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2014•2015
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef deel 1

Variabiliteitsmeting van Transcraniële magnetische stimulatie (14164)

Promotor :
Prof. dr. Raf MEESEN

Copromotor :
dr. Koen CUYPERS

Lennert Guarraci

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Framework

This master 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 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 master thesis is written by Lennert Guarraci. The central format has been used to frame this research.

The main purpose of this thesis is, first, to explore different aspects and factors that may have an influence on outcomes of transcranial magnetic stimulation, and secondly, to make suggestions on how to reduce possible variability caused by these factors. An insight in this aspect of revalidation may open up new perspectives and elements that are not yet discovered or may have been overlooked.

In part two of this master thesis, the main purpose is to investigate physical environmental factors, like temperature or humidity that may have an influence on transcranial magnetic stimulation. Findings can be used in future attempts to construct a generally accepted protocol for transcranial magnetic stimulation.

Content

Part 1: Literature study

1. Abstract

Background Transcranial Magnetic Stimulation (TMS) is a widespread tool used in the field of neurology and neurological revalidation. Despite its frequent diagnostic and therapeutic use, no complete information is found on factors influencing its efficiency and variability.

Aim To explore studies regarding variability in TMS and to extract and cluster responsible factors which lead to variability in the entire TMS procedure.

Methods A systematic search was conducted in the PubMed and Web of Knowledge databases with terminology based on the research question. Results were screened using established in- and exclusion criteria. Included articles were systematically analyzed, extracting core information and main results. This information was clustered and compared for similarities or contradictions in outcome.

Results Risk for variability is encountered in different steps of the TMS procedure. Even though influencing factors were evidently identifiable, results were sometimes contradictory or difficult to compare due to the large difference in methodology when using TMS. The influencing factors were identified as following: ‘coil shape’, ‘coil positioning and orientation’, ‘stimulus characteristics’, ‘(neuro)physiological differences’ and lastly ‘facilitatory or inhibitory effects on neural excitability through muscle training, attention, or other related factors’.

Discussion The difference in methodology among the selected studies made it difficult to judge the extent of variability caused by a single factor. The exclusion of the studies that address frequency and interval of multiple pulses, limits the view on variability, although this was essential to make results comparable.

Conclusion Variability in the TMS procedure is found in each of the established categories. Identifying the magnitude of influence each category had on variability was impossible due to vastly different approaches in the TMS procedure. An unambiguous protocol is needed for future studies that use TMS.

Keywords Transcranial Magnetic Stimulation, Stimulus, Variability, Corticospinal Excitability

2. Introduction

Transcranial Magnetic Stimulation (TMS) is a noninvasive diagnostic and therapeutic method that uses a generated magnetic field to induce an electric current in a selected area of the brain. Since the introduction (Barker, Jalinous, & Freeston, 1985), the technique has become a common practice among professionals in the field of neurology and neurological revalidation.

As mentioned, TMS can be used diagnostically or as therapy in some forms of neurological-related pathologies. As a diagnostic measure, TMS is often combined with electromyograms (EMG) to record a motor evoked potential (MEP) (Groppa et al., 2012). This action-reaction event is a measure for grading neural conduction and connectivity, processing time, activation thresholds and others (Anand & Hotson, 2002). An important sensitive indicator of abnormality in certain disorders is the corticomotor threshold. This can be defined as the power level at which 50% of the time a response is detected. Five responses out of ten stimuli are suggested as a standard, due to variable responses. Others find that manual calculation of cortical silent period (CSP) using TMS results in excellent reliability between raters with different experience levels (Kimberley et al., 2009).

TMS is preferred over other techniques such as transcranial electric stimulation (TES), since the generated magnetic field used in TMS has no significant nociceptive effect on the scalp (Paulus, Peterchev, & Ridding, 2013). Furthermore, to achieve noticeable, safe and consistent results, mapping out the brain is a necessary requirement. Bony landmarks on the subject's skull are commonly used to start determining relevant neural hotspots of the brain. However, large variability is found when using specific coil designs and different angles of stimulation (Cohen et al., 1990). Next to that, it is hypothesized that inter-individual anatomical form factors such as gyri, sulci or the orientation of interneurons could have an impact on variability between these individuals (Gangitano et al., 2002). This data gives the impression of a substantial level of inter-individual variability and a low level of intra-individual variability. This could imply a good inter-rater reliability which suggests that a certain level of consistency is required regarding the outcome of TMS.

