2015•2016
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Is there an influence of temperature and intensity on the variability of the magnetic field of a TMS device?

Promotor :
Prof. dr. Raf MEESEN

Copromotor :
dr. Koen CUYPERS

Lennert Guarraci

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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KNOWLEDGE IN ACTION

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Acknowledgement

I am grateful to my promotor, Prof. Raf Meesen, whose expertise and guidance throughout this project has made it possible for me to produce a scientific contribution in the discipline of my interest.

I would also like to thank Dr. Koen Cuypers for his efforts regarding patient recruitment. His aid has significantly facilitated the process of gathering sufficient participants.

Furthermore, I would like to thank my mother, Dr. Bernadette Verhegghen, and my mother-in-law, Prof. Ietje Pauw for their encouragement, motivation and knowledge to maintain a high level of quality during the writing of this work.

Finally, I would like to show my gratitude to my beloved and supportive partner, Dr. Freyja van Lint, for her endless patience and encouragement throughout this adventure, for it has only just begun.

Thank you

"If a cluttered desk is a sign of a cluttered mind, of what, then, is an empty desk a sign?"

— Albert Einstein

Genk, 2016 G.L.

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Research context

This master's thesis is situated in the neurological branch of revalidation sciences and is written by a student of 'Master in Rehabilitation Sciences and Physiotherapy', part of the 'Medicine' department of Hasselt University in Belgium. 'Variability in transcranial magnetic stimulation was assigned as this master's thesis topic and is promoted and co-promoted by Prof. dr. Raf Meesen and dr. Koen Cuypers respectively.

Originally, the thesis was meant to be written by two students. However, due to circumstances one student withdrew immediately after the assignment of the topic. For this reason, the entire thesis is written by Lennert Guarraci. The central format has been used to frame this research.

Since this master's thesis focusses solely on the technical side of transcranial magnetic stimulation, an additional assignment has been included into this work, regarding patient recruitment. The description and clarification of this assignment can be found in appendix A.

Abstract

Background: Variability in transcranial magnetic stimulation (TMS) can originate from many different factors influencing the procedure. Despite being clinically safe, the accuracy of the stimulating pulses could suffer from this variability in a scientific setup, since the margins used are much narrower.

Objectives: To find, explore and address possible influencing factors regarding the TMS stimulus. The focus lies on coil temperature and stimulus intensity.

Methods: An external antenna is fixated to the TMS device after which a series of impulse chains are sent. Data-analysis is done to take into account how much variability can be attributed to a single influencing factor.

Results: Stimulus intensity has a significant effect on variability. Throughout the whole intensity range of the TMS device, variability multiplies by almost tenfold when reaching the maximum intensity. Temperature does not significantly influence variability. Interesting outliers in the dataset are found and addressed.

Conclusion: Next to the distinct results of the effect of coil temperature and stimulus intensity on variability, recommendations regarding the control of sent pulses in a laboratory setting are made.

Introduction

Transcranial magnetic stimulation (TMS) is a frequently used therapeutic technique that directly influences neural tissue. Although studies are done with the goal of constructing a standard protocol (Cuypers, Thijs, & Meesen, 2014; Groppa et al., 2012), there is no basic norm to which all testing is done. Because of this, one could be interested in its consistency throughout a session and between sessions itself. Although single-pulse TMS is assumed to be safe (Anand & Hotson, 2002), no research has been done that checks if the magnetic field generated by the TMS device will stay within the limits of the intended pulse, when used in a laboratory setting. In this research we try to discover -and if necessary address- irregularities that can possibly have a negative effect on a lab based experiment. For example, it is imaginable that spikes or drops in output power could lead to misinterpreted results or false conclusions.

This thesis is a sequel on last year's literature study and study design where different aspects in variability in TMS were addressed. Two main categories of influential factors were established: a technical category containing 'coil shape', 'coil positioning and orientation' and 'stimulus characteristics' and a physical category containing 'physiological and neurophysiological differences between subjects' and 'facilitatory or inhibitory effects on neural excitability through muscle training, attention or other related factors'. With this plethora of variables, distinguishing one factor from another would be impossible without a simplification of the whole TMS procedure. It is only logical to start this research with the most controllable part of TMS, and so solely the technical category will be addressed. Although the final goal is to understand and control the whole TMS procedure, the elimination of the physical category and even different variables of the technical category gives us the chance to look at the stimulus itself. By controlling the coil's shape, while eliminating coil positioning and orientation in space, it is possible to study what happens when modifying the stimulus.

