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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effect of TMS measurement-related variables on the MEP size

Lien Jacobs
Alix Lumbeeck

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen

PROMOTOR :
dr. Stefanie VERSTRAELEN

COPROMOTOR :
Prof. dr. Raf MEESEN

BEGELEIDER :
De heer Marten NUYTS

2023
2024

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Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

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Research context

This master's thesis investigates "the effect of TMS measurement-related variables on MEP size", situating it within the field of technology-supported rehabilitation since the objective of this thesis was done in preparation of further research on using TMS in rehabilitation. By determining optimal variables for reduced MEP-variability, future measurements of CSE will be more accurate. This improvement aims to benefit future patients by enhancing the accuracy of prognosis measurement for motor recovery.

Our thesis is part of a larger study for the doctoral project of Drs. Marten Nuyts and Drs. Sybren Van Hoornweder, supervised by Dr. Stefanie Verstraelen and Prof. Dr. Raf Meesen titled "How much is enough? Deciding the optimal number of TMS pulses to obtain a stable estimate of corticospinal excitability.", which was funded by Fonds Wetenschappelijk Onderzoek (FWO, G1129923N). The data acquisition was done at 'UHasselt BIOMED A' , where we also took part in collecting the data during our scientific internship in the research team of Prof Dr. Raf Meesen and Dr. Stefanie Verstraelen.

The research question was developed in collaboration with Dr. Stefanie Verstraelen and Drs. Marten Nuyts. During the scientific internship the interest in the project of Drs. Marten Nuyts grew while we were performing the participant recruitment and data acquisition. After being allocated to this research for our thesis, the formation of this question was chosen through the interest in the TMS measurement-related variables. After consolation, the study design and research question of Drs. Marten Nuyts was modified based on our interest for the substudy.

We aimed to conduct our thesis together as much as possible. Where Lien was stronger in the statistical part, and Alix in scientific writing.

May 2024

Lumbeeck Alix, Keerbergen

Jacobs Lien, Dessel

ABSTRACT

Background: Transcranial magnetic stimulation (TMS) can be used over the primary motor cortex (M1) to elicit a motor evoked potential (MEP), which is measured through electromyography (EMG) electrodes to investigate the corticospinal excitability (CSE), a commonly used measure for prognosis in motor recovery. However, MEPs are known to have a variability due to biological and methodological factors.

Objectives: To investigate the effect of TMS intensity, coil orientation parameters (Angular error (Er.), Twist Er. and Target Er.) now called neuronavigation, and magnetic field strength (x-, y- and z-axis) on the MEP size in a group of healthy adults.

Methods: Neuronavigation was used for optimal coil positioning during MEP collection on 61 participants, with an age ranging from 18 to 30 years. Through EMG, MEPs were measured of their right first dorsal interosseus (FDI) muscle following single-pulse TMS. Lastly, the strength of the magnetic field was measured with MagProbe. After determining the hotspot and the resting motor threshold (rMT), TMS was administered in two clusters consisting of five blocks, including intensities between 110 -150%rMT, with increments of 10%.

Results: Analysis revealed two significant three-way interactions consisting of Angular Er.*Twist Er.*%rMT ($p<0.001$) and Target Er.*Twist Er.*%rMT ($p=0.0248$) on MEP size. A supplementary analysis showed a significant effect of MFx ($p <0.0001$) and MFz ($p <0.0001$) on the MEP amplitudes.

Conclusion: To minimise the MEP-variability minimal neuronavigational errors, an intensity close to the personal rMT and a MFx and MFz around a certain pivot point are needed.

Keywords: Motor evoked potential (MEP), Transcranial magnetic stimulation (TMS), intensity, neuronavigation, magnetic field

1. Introduction

Transcranial magnetic stimulation (TMS) is a form of non-invasive brain stimulation used to study the human brain (Cleland et al., 2023). In TMS, a rapidly-changing, transient electromagnetic field is generated perpendicular to a coil by a passing electric current, induced by a stimulator (Zewdie & Kirton, 2016, Siebner et al., 2022). When brought over the head, the magnetic field induces a secondary electric field in the underlying brain tissue (Siebner et al., 2022). One common brain target is the primary motor cortex (M1) representation area of the hand (Jung et al., 2010, Siebner et al., 2022). Within this neural target, neural tissue becomes depolarized and an action potential is created which travels through the corticomotor neuronal circuits to evoke a physiological response in the corresponding muscles (Cleland et al., 2023; Julkunen et al., 2009; Siebner et al., 2022). By placing electromyography (EMG) electrodes on the overlying skin, the corresponding peak-to-peak muscle output can be easily quantified, better known as a motor evoked potential (MEP) (Frye et al., 2008). A MEP is a sensitive neurophysiological measure which can be used to test corticospinal excitability (CSE), a commonly used measure of prognosis in motor recovery (Bestmann & Krakauer, 2015; Cleland et al., 2023; Schilberg et al., 2021; Sivaramakrishnan & Madhavan, 2020).

Unfortunately, MEPs have been shown to be quite variable (Jung et al., 2010), which greatly affects its accuracy. As a result of this, the current CSE and the changes within are more complex to establish (Cleland et al., 2023), but also its reproducibility, sensitivity and reliability are affected (Goldsworthy et al., 2016). Clinically speaking, this means that identifying intervention-related changes in CSE are more difficult to detect. The variability in MEP values can be manifested in several ways. Firstly, there is variability in the amplitude of MEPs. On the other hand, a variability in latency exists which describes the time needed for MEP generation following the TMS pulse (Sollmann et al., 2017). Variability in MEPs can be attributed to both experimental and biological factors (Ammann et al., 2020; Goldsworthy et al., 2016).

Biological causes of MEP-variability include sex (Jung et al., 2010), age (Jung et al., 2010), sleep (Goldsworthy et al., 2016), the state of arousal at the moment of the intervention (Goldsworthy et al., 2016), an increase in spontaneous oscillations of the brain state (Cleland

et al., 2023; Goldsworthy et al., 2016), changes in regional cerebral flow during the first TMS pulses (Hashemirad et al., 2017), pre-stimulus target muscle activation (Goldsworthy et al., 2016) and rapid fluctuating changes in spinal excitability (Cuypers et al., 2014). Furthermore, the variability could also be influenced by methodological factors such as coil placement (Cuypers et al., 2014; Goldsworthy et al., 2016; Hashemirad et al., 2017), TMS intensity (Pellegrini et al., 2018), number of trials (Goldsworthy et al., 2016), location of the hotspot (Cuypers et al., 2014), EMG electrode size (Jung et al., 2010), external noise in EMG (e.g. artefacts from muscle tension) (Goldsworthy et al., 2016) and the density of the electrical current in the coil (Lefaucheur et al., 2014). This study will focus on the methodological factors to investigate their contribution to the variability in trial-to-trial MEP amplitudes (de Goede et al., 2018).