Repetitive TMS (rTMS) is a more intensive form of TMS where two or more pulses are fired in rapid succession. Although there is no evidence of long-term neurological, cardiovascular or hormonal adverse effects in healthy subjects using single pulses of TMS, rTMS could cause pain, seizures or other adverse effects (Anand & Hotson, 2002). This variant (rTMS) will not be researched because of its completely different approach and usage.

Paulus describes that the main disadvantages of TMS are the high-powered, bulky equipment and coil heating due to the high electric current required for the procedure (Paulus et al., 2013). TMS therapy is contraindicated in the presence of pacemakers and/or other electronic implants.

These results open up perspectives for further investigation regarding factors that influence variability in the TMS-procedure. The aim is to distill, group and explore different components that cause inconsistencies when using TMS in a research and clinical setting.

3. Methodology

3.1 Research question

Which factors lead to variability in corticospinal excitability through stimuli provided by Transcranial Magnetic Stimulation?

3.2 Literature search

The onset of this literature search is January 2015 and is kept up-to-date to obtain the most recent and relevant articles. Used databases are PubMed (http://ncbi.nlm.nih.gov/pubmed) and Web of Knowledge (http://apps.webofknowledge.com). To asset the highest amount of matching and relevant articles, different Mesh-terminology and free terms are used and formed into four groups:

1: (("Transcranial Magnetic Stimulation"[Mesh]) OR Transcranial Magnetic Stimulation) OR TMS

2: (stimuli) OR stimulus

3: (cortical excitability) OR corticospinal excitability

4: (Variability) OR Variable

The rationale behind this search is explained by the fact that TMS is the constant factor in the whole equation. Measurable, variable outcomes will be inspected after different interventions regarding stimuli show their effect on cortical excitability.

The lack of MESH-terminology is compensated by adding comparable free terms to broaden the search: e.g. ‘variability’ and ‘variable’. MESH-terminology, free terms and abbreviations are then combined via Boolean operator ‘OR’. As a result, articles that only use abbreviations are included. The four groups are then combined with the Boolean operator ‘AND’ to narrow down the search. In the Web of Knowledge database, topics are used instead of MESH-terms to enlarge the total amount of researchable studies.

No limits are used to acquire an unbiased set of information; this method leads to inclusion of older articles as well, potentially illustrating formerly used procedures. Articles are then selected based on relevance by analyzing title, abstract and –if necessary– also the full text.

3.3 Selection criteria

The following inclusion criteria are used to screen the articles: (1) Technical research related to intensity, frequency and duration of the TMS-pulse, coil shape and orientation (and other physical differences); (2) Relevance to variability in TMS; (3) TMS on motor cortex.

Articles are excluded if: (1) Studies that are not original research (e.g. editorials, letters, or without abstract); (2) Comparison of techniques as treatment; (3) Repeated TMS; (4) Not written in the English or Dutch language.

3.4 Quality assessment

As the broad nature of this literature study withholds the use of a predefined checklist (e.g. Cochrane checklist), a general table was constructed and used as a benchmark to assess the quality of the found literature. As seen in appendix 8.4, various aspects of the selected studies were distilled and categorized in five columns next to the articles author, name and publication year. This methodological approach facilitates data extraction when comparing selected literature.

3.5 Data extraction

As described in part 3.4, extracted data is categorized in ‘aim of study’, ‘population’, ‘method’, ‘main results’ and ‘category’. Although most of these are self-explanatory, the latter describes the way in which the study researches variability in TMS.

4. Results

4.1 Results study selection

When reviewing all the included articles, different factors causing variability were identified. From the total of 29 included articles as seen in appendix 8.3 (seventeen from PubMed and twelve from Web of Knowledge, see appendix 8.1 and 8.2 respectively), two articles addressed coil shape, eight articles focused on coil placement and orientation, eleven articles analyzed factors associated with stimulus characteristics, neurophysiological variability was assessed in seven articles and nine articles reported variability in corticospinal facilitation and inhibition through muscle training, focus of attention, or other related factors. Three of the articles were only available as abstracts and are nevertheless included in case of unquestionable relevance.