Modifying the stimulus can be done by changing different characteristics. The most applicable and clinically relevant characteristic is the power of the stimulus (Crupi et al., 2013; Darling, Wolf, & Butler, 2006; Julkunen, Saisanen, Danner, Awiszus, & Kononen, 2012). Regarding this component, one could question if the magnetic field that is being generated is

of the same magnitude as the pulse that is being sent by the TMS device. If not, could factors like coil heating, atmospheric humidity (e.g. due to patient transpiration in a clinical setting) or other causes have an influence on pulse output? Coil heating is a known side-effect of using a non-cooled coil (Paulus, Peterchev, & Ridding, 2013; Wassermann, 1998).

Although this medically approved device can be regarded as safe in a patient-based setting, when using it in a laboratory setting, margins are much narrower and outcomes can be subjected to a closer level of examination. The primary focus of this research is thus to look for inconsistencies in coil output throughout different coil temperatures and intensities. We hypothesize that both temperature and intensity will result in more variability in the produced magnetic field. If this variability is found, secondary goals are to explore sources, patterns and solutions for these irregularities. With this, it will provide a first view on the variability of the stimulus in a laboratory setting. If this study aids in the controllability or prevention of variability in the TMS procedure, scientists using this technique could make more compelling claims in their research. When finally making the transfer to a patient-based setting, a controlled or restrained variability in output can lower possible loads on the patient.

Methods

The chosen method is based on the literature study written by Lennert Guarraci under the supervision of prof. dr. Raf Meesen and dr. Koen Cuypers and concerns a laboratory setting. The main goal is to eliminate all variables of the TMS procedure except stimulus intensity. In this way it is possible to link unexpected outcomes only to the modifications made to the stimulus.

Technical setup

A circular coil (Magstim, 80mm coil) in combination with a Magstim 200^2 (Magstim, Whitland, Dyfed, UK) was used for performing magnetic stimulation. A circular copper antenna ($2mm^2$ wire, looped twice) and a temperature sensor were firmly fixated to the circular coil using shrink foil and tie-wraps. The construct of the coil, antenna and sensor are suspended at one meter above ground with a piece of lumber using electrical tape. An electrical fan was placed below the coil to expedite the cooling process in-between experiments. Room temperature was measured by another temperature sensor suspended in the room, and was kept away from external heat or cold sources. Both temperature sensors were attached to a Fluke 52 II thermometer (Fluke Corporation, Everett, Washington, USA) simultaneously. The signal in the form of an electrical current running through the copper wire was measured through CED (Cambridge Electronic Design, Cambridge, UK) and into a computer running Windows XP with CED Signal (Version 4.03, Cambridge Electronic Design, Cambridge, UK) software and stored on a laboratory computer for offline analysis. This setup was kept unaltered for the duration of the study.

Procedure

Measurements start with the researcher recording the temperature of the room and the coil. The CED Signal software sends a chain of 250 to 300 consecutive stimuli, while randomizing the pulses' intensity. This is done by sending an electric current ranging from 0 to 5 volts from the CED device to the Magstim device. Based on this incoming voltage, the Magstim device fires pulses with an intensity that ranges from 10% to 100% of the maximum output, in steps of ten percent. The interstimulus interval, in other words, the duration of

time between pulses, ranges from five to eight seconds. The duration of the pulse is fixed at 1ms, with an approximate rise time of 100µs.

After each single pulse, the researcher manually records the coil temperature. The strength of the sent pulse is displayed both on the Magstim device and on CED Signal, and is being registered by CED Signal itself. The output percentage of the signal is manually recorded next to the manually recorded coil temperature. The computer automatically numbers the generated pulses and combines this with the incoming signal of the measuring device, also CED. By comparing both output percentages shown in the digital output file as in the manually recorded file, it is reassured that no errors could appear in the data. If the digitally recorded and manually recorded values match, the manually recorded temperature is linked to the accompanying sent pulse and the incoming measured signal. The data is discarded if discrepancies are found between these two files.