The opportunity to control these methodological factors is beneficial to reduce the variability and subsequently improve the quality of the MEP measurement. For example, a minimum of thirty trials are likely required to quantify CSE (Goldsworthy et al., 2016). Furthermore, the influence of neuronavigation-derived parameters was examined by De Goede et al. (2018), who found at group level that the change in coil location did not have a significant influence on the mean MEP amplitudes. Moreover, it has been stated that in neuronavigation with manual coil handling, shifting within a change of ten mm radius and up to twenty degrees Twist error (Er.). is accurate enough (de Goede et al., 2018). Unfortunately, only accounting for the neuronavigation is not enough to lower the intra-subject and inter-subject variability (Gugino et al. 2001; Julkunen et al. 2009; Jung et al. 2010; de Goede et al., 2018), due to the fact that other factors, such as TMS intensity also have an impact on the MEP-variability. According to Pellegrini et al. (2018) an increase in TMS intensity leads to a decrease in MEP-variability, with a significant decline between 120% and 135% of resting motor threshold (rMT).

We hypothesise that each of these variables, both individually and in their interactions, may significantly influence the MEPs and contribute to their variability. Therefore, the aim of this study is to investigate the effect of the measurement-related variables (neuronavigation-derived parameters, TMS intensity and magnetic field strength) and their interactions on MEP amplitude in order to achieve the effects on MEP-variability.

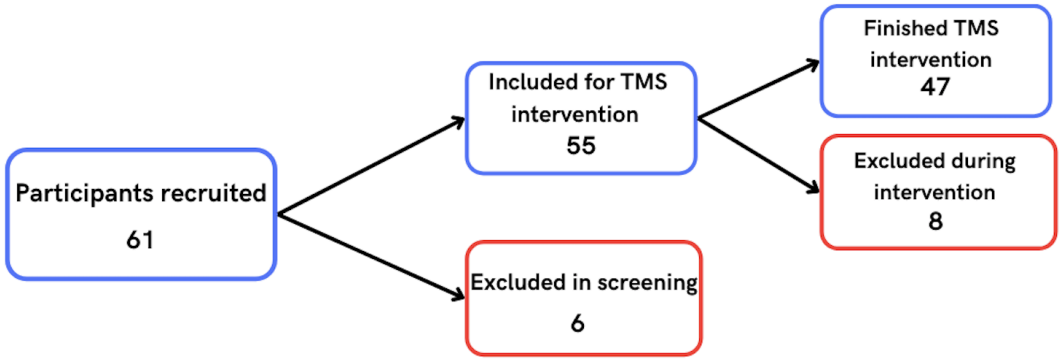
2. Methods

2.1. Participants

A total of 61 young healthy adults, 30 men and 31 females, were initially recruited for this study through social media, flyers, and face-to-face communication. To be able to enter the study, the participants had to be between the age of 18 to 30 years old, have normal or corrected to normal vision and be right-handed. The handedness was assessed with the Edinburgh Handedness Inventory (EHI), with a cut-off of ⩾ fifty (see Appendix A) (Oldfield, 1971). They were excluded if they had one or more of the contraindications to TMS, which were screened using a standard screening questionnaire for TMS (see Appendix B) (Rossi et al., 2009), nor could they have any neurological, cognitive or mental related problems. For this last one, the Beck Depression Inventory-II (BDI-II) (see Appendix C) (Beck, 1961) was used to score the mental health and if the participant scored ⩾ thirteen, they were excluded from the study. This resulted in a total of 47 inclusions and fourteen were excluded due to a rMT > 54 in six cases, too high scores on the BDI-II questionnaire in two cases, jaw contraction during stimulation in one case, four cases due to having a contraindication for TMS and high background EMG in one case (Figure 1). High background EMG was defined when the EMG signal exceeded 20 μV in the 100-50 ms period prior to the TMS pulse onset.
The study was approved by the medical ethics committee of Hasselt university (B1152023000001) and all participants were provided with the informed consent prior to starting the intervention. The study was also in line with the Declaration of Helsinki.

Figure 1

Recruitment Participants



Note. In total 61 participants were recruited, yet after screening six of them were excluded. During the intervention, another eight were excluded which leads to 47 participants who finished the TMS intervention. TMS= transcranial magnetic stimulation.

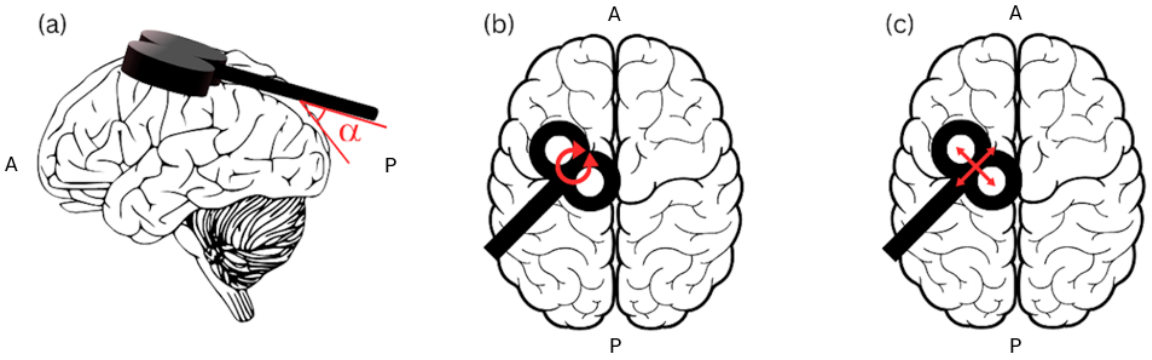
2.2 Preparation of TMS

Firstly, Angular Er. concerns the perpendicular alignment of the coil on the head surface (Figure 2a). Secondly, the bidirectional variable Twist Er. addresses the rotation of the coil relative to its optimal position (Figure 2b). Thirdly, Target Er. covers accurate placement of the centre of the figure-of-eight coil above the hotspot (Figure 2c). The optimal position of the coil consists of 0° Angular Er., 0° Twist Er. and 0 mm Target Er.. To register these errors, a neuronavigation system Brainsight 2 (Brainsight®2, Rogue Research Inc, Montreal, Quebec, Canada) was used. Next, the subject was given a headband with a tracker attached to it, which was used to identify the position of the head in space. A cortical representation of the hand motor area was obtained by first measuring head size and determining the spatial organisation of the various potential targets on the brain. The participant was then provided with earplugs to reduce loud clicking noise from the TMS machine. Moreover, a search was done on a rectangular grid of potential targets, projected on an average anatomical brain template, for the hotspot, which represents the brain region in the homunculus of the left M1 area that correlates with the right first dorsal interosseus (FDI) muscle. This process involved stimulating different brain regions with the BiStim² stimulator (Magstim, Whitland, Dyfed, UH) combined with a figure-of-eight coil with a 50mm diameter of inner circle (Magstim, Whitland, Dyfed, UH). The target spot that produced the largest and most stable

MEPs on five consecutive TMS pulses will be defined as the hotspot. Lastly, the minimum stimulation intensity required to produce MEPs with an amplitude of at least 50 mV, at least five times out of ten, better known as the rMT, was determined.

