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Correlating active and resting motor thresholds for transcranial magnetic stimulation through a matching model

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Dear Editor,

Transcranial magnetic stimulation (TMS) can relatively focally elicit action potentials in cortical neurons in the brain. Sufficiently strong pulses over the primary motor cortex can trigger cortico-spinal output signals leading to measurable motor-evoked potentials (MEPs) and even visually detectable muscle twitches [1]. The motor threshold (i.e., expressed as a percentage of the maximum stimulator output) as an indirect indicator of the motor cortex excitability represents the lowest stimulus strength that evokes a MEP with an amplitude around 50 μV at rest (resting motor threshold, RMT) and of around 200 μV during voluntary contraction of the tested muscle (active motor threshold, AMT) [2,3]. The AMT enhances both spinal and cortical excitability in the primary motor cortex through voluntary muscle contraction for higher sensitivity of the neural circuits and therefore typically leads to lower values than the RMT [4]. The motor threshold serves as the main metric for individualising the pulse strength in neuromodulation for both experimental brain research and clinical trials [2,5]. Additionally, the motor threshold is the reference pulse strength for practically all safety recommendations and limits [6]. Whereas repetitive TMS with fixed pulse rhythms is typically based on the RMT, patterned pulse protocols, such as theta-burst stimulation, preferably use the lower AMT as a reference stimulation strength [7]. However, it was found that the outcome of theta-burst stimulation does not only depend on the TMS pulse strength but also muscle pre-activation before the neuromodulatory intervention—which obviously is an inherent part of the AMT detection procedure [8,9]. Furthermore, the detection of the AMT is more complicated for both the subject and the operator, while the extra degrees of freedom and additional error sources may increase variability. Based on these issues, it would appear reasonable to use a measure that allows isolating and independently controlling such pre-activation and exclusively use RMT as a reference instead of AMT for necessary applications. However, a translation or matching of procedures to an RMT reference would need knowledge of the quantitative relationship between AMT and RMT, which is yet poorly established [10,11].

To fill this research gap, we collected individual motor threshold data from previous studies that collected both RMT and AMT in the first dorsal interosseuous muscle (see Supplementary material). As the statistical distribution of the (after all purely positive and therefore unlikely gaussian-distributed[1]) motor threshold values was strongly right-skewed (skewness $\gamma(RMT) = 0.973$ and $\gamma(AMT) = 0.843$), we normalised all motor threshold measurements using natural logarithmic transformation, resulting in $\gamma(\ln(RMT)) = 0.380$ and $\gamma(\ln(AMT)) = 0.184$ (Fig. 1 (**A**)). We selected AMT as the dependent variable and the remaining variables as independent predictors including both categorical and continuous types.

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[1] When random variables are purely positive, normal distributions are in general rarely mathematically correct as they have long-ranging tails and would, in contrast to a log-normal distribution, suggest a certain nonnegligible portion of negative values. For narrow distributions, i.e., low variability, normal and log-normal distributions practically converge into each other, though. However, the high variability in brain stimulation does not appear to be such case, as the different skewness levels indicate.