To minimize a possible pattern in the heating process of the coil, the setup is adjusted to vary the starting coil temperature. This varying starting temperature is realized by air-cooling the coil for a random period of time in between sets of measurements, ranging from five to ten minutes. Sets of measurements were defined by either the ending of the stimuli chain, or when the machine shut down due to overheating. When the temperature of the coil reaches approximately 36.6°C, the inbuilt coil temperature protection engages, putting the Magstim device into its safe inactive default condition. When CED Signal stops receiving signals from the coil, a setting has been activated that stops the program from sending new pulses and thus stops the stimuli chain.

Data-analysis

Statistical analysis is done using SPSS version 23 (IBM SPSS Statistics for Mac) and JMP version pro 12 (SAS Institute Inc, Cary, NC, USA). Output percentage and electric current (mV) is measured in Signal 4.03 and combined with manually recorded temperature values. The presence of outliers will be detected using a scatter plot. There are three possible reasons for finding outliers in the data-set: data entry errors, measurement errors and true unusual values. In the first two cases, errors will be corrected or removed from the data-set. True unusual values could be interesting and are kept in the data-set for close examination.

To understand the effect of temperature on the variation in generated output, linear regression will be run. To be able to run this test, the data-set must meet certain assumptions of linearity, independence of observations using Durbin-Watson statistic, and, in case of the presence of outliers, homoscedasticity and normality of residuals must be checked. The Durbin-Watson statistic can range from zero to four. A value of approximately two indicates that there is no correlation between residuals. Next to the linear regression, a One-way ANOVA will be used to determine if there are statistically significant differences in temperature in the ten groups of input percentage. To be able to run this test, again the data must have no significant outliers, it should be approximately normally distributed and there must be homogeneity of variances. Outliers are to be expected, if this is the case, the Kruskal-Wallis H test will be used as an alternative.

Results

In total, eighteen sessions were held in which a varying number of stimuli were fired, ranging from 154 to 301 stimuli. A total of 4605 measurements were recorded. Each numbered measurement consists of the output percentage, the received pulse, the coil temperature, the day it was measured and the session it was part of. No differences in the manually and the digitally recorded pulse intensity output lists were observed, so no data was needed to be discarded.

Using a scatterplot, five outliers were detected (Fig. 1). When looking at the data, all of these occurred during the first measurement of the day or session. Four outliers occurred when the Magstim device was at a power level 20%, one at a power level of 40%. As the electric current was close to zero in all five cases, it is logical to assume that the device apparently needed time to charge for the needed pulse. Therefore, the decision was made to exclude these five outliers.

When plotting the received signal against the percentage of signal that has been sent out, a strong linear correlation can be visually perceived. Also, variability in measured output seems to be directly proportional to the intensity of the pulse. At the minimum stimulation intensity, a difference of 0.025024 is seen between the highest and lowest received signal. When looking at the highest intensity this difference is 0.230103.