Figure 2

Neuronavigational Errors

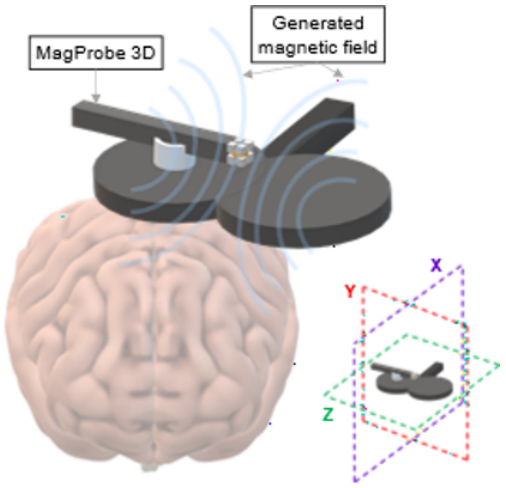


Note. (a) Angular Er. with alfa being the angle between the centre of the coil and the head surface. (b) Twist Er. explaining the rotation of the coil. (c) Target Er. covers the distance between the centre of the coil and the hotspot. A = anterior, P = posterior, α= alpha, Er. = error

The output of TMS was assessed using the EMG Bagnoli 16 system (Delsys Inc, Boston, USA) in combination with the adhesive DE-2.1, which measures the MEPs. Differential Surface EMG sensor and reference electrodes were placed on both the right and the left FDI muscle and the styloid process of the ulna, respectively. These left ones were installed for standardisation in order to compare their outputs to the ones on the right. In addition, a Humbug noise eliminator (Quest Scientific, North Vancouver, Canada) is connected to the EMG device to filter signals for noise. Lastly, the magnetic field, which was divided in x-, y- and z-axis as seen in figure 3 (Nuyts et al., 2024), was measured with Magventure MagProbe 3D (MagVenture, Farum, Denmark).

Figure 3

Components of the Magnetic Field



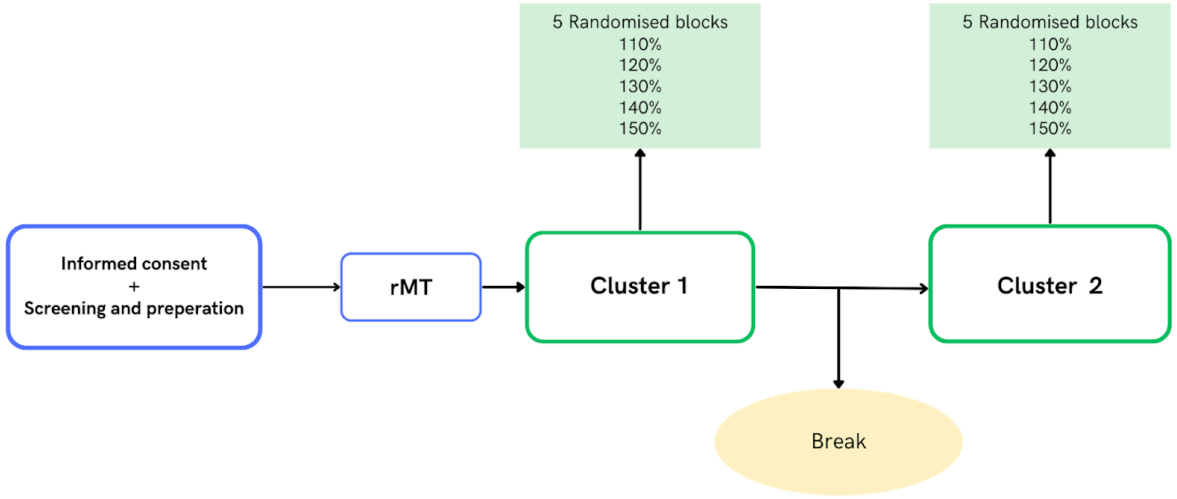
Note. Copied from *"How much is enough? Deciding the optimal number of TMS pulses to obtain a stable estimate of corticospinal excitability"*, door M. Nuyts, 2024, unpublished manuscript. Illustration of the magnetic field that is measured by the Magventure MagProbe 3D. The magnetic field consists of the x-, y- and z-axis which is presented in different colours in the right lower corner.

2.3 Data acquisition

In one TMS block, single-pulse TMS is administered 55 times at the same intensity. In total there are two clusters of five blocks at five different TMS intensities in the range of 110-150% of the rMT, with increments of 10%, randomised by a customised MATLAB script. The Maximum Stimulator Output (MSO), which is the absolute intensity of the %rMT, was installed as the TMS intensity. This results in a total of 110 trials being collected for each TMS intensity. During these blocks a nature documentary will be played to achieve a stable brain state during this resting-state intervention. To bypass temporal anticipation by the participant and cumulative effects of the TMS-pulses, an intertrial interval of approximately 10 seconds is set with a temporal jitter of 2 seconds. When the first cluster has ended, a break of 10 minutes is provided, which leads to a total duration of data acquisition of 2 hours and 10 minutes. An overview of the course of the experimental protocol can be seen in figure 4.

Figure 4

Course of TMS intervention



Note. Firstly, the informed consent of the participant was obtained, which was followed by a screening for exclusion criteria. Afterwards, the participant was installed for the preparation of TMS. Before the first cluster of TMS started, rMT was measured to calculate the intensity of the randomised blocks. After the first cluster, a short break of ten minutes was given and afterwards the study continued with cluster two. TMS= transcranial magnetic stimulation, rMT= resting motor threshold.

2.6. Statistical analysis

For this study, the data of 47 participants (mean age ± SD = 22 ± 1.92) was analysed using JMP for Windows Pro version 17. A full factorial mixed model was used to determine the fixed effects of %rMT and neuronavigation-derived parameters (Angular Er., Target Er. and Twist Er.) on MEP amplitude, with single-trial MEP amplitudes as the dependent variable and "Subject #" as the random effect (see Appendix D). Subsequently, this analysis started with a four-way interaction to which backward stepwise model building was applied with a significance level set at $\alpha = 0.05$. The residuals were examined for normality, dependency, and homoscedasticity both before and after the model simplification. Afterwards, a post-hoc test, more specifically the Bonferroni method, was carried out to determine between which intensities there was a mutual significant difference. Additionally, a supplementary analysis

of eight participants (mean age ± SD = 23 ± 1.41) was performed with the following fixed effects: magnetic field strength components (i.e., strength along the x-, y-, and z-axis of the coil) and the percentage MSO and their effect on the dependent variable which is the MEP amplitude. Again, “Subject #” was added as the random effect. Furthermore, the terms of normality, dependency and homoscedasticity of the residuals were verified at the beginning and after the model simplification. This model started with a three-way interaction in which MSO was not included in the interactions. Afterwards, backward stepwise model building was performed for all linear mixed effects models with a significance level set to $\alpha = 0.05$.

3. Results

3.1. Effect of %rMT and neuronavigation-derived parameters on MEP amplitude

Prior to conducting the analysis, the assumptions were evaluated. Firstly, normality was assessed using the Anderson-Darling test, yielding a p-value of <0.0001, indicating that the assumption was not met. Additionally, homoscedasticity was not achieved due to too much variation between the residual and the predicted MEPs. However, independence of the error terms was confirmed. The simplified mixed model included two significant three-way interactions on MEP-size: %RMT*TARGET ER.*TWIST ER. (p = 0.0028), and %RMT*ANGULAR ER.*TWIST ER. (p= <0.001). Due to these interactions being significant, the model could not be more simplified (Table 1a). The assumptions of this model did not differ from those of the whole model. To evaluate the parameter estimates of the different variables, table 2 was formed. Comparing the Akaike Information Criterion (AICc) value of both models, the simplified model shows a lower value indicating a better fit of the simplified model. Moreover, the determination coefficient (R^2) of the simplified model had a value of 0.09, meaning that only 9% of the variance in MEP amplitude can be predicted based on the fixed effects. Additionally, the intraclass correlation coefficient (ICC) was 0.5660 after the backwards stepwise model building (Table 3), which insinuates a moderate correlation within the subject. After this analysis, a post-hoc test was performed for the categorical variable %rMT, using the Bonferroni method. The significance level used is 0.005 and is formed by dividing the initial significance level alpha (0.05) by the total number of post-hoc hypothesis tests (10). As seen in table 4 all pairwise interactions are significant meaning that within any interaction containing %RMT, the influence of a different intensity is significant.