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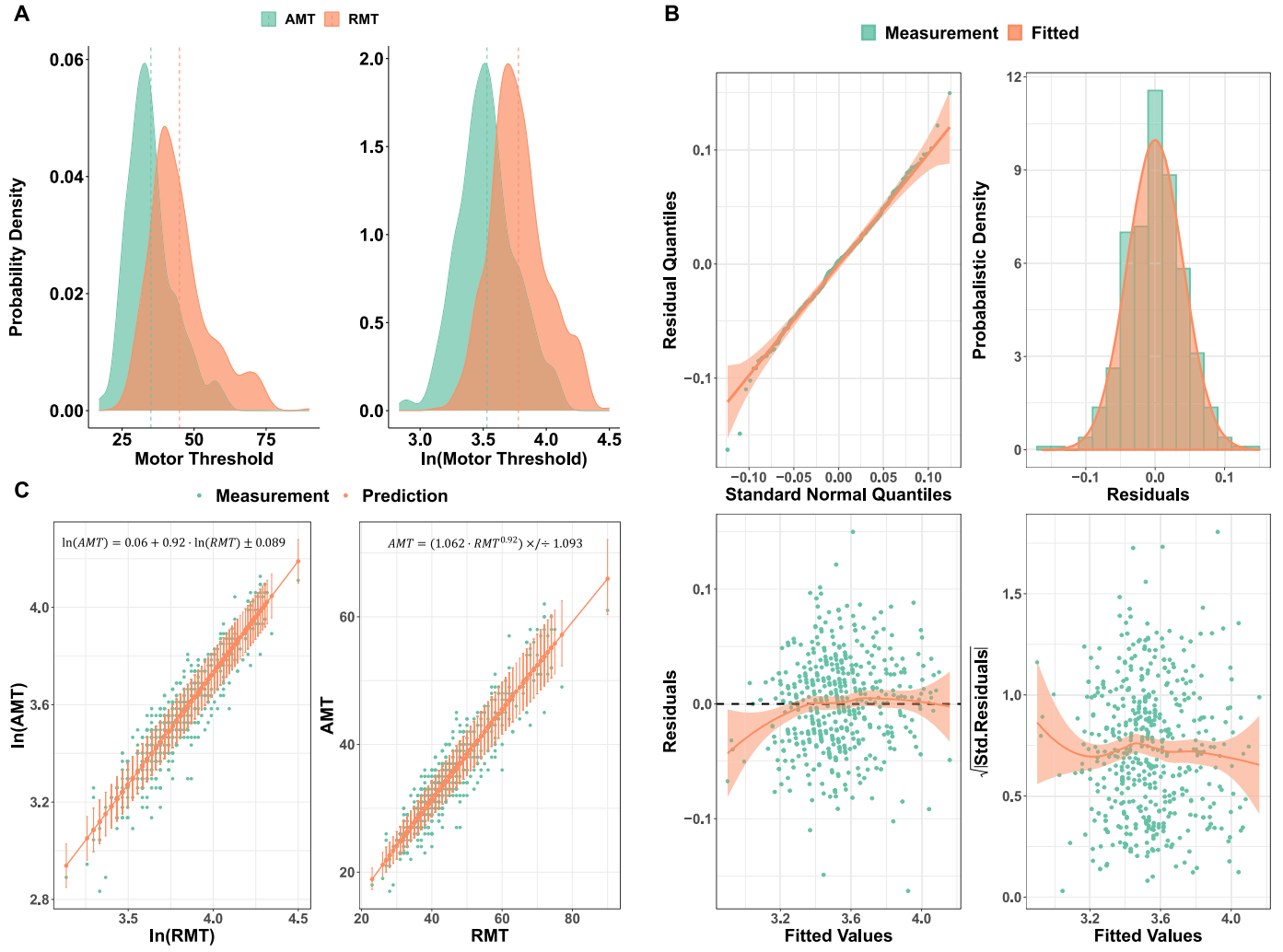

Fig. 1. Visualisation of the motor threshold distribution data and the corresponding mixed-effects model. (**A**) Distributions of original (left) and logarithmically (right) normalised AMT and RMT, respectively. Vertical dash lines represent the arithmetic means. (**B**) Q-Q plot for residuals of the model (left top), the histogram distribution of residuals (green bars) and the fitted normal distribution curve (orange curve) (right top), the linearity (left bottom) and homogeneity (right bottom) of variance for the residuals in which both orange curves are respectively the means of residuals and the square root of absolute standardised residuals over the fitted values. (**C**) Plots of logarithmic AMT over logarithmic RMT (left) and AMT over RMT (right) in which solid green dots represent the measurements, solid orange dots are the means of prediction, and the error bars indicate the error terms.

We employed a mixed-effect model to analyse the data and derive a functional relationship between AMT and RMT, taking into account biological differences among individuals and random sources in different experiment techniques, since it contains both fixed and random effects that can describe the hierarchical database in terms of multi-levels of interest (see Supplementary material). Overall, we selected RMT (continuous), AGE (continuous), SEX (categorical), STIMULATED HEMISPHERE (categorical), and PULSE SHAPE (monophasic vs. biphasic, categorical) as fixed-effect variables. In addition, this study considered two random-effect sources: STUDY and SUBJECT nested within STUDY, which is termed SUBJECT (STUDY). Package *lme4* (version 1.1–31) was used to calibrate the mixed-effect model in R. The restricted maximum likelihood technique served for estimating the variance components in the hierarchical database since it can be applied to unbalanced data and avoid the problem of biased variance estimation by maximum likelihood estimation [12]. We tested the significance of the fixed-effect variables with a type-III ANOVA with Satterwaite's method. Moreover, package *emmeans* (1.8.3) in R served for *post-hoc* analysis with Bonferroni correction. This study calls a p-value of less than 0.05 significant.

We calibrated the mixed-effect model with the database with in total 515 observations and 237 subjects coming from eight studies (see Supplementary material). Therefore, this mixed-effects model can be written as

$$y_{ijk} = \beta_0 + \sum_{h=1}^{p} \beta_h x_{hijk} + \gamma_k + \alpha_{jk} + \epsilon_{ijk}$$
$$\gamma_k \sim \mathcal{N}(0, \sigma_\gamma^2), \alpha_{jk} \sim \mathcal{N}(0, \sigma_\alpha^2), \epsilon_{ijk} \sim \mathcal{N}(0, \sigma_\epsilon^2) \quad (1)$$