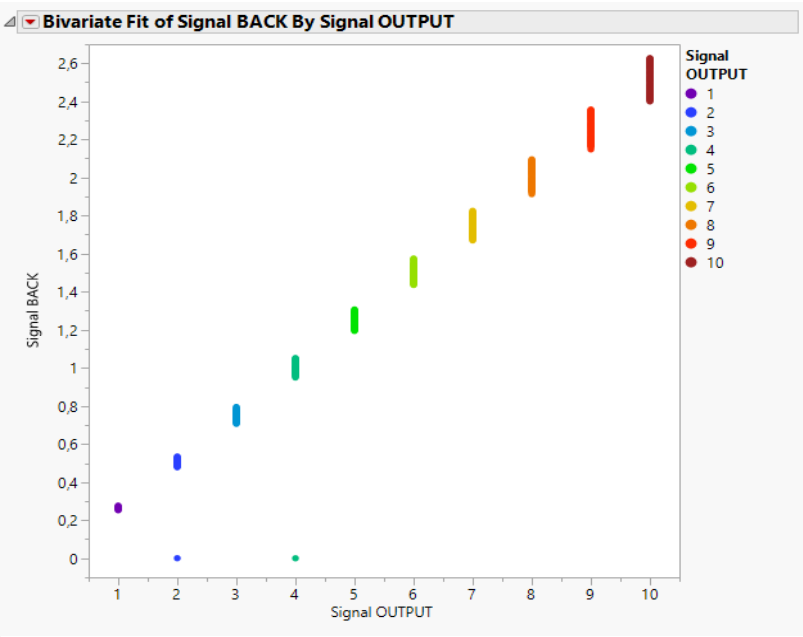


Figure 1. Correlation between output percentage (Signal OUTPUT) and received signal (Signal BACK) showing outliers in two output groups.

When plotting the received signal against the temperature of the coil, a visual representation of variability of the received signal per output percentage and temperature is shown (Fig. 2). Ten defined rows are visible, showing more variability as the output percentage increases. When temperature increases however, variability does not seem to grow.

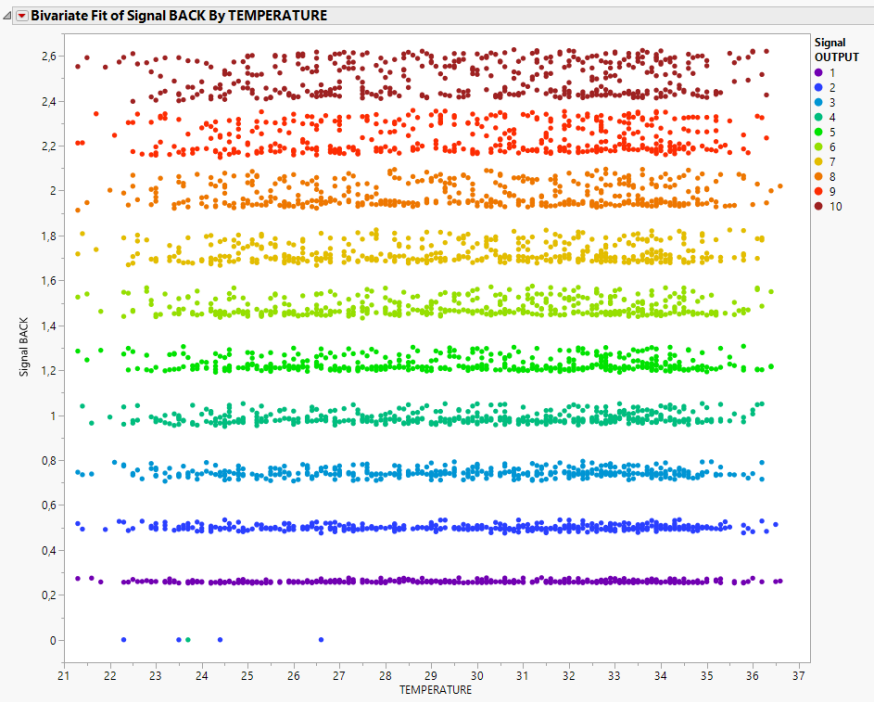


Figure 2. Received pulses sorted by temperature and intensity (Signal BACK). The difference in highest and lowest values of a colored row shows the amount of variability.

It was checked whether the data meets the assumptions for linear regression. A 'ratio' variable was used to exclude the substantial influence that the signal output percentage has on the signal that was received, as is perceived in Fig. 2. This variable was created by dividing the received signal by the signal output. A scatterplot of the temperature against the ratio variable was plotted (Fig. 3). Using a fit line, the scatterplot indicated a linear relationship between the variables.