Table 1

Results of Fixed Effects Tests

(a) Simplified Model of %rMT and Neuronavigation-derived Parameters on MEP amplitude

Fixed Effects	Mean ± SD	F Ratio	Prob > F
%rMT	-	404.98411	<.0001*
Target Er.	0.529 ± 0,497	1.4318801	0.2315
%rMT*Target Er.	-	2.7902836	0.0248*
Angular Er.	1.338 ± 0.906	0.1115357	0.7384
%rMT*Angular Er.	-	12.903355	<0.0001*
Target Er.*Angular Er.	-	0.0098426	0.9210
Twist Er.	0.091 ± 1.251	1.1405571	0.2855
%rMT*Twist Er.	-	4.3240869	0.0017*
Target Er.*Twist Er.	-	0.0336774	0.8544
%rMT*Target Er.*Twist Er.	-	4.0523058	0.0028*
Angular Er.*Twist Er.	-	0.6594545	0.4168
%rMT*Angular Er.*Twist Er.	-	10.771361	<.0001*

(b) Simplified Model of absolute TMS intensity (%MSO) and magnetic field strength on MEP amplitude

Fixed Effects	Mean ± SD	F Ratio	Prob > F
MFx	0.004 ± 38.450	54.7935	<.0001*
MFz	2.897 ± 0.054	128.6312	<.0001*

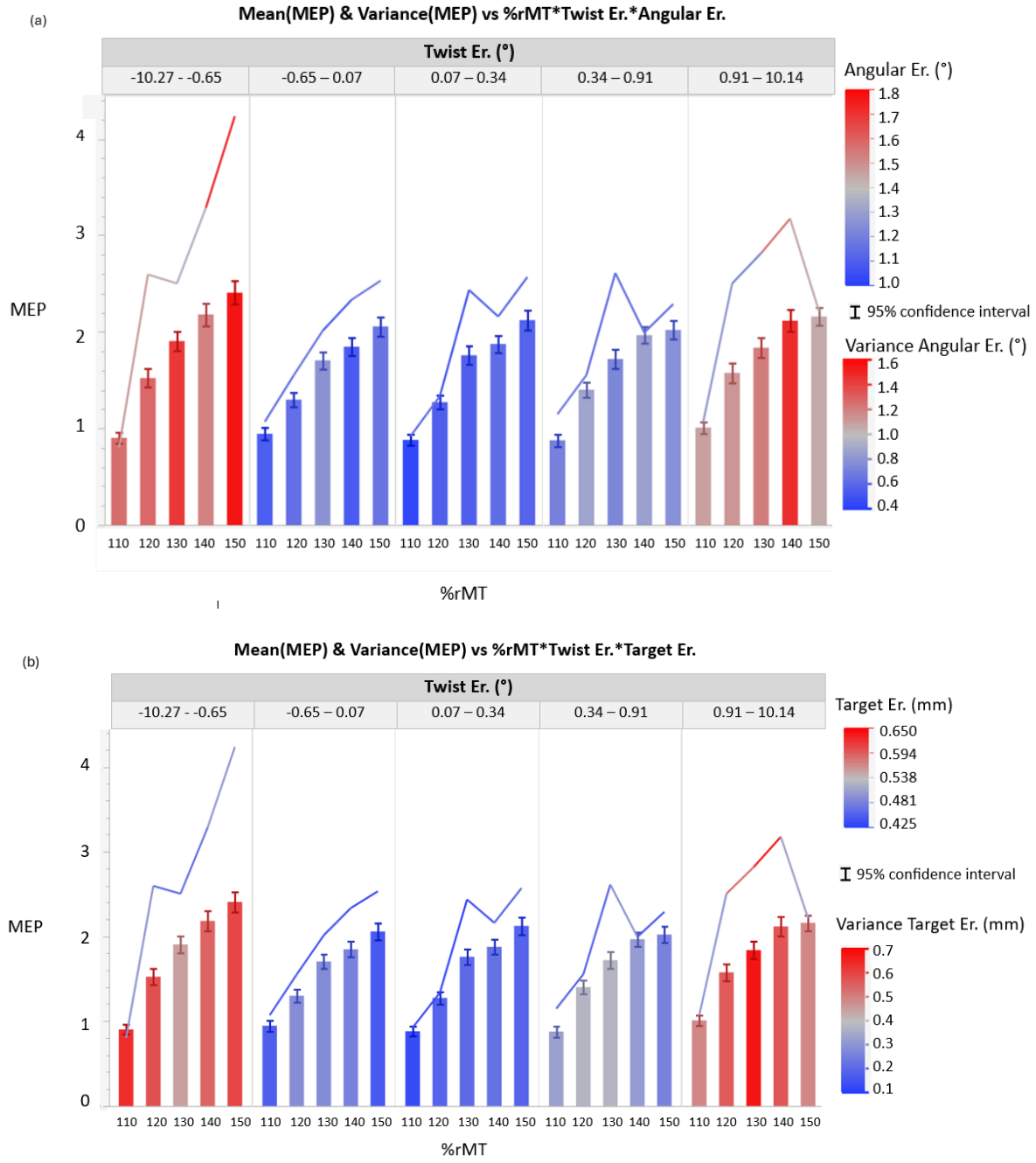
Note. %rMT = percentage of the resting motor threshold, Er. = error, MFx = x-axis of magnetic field, MFz = z-axis of magnetic field

Figure 5a illustrates the relation of the MEP amplitude and the interaction between %rMT*Twist Er.*Angular Er.. Here, also the variance of MEP amplitudes in combination with the variance of the Angular Er. is visualised by a line in each Twist Er. column to compare them to each other. Looking at the variance line, an interpretation of MEP-variability can be made as will be discussed. Furthermore figure 5b illustrates the interaction between %rMT, Target Er. and Twist Er. in relation to MEP amplitude. Here also the variance of MEP

amplitude is shown, but now in combination with the variance of the Target Er.. Lastly, also the 95% confidence intervals are shown.

