **e** Bland-Altman Plot with limits of agreement between R-R method and nML algorithm showing good agreement in the affected hemisphere. **f** Bland-Altman Plot with limits of agreement between R-R method and nML algorithm showing good agreement in the unaffected hemisphere

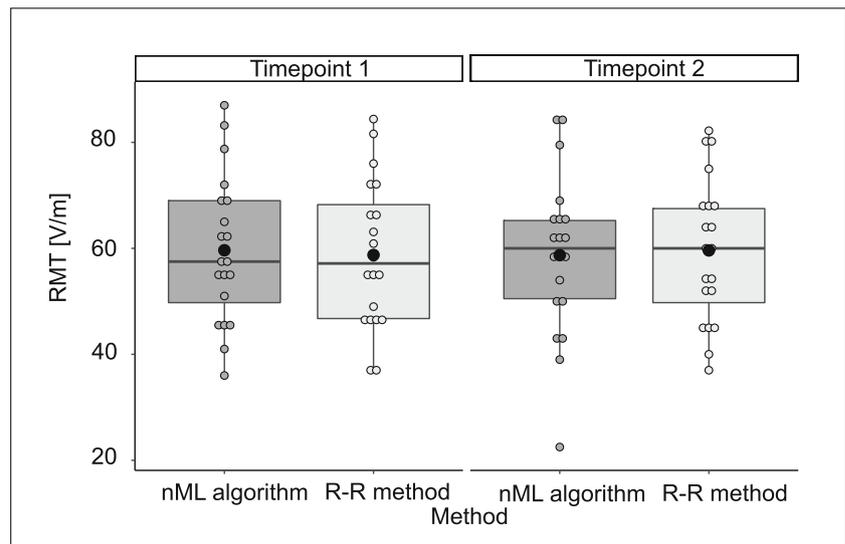
0.981, $p < 0.001$; Fig. 4a) and the nML algorithm ($\rho = 0.93$, $p < 0.001$; Fig. 4b). The reliability of both methods is further supported by a high agreement in the intraclass correlation coefficient for the R-R method ($ICC = 0.972$, $p < 0.001$) and the nML algorithm ($ICC = 0.937$, $p < 0.001$). Figure 4c shows the Bland-Altman Plot for the individual RMT estimates using the R-R method with limits of agreement of -7.2 to 5.5 V/m and a mean difference between both methods of -0.9 ± 3.2 V/m. Figure 4d shows the same relationship for the nML algorithm with limits of agreement of -9.3 to 11.1 V/m and a mean difference between both methods of 0.9 ± 5.2 V/m.

Discussion

The present study compared the R-R method and nML algorithm as estimation methods for the RMT in patients with brain tumors and healthy controls. Both methods yielded similar estimations of the RMT and were relatively robust over time. However, the nML algorithm was more efficient, using a significantly lower number of pulses for RMT determination.

A significant difference in RMT estimations between both methods was only observed in the unaffected hemisphere of patients with a moderate effect size. However, the limits of

Fig. 2 Boxplots for RMT estimates at different timepoints obtained by the R-R method and nML algorithm in healthy subjects. The black dot corresponds to the respective group average; smaller gray dots represent individual participant values



agreement for all comparisons made in this study were in the range of ± 12 V/m, meaning that 95% of the observed deviation between both methods was within this range [4]. We argue that this is an acceptable range of deviation, since it is within the

range of within-session variation in RMT estimates reported in previous studies [19, 20]. Further, no trends or systematic deviations for specific RMT ranges were observed in the Bland-Altman Plots, excluding performance differences between both