4.2 Results quality assessment

Appendix 8.4 displays the results of the quality assessment. Since no uniformity was found in the method section of the articles, articles with poor methodology were included as well to make sure no selection bias would occur. Lack of uniformity is shown in discrepancies in the number, sex, age, health and handedness of the participants. Another aspect of lack of uniformity is related to the technical setup, such as the brand and model of the used device, and the possible addition of cooling of the coil. When addressing methodology, different approaches on calculating thresholds, differences in coil-to-cortex distance and stimulus characteristics are found. Although all of these factors are relevant to the aim of this study, differences between articles make comparison much more difficult. On the other hand, this broad approach generates a full overview of all possible influential factors.

4.3 Results data extraction

To answer the question which factors lead to variability in corticospinal excitability through stimuli provided by transcranial magnetic stimulation (TMS), the process is divided into different components that supposedly have influence on the entire TMS-procedure. These different components are defined by analyzing the included literature and determined to be relevant to this research question. The components include ‘coil shape’, ‘coil positioning and orientation’, ‘stimulus characteristics’ such as intensity, frequency, duration and interval of the provided transcranial magnetic stimulus, ‘physiological and neurophysiological differences between subjects’ and lastly ‘facilitatory or inhibitory effects on neural excitability through muscle training, attention, or other related factors’.

Coil shape

The generated magnetic field induces electric current in the cortical area, and therefore, the shape and size of the coil will directly influence the shape and size of the generated magnetic field. This may have an effect on skull penetration, surface area, electric current intensity or focal point of the induced electric current.

In 2012, Fleming found poor reliability in circular coils for MEP resulting from stimuli of 120% resting motor threshold (rMT). He also suggested using figure-of-eight coils confidently when investigating cortical excitability over time (Fleming, Sorinola, Newham, Roberts-Lewis, & Bergmann, 2012).

Next to the shape, the size influences variability as well. For comparable mean MEP areas, in most subjects a greater variability is found when using a smaller, more focal, coil (Kiers, Cros, Chiappa, & Fang, 1993). Although difference in coil shape and size is considered in a few studies, data is conflicting. Nevertheless, the limited data regarding this subject clearly suggests differences in outcome, and is therefore of interest to this research.

Coil positioning and orientation

To achieve the most optimal result, it is important to consider the positioning of the coil in relation to neural focal points on the skull. Before both positioning and orientation, mapping of the skull has to take place. Although it is assumed that the laborious procedure of mapping will be done thoroughly, it might still be a cause for variability.

Traditional ways of cortical mapping are time consuming and can lead to variability (Littmann, McHenry, & Shields, 2013). Although techniques have been improved, there are still studies being performed which try to reduce mapping time by analyzing the minimum of Interstimulus Intervals (ISI) for the delivery of stimuli, and by analyzing the minimum number of stimuli needed to create a map as well (van de Ruit, Perenboom, & Grey, 2015). Littmann tests variability of motor cortical excitability of a new mapping procedure and finds highly reliable MEP amplitudes between sessions (Littmann et al., 2013). When looking for the Center of Gravity, the position where the highest MEP amplitude weight is recorded for a positive TMS site on the map, Littmann finds minimal shifts between sessions in the new mapping procedure. Julkunen did not find a significant difference either in variability of motor threshold between navigated and non-navigated TMS mapping procedures. However, this study did find a significant more stable MEP with a higher amplitude and shorter latency in navigated TMS (Julkunen et al., 2009).

Additionally, coil-to-cortex distance (CCD) is studied by measuring motor threshold after artificially increasing the distance. Stimulation intensity is found to be correlated with CCD, while the cortical electric field at MT level (EFmt) is not (Julkunen, Saisanen, Danner, Awiszus, & Kononen, 2012). Furthermore, Julkunen found that CCD had a significant, albeit minor, within-subject effect on single-trial MEPs at various stimulation intensities (Julkunen et al., 2012). Ellaway compares hand-held coil positioning to trials in which the coil was clamped into position. However, no significant differences were found in the mean coefficient of variation of amplitude of the Compound Motor Evoked Potential (cMEP) (Ellaway et al., 1998). This is backed by Jung, where also no difference in coefficient of variance of MEP is found between navigated and non-navigated TMS in input-output curves (Jung et al., 2010). When combining location, orientation, tilt and stimulus strength, Schmidt finds that confounding effects in physical variance were mainly due to fluctuations in location (36%) (Schmidt et al., 2015).