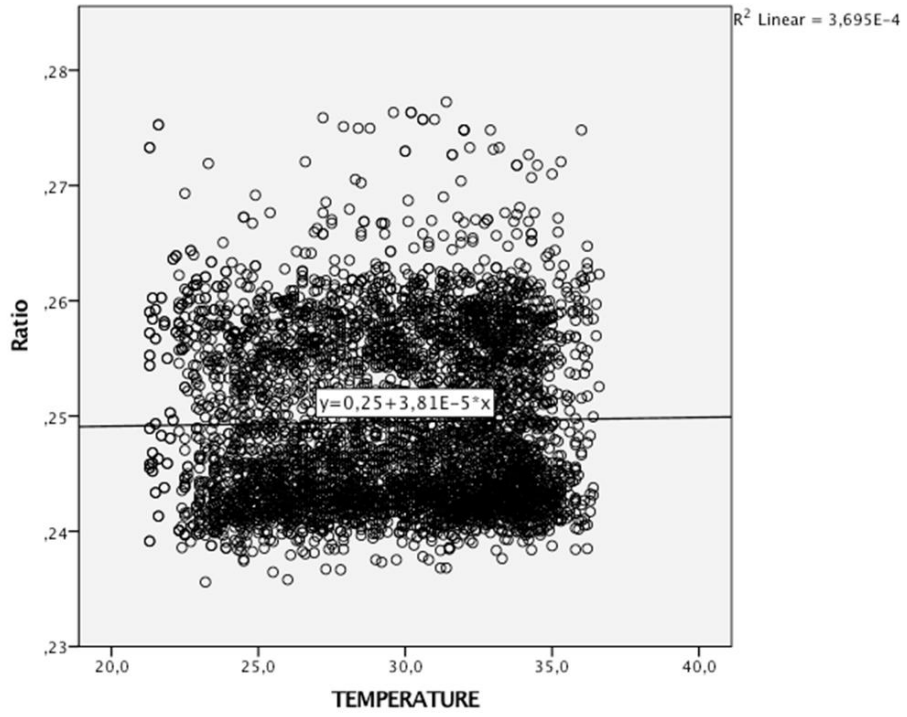


Figure 3. Linearity: Scatterplot with fit line.

There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.861. After removing the five outliers mentioned above, 33 more outliers were observed. As these true measured outliers must be part of the data, there was decided to include these. This decision is supported by the fact that there was homoscedasticity, as assessed by visual inspection of a plot of standardized residuals versus standardized predicted values (Fig. 4). Next to that, residuals were normally distributed as assessed by visual inspection of a normal probability plot (Fig. 5).