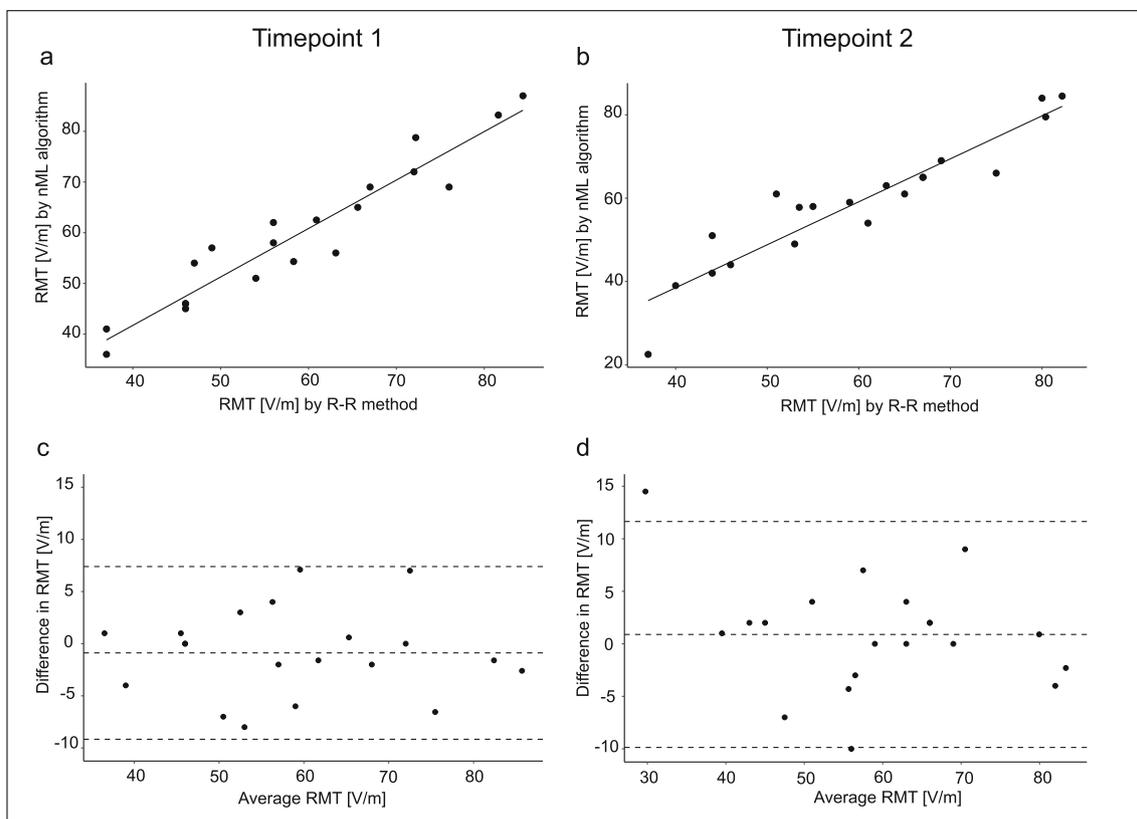


Fig. 3 Comparison of the R-R method and nML algorithm at different timepoints in healthy subjects. **a** Scatterplot with regression line showing a high correlation between the RMT estimated by the R-R method and nML algorithm at timepoint 1. **b** Scatterplot with regression line showing a high correlation between the RMT estimated by the R-R method and

nML algorithm at timepoint 2. **c** Bland-Altman Plot with limits of agreement between R-R method and nML algorithm showing good agreement at timepoint 1. **d** Bland-Altman Plot with limits of agreement between R-R method and nML algorithm showing good agreement at timepoint 2