Figure 5

Visualisation of the Threeway Interactions on MEP



Note. (a) This figure illustrates the effect of interaction %rMT, Twist Er. and Angular Er. on the amplitude of the MEP. Here, the x-axis is divided in five different columns by different gradations of Twist Er.. The variance of the MEP amplitude in combination with the variance of the Angular Er. is displayed by the lines in each column of Twist Er. The colour presents the degree of Angular Er.. Lastly, the 95% confidence interval is shown in each %rMT beam. (b) Visualisation of the interaction of %rMT, Target Er. and Twist Er. on the MEP amplitude. The y-axis consists of the different amplitudes of the MEPs, which are divided per %rMT on the x-axis. The influence of Target Er. is displayed through colour. The Twist Er. divides the %rMT of the x-axis in five different columns to address these values. The variance of MEP amplitude along with the variance of Target Er. is visualised with the line in the different columns of the Twist Er.. The 95% confidence interval is shown in each %rMT beam. For both (a) and (b) the colour red represents larger errors and blue being a better error value (i.e. closer to zero). The more internal columns indicate a better Twist Er. (i.e. closer to 0°). MEP= motor evoked potential, %rMT= percentage of the resting motor threshold, Er.= error

3.2. Effect of MSO and magnetic field strength on MEP amplitude

This dataset included a total of eight participants (mean age ± SD = 22.63 ± 1.41). This supplementary analysis considered the three directions of the magnetic field (MFx, MFy and MFz) relative to the coil and the MSO. The analysis involved examining their interactions, of which, in the simplified model, only the main effects of MFx ($p < 0.0001$) and MFz ($p < 0.0001$) remain significant (Table 1b). To verify whether the model is suitable for the analysis, the AICc was tested (Table 3), which indicates that the simplified model is more fitting. Additionally, the simplified model had an R^2 of 0.003, suggesting that the variance in MEP amplitude can be poorly explained by these fixed effects. Before and after the backward stepwise model-building procedure was done, the assumptions of normality, homoscedasticity, and independence of the error terms were assessed. Normality was tested using the Anderson-Darling test at both before and after simplification and were both not significant, indicating that the assumption of normality was not fulfilled. Likewise, homoscedasticity was not achieved in either model. On the contrary, the assumption of independence among the error terms was met in both instances. Lastly, the ICC was administered (Table 3), suggesting a moderate within subject correlation.

Table 2

Results Parameter Estimates

(a) Simplified Model of %rMT and Neuronavigation-derived Parameters on MEP amplitude				
Fixed Effects	Estimates	StD Error	t-Ratio	Prob > |t|
Intercept	1.6469	0,3217	9.98	<.0001*
%rMT(110%)*Target Er.*Twist Er.	-0.059686	0.016361	-3.65	0.0003*
%rMT(120%)*Target Er.*Twist Er.	0.0214969	0.0166843	1.29	0.1967
%rMT(130%)*Target Er.*Twist Er.	-0.011793	0.0167875	-0.70	0.4824
%rMT(140%)*Target Er.*Twist Er.	0.0226558	0.0175936	1.29	0.1979
%rMT(110%)*Angular Er.*Twist Er.	0.0558916	0.01096	5.10	<.0001*
%rMT(120%)*Angular Er.*Twist Er.	-0.005957	0.0098345	-0.61	0.5447
%rMT(130%)*Angular Er.*Twist Er.	0.001776	0.0101317	0.18	0.8609
%rMT(140%)*Angular Er.*Twist Er.	-0.05141	0.0095179	-5.40	<.0001*
(b) Simplified Model of MSO and magnetic field strength on MEP amplitude				
Fixed Effects	Estimates	StD Error	t-Ratio	Prob > |t|
Intercept	-1,7967	0,3217	-5,58	0,0005
MFx	284,6144	38,4496	7,40	<.0001*
MFz	0,6098	0,0538	11,34	<.0001*

Table 3

Model Evaluation Matrix

	Simplified Model of %rMT and Neuronavigation-derived Parameters	*Simplified Model of MSO and magnetic field strength*
AICc	70652.294	8512.0644
R^2	0.090565	0.003867
ICC	0.5660	0.6517

Note. AICc = Akaike Information Criterion, R^2 = Determination coefficient, ICC = Intraclass correlation coefficient

Table 4

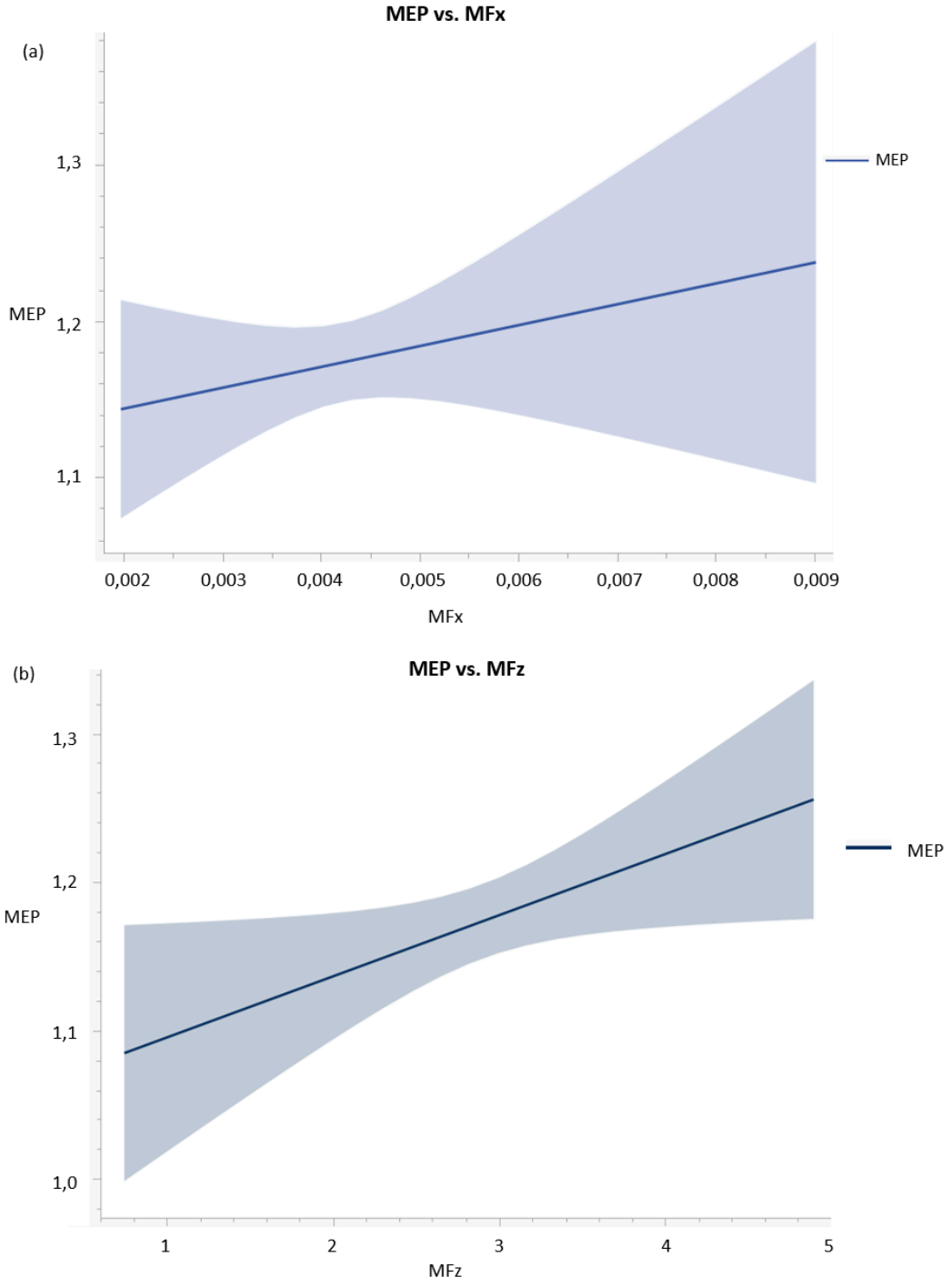
Results Post-Hoc Tests

%rMT	-%rMT	Difference	Std Error	T Ratio	Prob>|t|
110	120	-0. 480	0.019	-24.63	<.0001
110	130	-0.848	0.020	-43.40	<.0001
110	140	-1.059	0.0195	-54.31	<.0001
110	150	-1.229	0.020	-62.91	<.0001
120	130	-0.368	0.019	-18.88	<.0001
120	140	-0.579	0.019	-29.79	<.0001
120	150	-0.749	0.019	-38.44	<.0001
130	140	-0.211	0.019	-10.86	<.0001
130	150	-0.381	0.020	-19.52	<.0001
140	150	-0.170	0.019	-8.70	<.0001

Note. %rMT= percentage of the resting motor threshold, Std= standard

Figure 6

Visualisation of the Influence of MFx and MFy on the MEP



Note. (a) This figure illustrates the effect of MFx on the MEP amplitude. The blue straight line represents the mean of the different MEP amplitudes per MFx value. The blue surrounding the straight line represents the MEP-variability per MFx value. (b) Here, the effect of MFz on the MEP amplitude is visualised. The different MEP amplitudes per MFz strength is displayed by the grey line. The MEP-variability is seen by the deviations around the line. MEP= motor evoked potential, MFx= x-axis of magnetic field, MFz= z-axis of magnetic field.