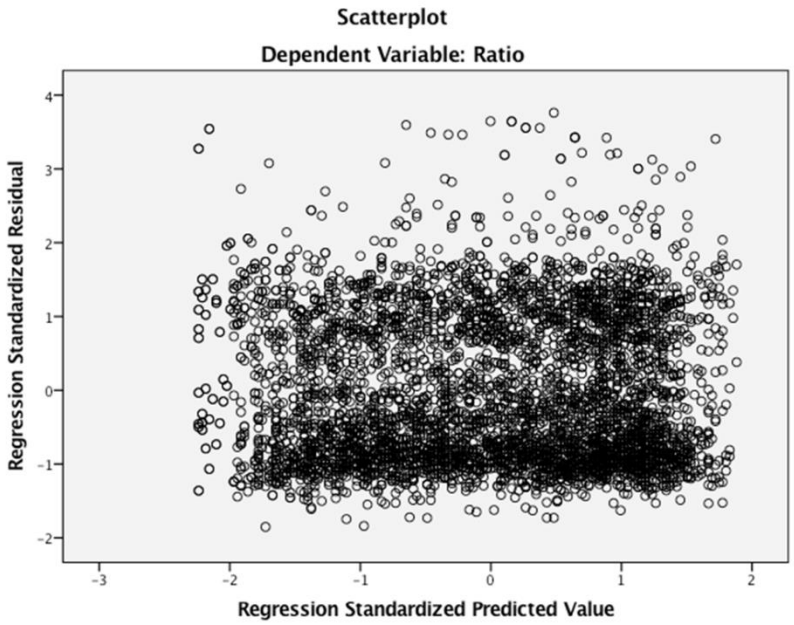


Figure 4. Homoscedasticity

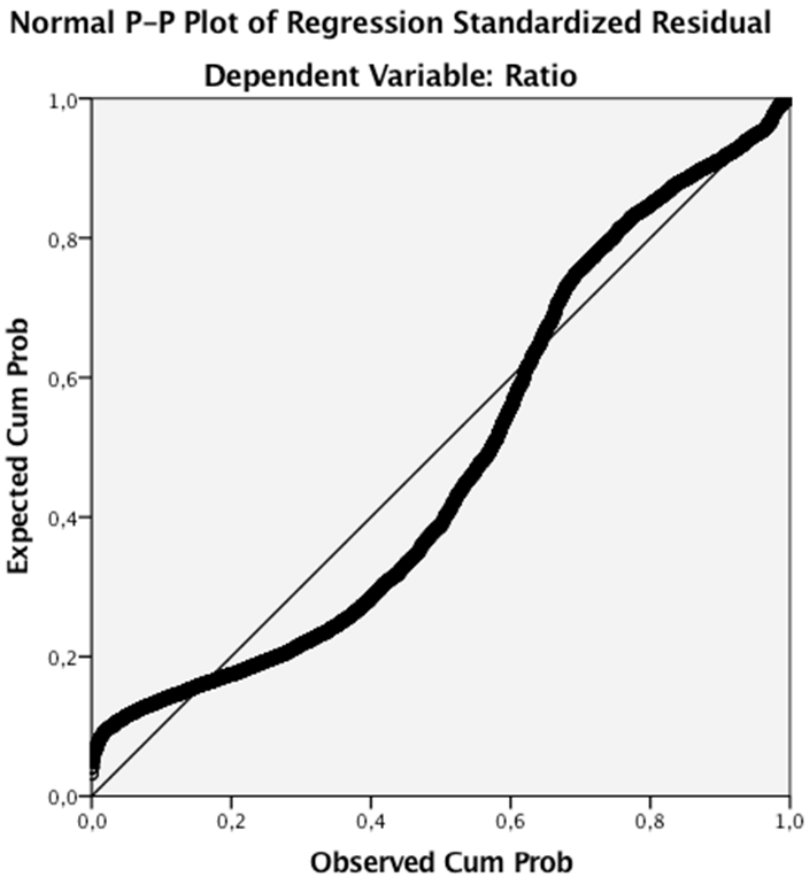
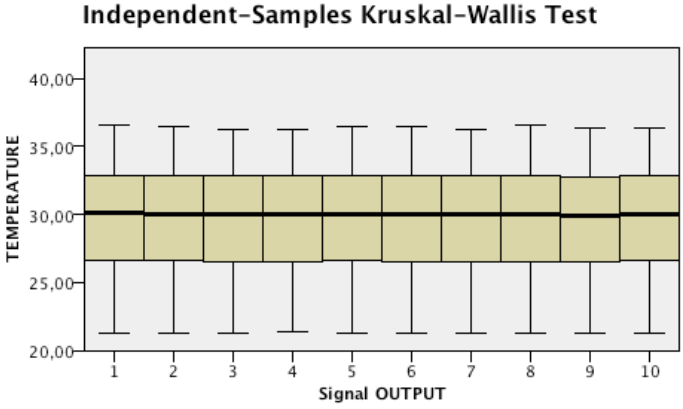


Figure 5. Normality. Plotted points show no major cause for concern.

As a result, the temperature accounted for 0% of the variation in generated output with adjusted R^2 = 0%. Temperature did not significantly predict generated output, $F(1, 4596) = 1{,}69$, $p = 0.193$.

Since 33 outliers remained as part of the data, the One-way ANOVA could not be run reliably. Therefore, a Kruskal-Wallis H test was run to determine if there were differences in temperature between the different input-percentage levels, ranging from 10 to 100%. Distributions of temperature were similar for all groups, as assessed by visual inspection of a boxplot. Median temperatures were not statistically significantly different between groups, $\chi^2(9) = 0.151$, $p = 1.000$ (Fig. 6).



Total N	4.598
Test Statistic	,151
Degrees of Freedom	9
Asymptotic Sig. (2-sided test)	1,000

1. The test statistic is adjusted for ties.
2. Multiple comparisons are not performed because the overall test does not show significant differences across samples.

Figure 6. Kruskal-Wallis H Test. Similarity in distribution shape.

Discussion

The data provided an interesting perspective to this thesis' goal of maximizing the controllability of variability in TMS in a laboratory setting. As expected, a correlation was shown between the output of the device and the recorded measurements. However, a linear diverging rate of variability was observed when increasing the output of the device. Signal variability is multiplied almost by factor ten.