where y_{ijk} is the i-th response of the j-th individual in the k-th study; x_{hijk} the explanatory value of the j-th individual in the k-th study for the h-th predictor β_h (i.e., the fixed-effect variable); γ_k is the study-specific random-effect variable with a mean of zero and variance of σ_γ^2; α_{jk} is the subject-specific random-effect variable in the k-th study with mean of zero and variance of σ_α^2; ϵ_{ijk} is the residual with mean of zero and variance of σ_ϵ^2 for each y_{ijk}; β_0 is the constant intercept for all responses y_{ijk}. The model has a constant level ($\beta_0 = 0.41$) and demonstrates a significant dependence of the AMT on the RMT ($\beta_{\mathrm{RMT}} = 0.84$, $F(1, 468.38) = 1339.89$, $p < 2 \cdot 10^{-16}$) and less so of the AGE ($\beta_{\mathrm{AGE}} = 1.8 \cdot 10^{-3}$, $F(1, 227.67) = 6.01$, $p = 0.015$), while other fixed-effect variables did not show significant effects. In addition, this model has high marginal and conditional coefficients of determination, which are respectively equal to $R_{\mathrm{M}}^2 = 0.813$ and $R_{\mathrm{C}}^2 = 0.948$.

Among the random-effect variables, STUDY obeys the distribution of $\gamma_k \sim \mathcal{N}(0, 2 \cdot 10^{-3})$ and SUBJECT (STUDY) obeys the distribution of $\alpha_{jk} \sim \mathcal{N}(0, 4 \cdot 10^{-3})$. As shown in Fig. 1 (**B**), the distribution of the residuals appears to be Gaussian ($\epsilon_{ijk} \sim \mathcal{N}(0, 2.5 \cdot 10^{-3})$) satisfying the residual distribution assumptions, since the Chi–square normality test and Levene's test show that the model (with properly log-transformed RMT and AMT) does not violate the mixed-effect model assumptions of residual normality ($P = 26.214$, $p = 0.243$) and homogeneity of variance ($F(234, 278) = 0.575$, $p = 1$).

Our findings suggest that the relationship between AMT and RMT does not depend on the pulse shape (for the included monophasic and biphasic pulses), sex, and stimulated hemisphere, but is at most influenced by a subject's age. This observation implies that the RMT and AGE explain most of the variability of AMT and allow a good prediction of the AMT. We calibrated a linear regression model including both RMT and AGE. However, RMT explains the 84.06% of the total variance of the measurements, while AGE only explains $2.4 \cdot 10^{-3}$ %. Therefore, we further calibrated the model with RMT only and the prediction equation would be

$$\ln(AMT) = 0.06 + 0.92 \cdot \ln(RMT) \pm 0.089, \tag{2}$$

where ±0.089 is the standard uncertainty. This matching model would allow estimating AMTs and the necessary pulse strength in repetitive and accelerated stimulation paradigms down to a root-mean square error of less than $8.93 \cdot 10^{-2}$ without the need to measure the AMT with muscle contraction. In addition, RMT explains 84.06% of the total variance of the measurements. The left panel of Fig. 1 (**C**) shows the logarithmic AMT prediction based on logarithmic RMT for this model. Not only is the determination of RMT usually technically less challenging and variable but also avoids influencing the brain or circuit state of the motor system with the muscle pre-activation needed for AMT determination.

In conclusion, this study derives a quantitative functional relationship between AMT and RMT based on threshold data of 237 subjects. Taking exponential on both sides and simplifying Equation (2), the relationship becomes

$$AMT = \left(1.062 \cdot RMT^{0.92}\right) \times/\div 1.093. \tag{3}$$

Equation (3) predicts AMT over RMT in normal scale as shown in the right panel of Fig. 1 (**C**). This relationship can provide a reliable link to reference all necessary stimulation strength values to the RMT for an easier procedure and separate any influence of muscle pre-activation before the neuromodulatory intervention. In some previous research, ethnicity appeared to influence the RMT but not AMT, thus potentially also impacting the relationship between both [13]. However, other research disagrees with these reports and considers methodological reasons leading to such apparent influences [14]. Our dataset with parts from Japan, Australia, and Europe with local subject populations did not indicate any site influence on the relationship between RMT and AMT (see Supplementary material). In addition, the dataset only used voluntary muscle contraction levels of $5 - 20\%$ during the AMT measurement. By isolating muscle pre-activation and exclusively using RMT as the reference, our approach facilitates the accurate estimation of AMT, advancing standardised and effective neuromodulatory interventions using TMS.

CRediT authorship contribution statement

SMG and KM designed the research. KM derived the mathematical model and initial method as well as code for the mixed-effect model. SMG helped supervise the project. KM, MH, VDL, BH, AG, and GMO collected the TMS data. KM and SMG wrote the text. All authors proofread, polished, and approved the text.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix. Supplementary material

A supplementary document to this article can be found online (https://github.com/BIOMAKE/CorrelatingAMTandRMT).

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