4. Discussion

Although in the past the effects of each variable on MEP amplitude have been investigated individually, little is known about the effect on the MEP amplitude and eventually on the total MEP-variability when these variables and their interactions are combined into a larger model. The present study aimed to identify the effect of multiple measurement-related variables on MEP amplitude in healthy adults. There are four main interactions divided over the overall mixed model and the supplementary analysis.

4.1 Interpretation of the simplified model of %rMT and neuronavigation-derived parameters on MEP amplitude

The first significant interaction involves %rMT, Angular Er. and Twist Er. in relation to MEP amplitude. According to Pellegrini et al. (2018) an increase in %rMT results in a higher MEP amplitude, which is coherent with the findings of this study (Figure 5a). The other components of this first interaction is the Angular Er. and Twist Er. of the neuronavigation, which contribute to an accurate coil position relative to the predefined hotspot (Caulfield et al., 2022). The combination of the effects of these three variables implies that the correlation between Twist Er. and Angular Er. on MEP amplitude is assisted by the %rMT, thus an increase in %rMT magnifies the MEP values when both errors are high.

As for the MEP-variability, which is illustrated in figure 5a, it can be seen that the variance values of the MEP amplitude increases as the %rMT rises and even more so when the errors become larger. This is consistent with the findings from Julkunen et al. (2009)**,** in which the use of neuronavigation lowers the variation in MEP amplitude significantly, this in combination with the results of Julkunen et al. (2009) where a more precise stimulation is obtained through navigated TMS. Lastly, an increase in MEP-variability with higher TMS intensities is observed, which contrasts with the findings of Pelligrini et al. (2018), where MEP-variability decreased with increasing TMS intensity.

The second interaction %rMT*Target Er.*Twist Er. on MEP, as seen in figure 5b, shows a larger MEP value when %rMT increases. Furthermore, it shows that there also is a positive interaction between the Twist Er. and the Target Er. Specifically, when the Twist Er. is in the

most optimal range (-0.072 - 0.3405) the Target Er. also presents the lowest score (+- 0.425). On the other hand, a less optimal Target Er. results in a less optimal Twist Er. (Figure 5b). The correlation between %rMT, Target Er. and Twist Er. with the MEP is minimal yet positive (Table 2). The combined effect of all these variables suggests that %rMT serves as a supporting variable to this correlation, e.g. if Twist Er. and Target Er. are high, an increase in %rMT further amplifies the MEP values.

Regarding the variability of the MEP, researchers have found that these neuronavigational errors are correlated with MEP-variability, with coil position being the primary cause of fluctuations (Schmidt et al., 2015). Schmidt et al. (2015) states a significant increase in variability results from a Target Er. larger than 2 millimetres. The variability is illustrated through the variance line in Figure 5b, where a similar correlation between variability, %rMT, and neuronavigational errors can be seen as in the line of Figure 5a.

In conclusion, MEP-variability could be reduced by keeping neuronavigational errors to a minimum and by using an intensity close to the personal rMT of the participant. The reason for the higher error values in this study could be that not all the researchers were equally experienced in performing TMS, which future research should consider.

4.2. Interpretation of the simplified model of MSO and magnetic field strength on MEP amplitude

The greatest current density with a figure-of-eight coil is achieved beneath the centre of the coil, where the target cells that control a particular muscle are in the maximum of the electrical field (Groppa et al., 2012; Herwig et al., 2002; Richter et al., 2013). Research indicates that increasing the distance between the centre of the figure-of-eight coil and the cortical surface results in an exponential weakening of the electromagnetic field induced in neural cells (Cukic et al., 2009; Schecklmann et al., 2020). The orientation of the magnetic field can also significantly amplify the field strength. More specifically, the strength increases significantly when it is positioned perpendicular to the local gyrus, with a different effect in spatial distribution between grey and white matter (Opitz et al., 2011). Yet, this is a topic that is outside the scope of this study and will not be further discussed. Therefore, to

minimise the distance, the coil should be held parallel to the cortical surface and the magnetic field should be oriented perpendicular to the gyrus in order to maximise the strength. Additionally, because the magnetic field is not attenuated by extracerebral tissue and the M1-area is both superficial and major, even a moderately low stimulus intensity is effective (Groppa et al., 2012; Lefaucheur, 2019; Siebner et al., 2022). Based on previous studies, there is a positive correlation between magnetic field strength and MEP amplitude (Cukic et al., 2009; Mosayebi-Samani et al., 2021; Schmidt et al., 2015), which is consistent with the findings in this study.

As shown in figure 6a, higher MFx values correspond to larger MEP values and the relationship between MEP-variability and MFx values forms a parabolic pattern. Specifically, the figure illustrates a pivot point of the variability at around 0.0045, where MFx values both above and below this point will result in a higher variability in MEP. This trend is similarly observed in figure 6b, where the increase in MEP values in correlation with higher MFz values is more pronounced. Additionally, MEP-variability is generally smaller, but still follows a similar trend as before, albeit with a pivot point of three.

4.3 Implications

Since only measurement-related variables were investigated, it could be interesting for future studies to consider the impact of the biological factors to enhance the research and have a full overview on the causes of MEP-variability. Moreover, further standardisation of the study could involve using an MRI scan for each participant to individualise neuronavigation (Janssen et al., 2015), which does not alter the fact that an extensive hotspotting procedure is already used. Additionally, literature states that robot-assisted neuronavigation could be utilised for accurate coil positioning in resting-state studies (Goetz et al., 2019). After envisioning an ideal setup and integration of TMS in the laboratory, extending this integration into the clinical setting becomes imperative. Given that single-pulse TMS is commonly used for prognostic purposes, it is important to look at which parameters should be considered to create a reliable MEP output, in order to have a reliable measurement for the prognosis of motor recovery.