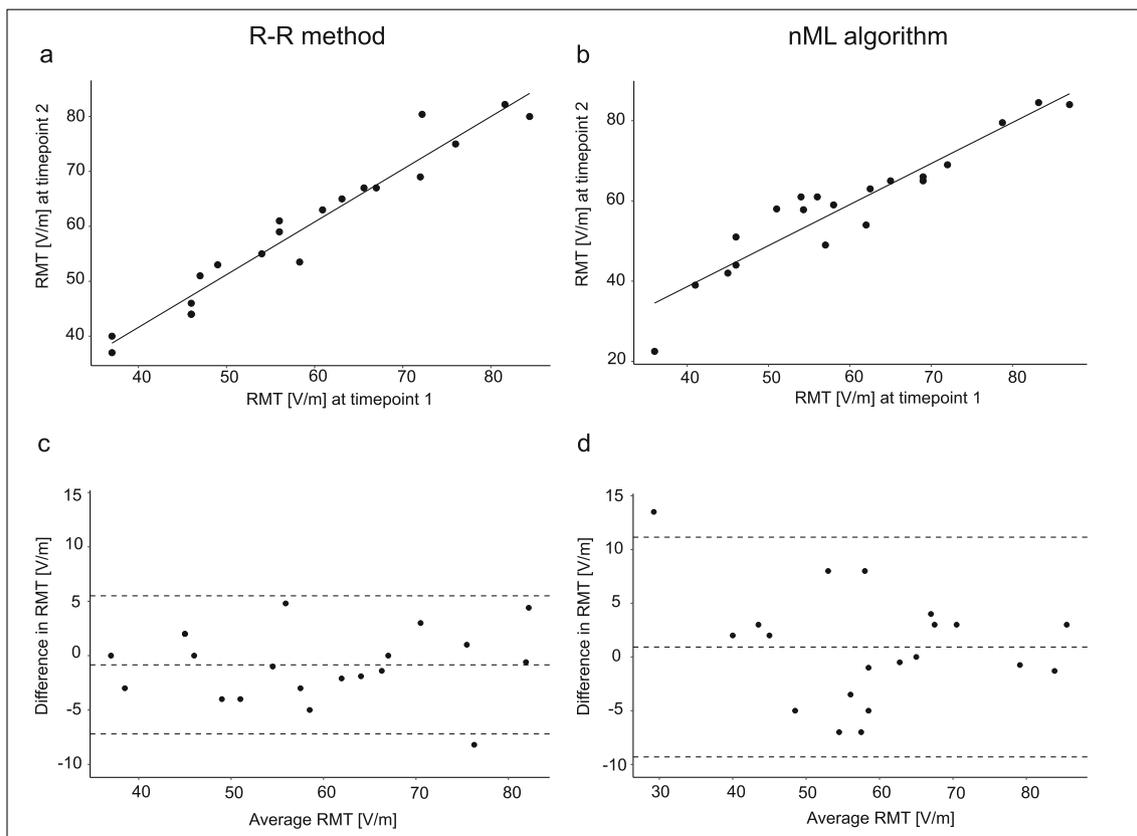


Fig. 4 Test-retest reliability of the R-R method and nML algorithm in healthy subjects. **a** Scatterplot with regression line showing a high correlation between the RMT estimates obtained with the R-R method at timepoints 1 and 2. **b** Scatterplot with regression line showing a high correlation between the RMT estimates obtained with the nML algorithm

at timepoints 1 and 2. **c** Bland-Altman Plot with limits of agreement between RMT estimates at timepoints 1 and 2 showing good agreement using the R-R method. **d** Bland-Altman Plot with limits of agreement between RMT estimates at timepoints 1 and 2 showing good agreement using the nML algorithm

algorithms for certain stimulation intensities. Thus, both methods can be regarded as delivering similar results.

No outliers, i.e., points deviating more than 3 standard deviations from the mean difference between both methods, were removed from the analysis as these might carry important information about flaws of either estimation method. Most outliers were observed in the affected hemisphere (Fig. 1e). The TMS results and tumor localization of these cases were examined in more detail and revealed motor function in proximity or overlapping with the tumor or tumor related edema. It could be hypothesized that RMT estimation in these cases posed a special challenge as compression, infiltration, and edema can affect axonal membrane potential and local connectivity, thereby resulting in variable sensitivity to depolarizing stimuli [10, 17, 18].

As pointed out previously [2, 13, 14], a constant level of relaxation of the stimulated muscle is crucial in order to give reliable estimates of the RMT. However, this might pose a challenge for some patients or participants, especially if the time of an experiment increases. Thus, reduction of experimental time is a crucial factor to reach reliable RMT estimates and a supporting point for the nML algorithm. In addition, due

to the faster acquisition time, the nML algorithm might be capable of tracking state-dependent changes in cortical excitability more accurately [1], thereby also making it more useful for interventional studies.

As a limiting factor of the present study, no randomization of the order of both RMT estimation methods was performed in healthy subjects and the R-R method was always measured first. However, a direct influence on the results of the nML algorithm seems unlikely as the starting intensity for stimulation was based on pulses used for the hotspot determination and thus unaffected by the RMT determined by the R-R method. Further, since the patient data analyzed in this study was gathered over multiple years, two different TMS devices were used. Yet, the nML algorithm implemented in both devices was identical and RMT estimates were only compared within-subjects. The only remaining difference was a minimum number of required stimuli for the nML algorithm of 16 stimuli, which was implemented in the newer device. Thus, for older data, estimations with fewer stimuli were possible, if the defined accuracy criterium was reached. Again, this does not seem to affect the reliability of the nML algorithm in comparison to the R-R method.

Lastly, it could be argued that comparison of only two algorithms is insufficient due to the mentioned concerns about the R-R method [3]. However, as this method is still the standard in most studies, any new algorithm will also have to be evaluated in comparison with the R-R method. In addition, measuring a third algorithm was not feasible in clinical practice due to time constraints.

Conclusion

In conclusion, the present study supports the comparability of RMT estimates using a Maximum Likelihood method with the Rossini-Rothwell method. However, estimation using the nML algorithm was significantly faster and seems less prone to biases such as hysteresis or modifications by researchers. Thus, these findings go along with the recommendation of the ICFN for use of adaptive threshold-hunting algorithms for RMT determination, while being the first to highlight this advantage in a large patient sample. Ultimately, this might help overcome skepticism of clinicians towards automated RMT estimation and make the clinical routine more effective.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Commission of the Charité University Hospital Berlin (Germany)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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