To focus solely on temperature, the recorded signal was divided by the value of output strength. It was concluded that the standard variability of the output ratio did not depend on temperature. Next to that, it is possible to conclude that temperature does not significantly predict variability in the generated output ($F(1, 4596)=1,69$, $p = 0.193$). Furthermore, median temperatures were not statistically significantly different between the different input-percentages ($\chi^2(9) = 0.151$, $p = 1.000$). The part of our hypothesis in which temperature affects variability in TMS can be rejected. However, the linear diverging rate of variability when increasing intensity shows us that this part of the hypothesis can be accepted. This has significant implications on the laboratory setting since a larger margin of error has to be taken into account when using larger stimulus intensities.

Although the five excluded misfires are not significant for our primary question -whether temperature influences output variability-, these can be relevant in both a laboratory and clinical setting. Even though these outliers always appeared at the negative side of the spectrum, explorative research could be done regarding these unexpected pulses. These five underpowered misfires always appeared at the beginning of a stimuli chain. A possible explanation could be that the Magstim device fires before being completely charged. Another possible cause could be the measuring device that is not ready for data input. When longer stimuli chains are needed, a single misfire can be overlooked. When dealing with shorter sessions, a single misfire can significantly distort recorded data.

As is discovered, both in the lower end as in the higher end of stimulus intensity, there are elements that undermine signal accuracy. When dealing with unwanted misfires in the lower end of the spectrum, a possible solution is to let the used setup fire several times without recording. This, however, will not address the lack of accuracy when turning up the Magstim's intensity. A fitting solution for all stimulation intensities is to record every fired

pulse with an antenna like the one used in this setup. The easy obtainable materials for constructing this antenna are uncostly and are easy to add to the setup. Since the firmly attached copper wire does not interfere with TMS experiments, it can remain on the coil throughout sessions and trials. The antenna provides the researcher with accurate information regarding every sent pulse.

Due to logistical circumstances, only one setup could be tested. Even though this database consisted of many measurements, it would be relevant to investigate whether different devices respond differently to variation in temperature. In future studies, it would furthermore be relevant to compare different coils, devices and pulse lengths as these might also influence the variation (Deng, Lisanby, & Peterchev, 2014; Epstein & Davey, 2002; Rothkegel, Sommer, Paulus, & Lang, 2010).

As no previous studies have been published regarding this specific subject, this outcome is a first indication that the Transcranial Magnetic Stimulation device seems to be a reliable instrument when used in a laboratory setting, regarding variance due to temperature. However, for increased reliability and precision it is recommended to pre-fire the setup before use and using a low-cost antenna as supervision.

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Appendix A: Bimanual dexterity study

One of the key competences that Hasselt University grades, is the student's ability to recruit participants for a study. Since the original setup of this master's thesis did not require the inclusion of patients, the student was put in charge of the recruitment of a similar study realized by prof. dr. Raf Meesen. To minimize the chance of selection bias, the recruitment was done via social media (Facebook groups for students), flyers that were put up in the city of Hasselt and Diepenbeek (Belgium) and via direct contact. Also, the study was introduced to the university group for seniors (Seniorenuniversiteit) of Hasselt University. A total of 40 healthy volunteers participated in this study, consisting of two age groups: junior (n=20, aged 18-30 years) and senior (n=20, aged 65-77 years). All participants provided a written informed consent prior to participation. Also, participants were informed about the exclusion criteria both in advance via email of telephone conversation, and on the day of testing via a document. All subjects were right-handed and had normal or corrected-to-normal vision. No subjects had a history of neurological disorders (brain trauma or surgery, therapy resistant epilepsy, meningitis, being unconscious for a period longer than one hour or migraine). Nor did any of the subjects have the presence of metal (e.g. shrapnel) in their body or had a history as metalworker. Final criteria were that no subject had tattooed eyeliner done in the past year, nor that no female subject could be pregnant. This last criterion was checked using a standard pregnancy test. No financial compensation was promised to minimize the chance of people participating wrongfully. Afterwards, participants did receive a voucher for a book or movie ticket.

Auteursrechtelijke overeenkomst

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Is there an influence of temperature and intensity on the variability of the magnetic field of a TMS device?

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2016**

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Guarraci, Lennert