4.4 Strengths and weaknesses

In this study, several strengths were identified. First, due to the large sample size (n = 47) the reliability of this study increases. Secondly, even though the effect of measurement-related variables already has been studied individually, their combined effect was still unknown. Despite its strengths, the study was also subject to some limitations. Firstly, the data of the magnetic field for the first 39 participants was not saved, resulting in a small sample size for the supplementary analysis. Secondly, during the statistical analysis of the subjects, the assumptions of normality and homoscedasticity of the mixed model were not met. However, the study of Schielzeth et al. (2020) demonstrated that mixed-effects models remain applicable even though the assumptions are violated. Moreover, the testing of homoscedasticity was not performed with an objective test (e.g. Levene's Test), due to its unavailability in the mixed model analysis. Thirdly, only healthy adults were investigated, leading to the fact that the effect of the study for neurological patients and other age groups is unknown. Moreover, the TMS machine could not handle high intensities (rMT > 54) wherefore a participant was excluded, due to the coil heating up too much over time. Furthermore, the complexity and duration of TMS sessions, often exceeding 2 hours, could lead to fluctuations in participants' alertness and attention levels, potentially influencing MEP amplitude (Noreika et al., 2020). To encounter this, a nature documentary was displayed for the participant to watch during the two clusters of the TMS intervention. Notably, personal factors such as sex, hours of sleep, and the presence of alcohol in the system were not investigated as they fall beyond the scope of this study, which could also have affected MEP-variability (Manganotti et al., 2001; Manganotti et al., 2004; Cantone et al., 2019; Kahkonen et al., 2003). Additionally, neither the researchers nor the participants were blinded from the intensities, which could introduce performance bias into the study findings because of possible alterations in the brain activity in anticipation of higher intensities. Also, a confounding bias was present due to having multiple researchers performing the intervention, which could affect the replicability of the study due to the potential of not consistently repeating the exact procedures. Moreover, it affects the neuronavigational error which could lead to a greater variability of the MEP.

5. Conclusion

This experimental study provides insights into the effect of several measurement-related factors that could be a source of MEP-variability in healthy individuals. At the group level, two interactions were found to have a significant effect on MEP amplitude. These interactions involved neuronavigation errors and %rMT, namely %rMT*Twist Er.*Angular Er. and %rMT*Twist Er.*Target Er.. The supplementary analysis, which included the magnetic field strength components and MSO, found that only MFx and MFz had significant main effects on MEP amplitude. By looking at the variances from these analyses, two main conclusions were drawn. The first is that minimal neuronavigational errors and an intensity closer to the personal rMT could minimise MEP-variability. Secondly, when minimising the MEP-variability, only MFx and MFz should be considered, with the optimal value around 0.0045 for MFx and around three for MFz.

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7. Appendices

Appendix A

Participanten nummer: ____ ____
(in te vullen door de onderzoeker)

Vragenlijst voor voorkeurshand (Oldfield) (vertaling)

Oldfield, R.C. (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, **9**(1), pp. 97-113.

NAAM: …….
GEBOORTEDATUM: .....
TESTDATUM .....
LQ10 + percentiel 10 .....

INSTRUCTIES:

- Geef bij de onderstaande activiteiten weer welke hand u verkiest te gebruiken door een '+' te plaatsen in de passende kolom.
- Als de voorkeur voor die hand zo sterk is dat u nooit de andere hand zou gebruiken bij die taak, geef dit dan weer met een '++'.
- Als u echt geen voorkeur hebt voor één van beide handen, plaats dan een '+' in beide kolommen.
- Voor sommige zijn beide handen nodig. Tussen haakjes staat dan aangegeven voor welke hand de voorkeur gevraagd is.
- Probeer alle vragen te beantwoorden, en laat enkel een vraag onbeantwoord als u echt geen ervaring hebt met de taak.

		links	rechts
1	**Schrijven**		
2	**Tekenen**		
3	**Werpen**		
4	**Knippen**		
5	**Tanden poetsen**		
6	**Mes (zonder vork)**		
7	**Lepel**		
8	**Bezem (bovenste hand)**		
9	**Een lucifer aansteken (hand die de lucifer vasthoudt)**		
10	**Een doos opendoen (hand die het deksel vastgrijpt)**		

Berekening van de lateraliteitsquotient:

LQ= 100 * [(Som van "+" voor rechts) – (Som van "+" voor links)] / (Som van alle "+")

Positief LQ: Rechtshandig; Negatief LQ: Linkshandig

Subject number: __ __ (in te vullen door de onderzoeker)

Appendix B

Screeningsvragenlijst voor Transcraniële Magnetische Stimulatie (TMS)*

		Omcirkel
1.	Heeft u epilepsie of een familiale voorgeschiedenis van epilepsie?.....	J - N
2.	Bent u ooit flauwgevallen? Zo ja, beschrijf de omstandigheden van het voorval.....	J - N
3.	Heeft u ooit een zwaar hoofdtrauma gehad? (vb. gevolgd door bewustzijnsverlies).....	J - N
4.	Heeft u gehoorproblemen of last van een voortdurende ruis?.....	J - N
5.	Bent u mogelijk zwanger?.....	J - N
6.	Heeft u metaal in de hersenen/schedel (behalve titanium)? Vb. Splinter, fragmenten, clips, etc.	J - N
7.	Heeft u een hoorapparaat?.....	J - N
8.	Heeft u een geïmplanteerde neurostimulator?.....	J - N
9.	Heeft u een pacemaker, draden of metaal in uw lichaam?.....	J - N
10.	Heeft u een geïmplanteerde medicatiepomp?.....	J - N
11.	Neemt u momenteel medicatie? Zo ja, gelieve hiervan een overzicht te geven.....	J - N
12.	Heeft u een operatie gehad aan het ruggenmerg?.....	J - N
13.	Heeft u spinale of ventriculaire afwijkingen?.....	J - N
14.	Heeft u reeds TMS gehad in het verleden?.....	J - N
	Een positief antwoord op een of meerdere vragen (1-13) verwijst niet meteen naar een absolute contra-indicatie voor TMS, maar de risico/voordeel verhouding moet dan door de verantwoordelijke onderzoeker (PI) bekeken worden.	

Naam deelnemer:_____ Datum:_____ Handtekening:_____

Handtekening onderzoeker: _____

**Deze vragenlijst is gebaseerd op: Safety, ethical considerations, and application guidelines for the use of transcranialmagnetic stimulation in clinical practice and research..*
Rossi et al. (2009), in Clin Neurophysiol. 2009 Dec; 120(12): 2008–2039. doi: 10.1016/j.clinph.2009.08.016

Appendix C

Subject number: __ __ (in te vullen door de onderzoeker)

Datum: ___ / ___ / 20___

Vragenlijst voor gemoedstoestand (Beck – BDI-II)

Uitleg: Deze vragenlijst bestaat uit een aantal uitspraken die in groepen bij elkaar staan. Lees iedere groep aandachtig door. Kies dan bij elke groep die uitspraak die het best weergeeft hoe u zich de afgelopen week, met vandaag erbij gevoeld heeft. Omcirkel het cijfer dat voor de door u gekozen uitspraak staat. Als in een groep meerdere uitspraken evengoed op u van toepassing lijken, omcirkel dan van deze de uitspraak met het hoogste cijfer. Let erop dat u alle uitspraken van een bepaalde groep leest voordat u uw keuze maakt en dat u slechts 1 cijfer omcirkelt.