Another factor Ellaway addressed is coil orientation in relation to the cortex. The study showed that the direction of coil orientation did have an influence. Coil orientations that induce posterior to anterior (P/A) flowing currents in the brain have the shortest latency in cMEP, followed by the anterior-medial (A-M) direction and finally the lateral to medial (L/M) direction (Ellaway et al., 1998). Next to that, the highest reproducibility of MEPs was along an axis of approximately 45° to the nasion-inion line. This reflects the imaginary line between the forehead and the nose, and the lowest point of the skull from the back of the head (Littmann et al., 2013).

The differences in addressing cortical mapping seem to have no major effect on variability. There appears to be good understanding of coil positioning, although ways to reduce mapping time are still sought for. Except for articles regarding the coil-to-cortex distance, the major part of the studies do not address this factor when describing the procedure. Since the description of coil orientation is not an accustomed practice, it suggests that variability could, partially, be explained by this factor.

Stimulus characteristics

Next to coil shape, placement and positioning, the characteristic of the generated stimulus could be a reason why variability exists. When looking at the used stimulus and the resulting MEP, relation, linearity and other points of interest are researched as well in studies.

As expected, stimulus intensity through TMS has a direct relation to the recorded MEP amplitude (Crupi et al., 2013; Darling, Wolf, & Butler, 2006; Julkunen et al., 2012; A. E. Smith, Sale, Higgins, Wittert, & Pitcher, 2011). Remarkably, Fox describes a nonlinear relation between the two (Fox et al., 2006). This could be the result of the following: Smith et al. (2011) finds a decrease in the Coefficient of Variation regarding MEP amplitude as stimulus intensity increases from 100% rMT to 140% rMT (A. E. Smith et al., 2011). Low-intensity stimuli get a variable response (Poh, Riek, & Carroll, 2013) and this variability decreases as stimulation intensity increases (Darling et al., 2006; Kiers et al., 1993).

Regarding the same subject Cuypers et al. (2014) wishes to optimize the TMS-protocol for the acquirement of a reliable Corticospinal Excitability (CSE) estimation using single-pulse TMS. The effects of two stimulations intensities (110%rMT and 120%rMT) are evaluated. Data shows that stimulation intensity has no significant influence on CSE estimation (Cuypers, Thijs, & Meesen, 2014). Temesi suggests that higher intensities (120-130%rMT) potentially cause increased coactivation and discomfort, while lower intensities (120% active Motor Threshold (aMT)) have a tendency to underestimate evoked responses (Temesi, Gruet, Rupp, Verges, & Millet, 2014).

Rothkegel et al. (2010) explains that intensity of TMS usually is adjusted by changing the amplitude of the generated electrical field, while using a fixed duration. Therefore, the study uses two pulse durations to assess influence on several physiological parameters. Found is that a 1.4 times longer duration of the pulse decreases motor thresholds by 20%, compared to the standard pulse. Rothkegel also finds a reduction of pulse-to-pulse variability in contralateral cortical silent period when using this longer pulse. To elongate pulse duration is thus suggested as possible alternative in subjects with a very high motor threshold, since both amplitude and pulse duration affect the strength of a TMS pulse (Rothkegel, Sommer, Paulus, & Lang, 2010).

Although MEP amplitudes at low intensity stimuli are not affected, exercise prior to high intensity stimuli can lower MEP amplitudes of the specific muscle (Crupi et al., 2013). Analogously, this effect is also found when comparing high intensity (70% MEPmax) and low intensity (20% MEPmax) stimulation after ballistic exercise. Results show that ballistic exercise significantly facilitates MEP size for stimuli in the high-intensity range (Poh et al., 2013). For this reason it has to be taken into account when providing high-intensity stimuli through TMS in people that have been exercising recently, that MEP may be divergent.

Included studies show that stimulus characteristics are one of the most discussed and researched factors when it comes to Transcranial Magnetic Stimulation. Stimulus intensity seems to show a present but non-consistent effect on variability. A probable explanation is the difference in methodology between studies, resulting in contradictory outcomes. Pulse duration is found to be a rarely researched topic in TMS. Although methods are often adequately described, pulse duration is seldom explained in the text. Since rTMS is not included in this research, frequency and interval are not extracted from the data.

Physiological and neurophysiological differences between subjects: age, interhemispherical connection or other related factors

As seen in most of therapeutic interventions, (neuro-)physiological differences between subjects are often a factor leading to discrepancies in effectivity of given intervention. This, among other elements, is the reason why many studies tend to look for components in this terrain.