- **A. Verdriet**
  - 0. ik voel me niet verdrietig.
  - 1. ik voel me vaak verdrietig.
  - 2. ik ben voortdurend verdrietig en ik kan het niet van me afzetten.
  - 3. ik ben zo verdrietig of ongelukkig dat ik het niet meer verdragen kan.
- **B. Pessimisme**
  - 0. ik ben niet ontmoedigd over de toekomst.
  - 1. ik voel me meer ontmoedigd over de toekomst dan vroeger.
  - 2. ik verwacht dat het niet goed gaat komen met me.
  - 3. ik heb het gevoel dat de toekomst hopeloos is en dat alleen maar slechter kan worden.
- **C. Mislukkingen in het verleden**
  - 0. ik voel me geen mislukking.
  - 1. ik heb meer mislukkingen in mijn leven dan gemiddeld.
  - 2. als ik terug kijk in mijn leven zie ik vele mislukkingen.
  - 3. ik heb het gevoel dat ik als mens een totale mislukking ben.
- **D. Verlies van plezier**
  - 0. ik beleef overal net zoveel plezier aan als vroeger.
  - 1. ik geniet niet meer zoals vroeger.
  - 2. ik vind niet meer echte bevrediging in dingen waar ik vroeger van kon genieten.
  - 3. ik heb nergens meer voldoening van.
- **E. Schuldgevoelens**
  - 0. ik voel me niet bijzonder schuldig.
  - 1. ik voel me schuldig over vele dingen die ik gedaan heb of gedaan had moeten hebben.
  - 2. ik voel me vaak schuldig.
  - 3. ik voel me voortdurend schuldig.
- **F. Strafgevoelens**
  - 0. ik heb niet het gevoel dat ik ergens voor gestraft word.
  - 1. ik heb het gevoel dat ik nog wel eens gestraft zal worden.
  - 2. ik verwacht dat ik gestraft zal worden.
  - 3. ik heb het gevoel dat ik nu gestraft word.
- **G. Zelfongenoegen**
  - 0. ik denk het zelfde over mezelf zoals altijd.
  - 1. ik heb het vertrouwen in mezelf verloren.
  - 2. ik ben teleurgesteld in mezelf.
  - 3. ik vind mezelf niet leuk.

- **H. Zelfkritiek**
  - 0. ik heb niet meer kritiek op mezelf dan anders.
  - 1. ik ben meer kritisch voor mezelf dan vroeger.
  - 2. ik bekritiseer mezelf voor al mijn fouten.
  - 3. ik geef mezelf de schuld van alle slechte dingen die gebeuren.
- **I. Zelfmoordgedachten**
  - 0. ik overweeg absoluut niet om een eind aan mijn leven te maken.
  - 1. ik overweeg wel eens om een eind aan mijn leven te maken, maar ik zou dat nooit doen.
  - 2. ik zou een eind aan mijn leven willen maken.
  - 3. ik zou een eind aan mijn leven maken als ik de kans krijg.
- **J. Huilen**
  - 0. ik huil niet meer dan normaal.
  - 1. ik huil nu meer dan vroeger.
  - 2. ik huil nu om alles.
  - 3. ik wil wel huilen, maar ik kan het niet.
- **K. Agitatie**
  - 0. ik ben niet meer rusteloos of geprikkeld dan anders.
  - 1. ik ben meer rusteloos en sneller geprikkeld dan vroeger.
  - 2. ik ben zo rusteloos of geagiteerd dat ik bijna niet meer stil kan zitten.
  - 3. ik ben zo rusteloos of geagiteerd dat ik moet blijven bewegen of iets moet doen.
- **L. Verlies van interesse**
  - 0. ik heb mijn belangstelling voor andere mensen of activiteiten niet verloren.
  - 1. ik heb nu minder belangstelling voor andere mensen en dingen dan vroeger.
  - 2. ik heb mijn belangstelling voor andere mensen en activiteiten grotendeels verloren.
  - 3. het is moeilijk om nog ergens belangstelling voor te hebben.
- **M. Besluiteloosheid**
  - 0. ik neem nu nog net zo goed beslissingen als vroeger.
  - 1. ik vind het nu moeilijker om beslissingen te nemen dan anders.
  - 2. ik heb nu meer moeite met het nemen van beslissingen.
  - 3. ik kan helemaal geen beslissingen nemen.
- **N. Waardeloosheid**
  - 0. ik voel me zeker niet waardeloos.
  - 1. ik beschouw mezelf minder waardevol en nuttig als vroeger.
  - 2. ik voel me waardeloos ten opzichte van andere mensen.
  - 3. ik voel me volkomen waardeloos.
- **O. Energieverlies**
  - 0. ik heb evenveel energie als anders.
  - 1. ik heb minder energie.
  - 2. ik heb niet voldoende energie om veel te doen.
  - 3. ik kan niets doen omdat ik niet genoeg energie heb.

- **P. Veranderingen in slaappatroon**
  - 0. Er is niets veranderd in mijn slaappatroon.
  - 1a. ik slaap een beetje meer dan normaal.
  - 1b. ik slaap een beetje minder dan normaal.
  - 2a. ik slaap veel meer dan normaal.
  - 2b. ik slaap veel minder dan normaal.
  - 3a. ik slaap bijna de hele dag.
  - 3b. ik word uren te vroeg wakker en kom dan niet meer in slaap.
- **Q. Irritatie**
  - 0. ik ben niet sneller geïrriteerd dan anders.
  - 1. ik ben iets sneller geïrriteerd dan anders.
  - 2. ik ben veel sneller geïrriteerd dan anders.
  - 3. ik ben de hele tijd geïrriteerd.
- **R. Veranderingen in eetlust**
  - 0. ik heb niet minder eetlust dan anders.
  - 0a. mijn eetlust is een beetje verminderd.
  - 0b. mijn eetlust is een beetje groter geworden.
  - 1a. mijn eetlust is veel minder dan vroeger.
  - 1b. mijn eetlust is veel groter dan vroeger.
  - 2a. ik heb helemaal geen eetlust meer.
  - 2b. ik verlang altijd naar eten.
- **S. Concentratieproblemen**
  - 0. ik kan me net zo goed concentreren als vroeger.
  - 1. ik kan me niet meer zo goed concentreren als vroeger.
  - 2. het is moeilijk om lang mijn gedachten erbij te houden.
  - 3. ik kan me op niets meer concentreren.
- **T. Vermoeidheid**
  - 0. ik ben niet meer moe dan anders.
  - 1. ik ben sneller en gemakkelijker vermoeid dan anders.
  - 2. ik ben te moe om veel dingen te doen die ik vroeger wel deed.
  - 3. ik ben te moe om de meeste dingen die ik vroeger deed nog te doen.
- **U. Verlies van interesse in seks**
  - 0. ik ben me niet bewust dat er de laatste tijd iets is veranderd aan mijn belangstelling voor seks.
  - 1. ik heb minder interesse voor seks dan vroeger.
  - 2. ik heb tegenwoordig veel minder belangstelling voor seks.
  - 3. ik heb mijn belangstelling voor seks helemaal verloren.

Appendix D


Continue gegevens
Invloed categorische en/of continue variabelen
gegevens onafhankelijk
herhaalde metingen
gemengd model
1 verklarende variabele
meerdere verklarende variabelen
continu
categorisch
enkel categorisch
enkel continu
continu en categorisch
Onderstellingen:
- lineariteit
- homoscedasticiteit
- normaliteit
andere boom
"Continue gegevens
- 2 of meer groepen"
andere boom
"Continue gegevens
- 2 of meer groepen"
Onderstellingen:
- lineariteit
- homoscedasticiteit
- normaliteit
Onderstellingen:
- lineariteit
- homoscedasticiteit
- normaliteit
enkelvoudige lineaire regressie
meervoudige lineaire regressie
linesir model