Despite that age is a frequent factor for variability, there is evidence that advancing age does not alter the corticospinal stimulus-response characteristics in males (Pitcher, Ogston, & Miles, 2003; A. E. Smith et al., 2011). Smith (2011) also suggests that prior studies finding age-related differences are likely due to influences of female change over age. Smith previously stated that aMT is higher in old men than in young (Ashleigh E. Smith, Ridding, Higgins, Wittert, & Pitcher, 2009). Pitcher (2003) also found a similar interaction between age and motor threshold (Pitcher et al., 2003). An ageing-effect is found in direction and magnitude of paired associative stimulation (PAS); this could be explained by the measure of plasticity of the brain related to age (Muller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008).

In 2014, Cuypers finds no significant influence of gender when searching a method for reliable CSE estimation in healthy adults (Cuypers et al., 2014). Although no evidence is found for other neurophysiological variables (e.g. MEP amplitude, resting and active MT, short-interval intracortical inhibition, intracortical facilitation and cortical silent period duration) to consistently predict responses to PAS, greater session-reproducibility was found in sessions that took place in the afternoon. While underlying reasons are not known, hypothesized is that hormonal and neuromodulatory factors are to influence neuroplasticity (Sale, Ridding, & Nordstrom, 2007). Lastly, Van der Kamp (1996) finds no diversity between right- and left-handed groups regarding mean ages and sex distributions (van der Kamp, Zwinderman, Ferrari, & van Dijk, 1996).

It is observed that physiological and neurophysiological differences between subjects show different outcomes. Again, the large diversity in methodology can be suspected as the culprit of these irregular results.

Facilitatory or inhibitory effects on neural excitability through muscle training, (visual) attention, or other related factors

Controllable variables that affect levels of neural excitability are often researched in studies regarding MEPs through TMS. One of the more obvious components is muscle alteration originating through active tasks like muscle training. There is evidence that, depending on task duration, there is a decrease of amplitudes of MEPs at rest. Also, fully compensatory increases in premovement facilitation are induced after exercise with a duration of five minutes. If this exercise lasts ten minutes, only partially compensatory increases are generated, with loss of temporal modulation (Crupi et al., 2013). Strength training is found to significantly increase CSE-measures and to reduce short-interval intracortical inhibition (ICI) (Weier, Pearce, & Kidgell, 2012). Another study finds that ballistic training has the advantage to significantly facilitate MEP size for high-intensity stimuli (Poh et al., 2013). Poh also demonstrates that momentary effects of corticospinal excitability (CSE) are more subtle in the untrained limb than after cyclic flexion-extension movements of the biceps and maximal voluntary contractions in the trained limb.

Next to ballistic training, also attention, visual response or the grade of tiredness caused by exercise will probably generate ipsilateral CSE-effects in opposite direction (Poh et al., 2013). Visually controlled low-level contraction significantly increased amplitude of TMS evoked MEPs (Darling et al., 2006). However, spatial attention alone does not show significant difference regarding baseline MEP amplitudes (Kotb et al., 2005). Kotb also finds that both short- and long-latency afferent inhibition were significantly larger during a right spatial attention task in right-handed healthy volunteers (Kotb et al., 2005).

One study suggests that fluctuations in CSE result in variability in TMS-based MEP (Ellaway et al., 1998). Evidence shows that anesthesia has no impact on muscle strength (Rossi, Pasqualetti, Tecchio, Sabato, & Rossini, 1998). When being exposed to fear-related music, Giovanelli finds that MEP increased in size compared to neutral music or a control stimulus. Music inducing other emotional experiences yielded no effect (Giovannelli et al., 2013).

Its clinical relevance is shown when applying TMS on frightened individuals; since fear can generate discrete level of muscle contraction, increased levels of MEP amplitude could be recorded. Muscle training and attention seem to have an indisputable, but temporary, effect on variability in TMS.

5. Discussion

5.1 Reflection about quality assessment

Due to lack of methodological uniformity in the obtained articles, quality assessment could not be done using a predefined checklist. Therefore, general aspects of included articles were extracted into the following subcategories: aim of study, population, method, main results and category of variability. The different approaches of TMS have to be kept into account especially when extracting the main results from the article. In some articles, no full text was available, so general results were based on the abstract of the article. These articles are marked in appendix 8.4, which further describes the main components of each article. The deliberate (although necessary) decision to exclude pulse frequency and interval when addressing pulse characteristics, narrows down the results to make the assessment of quality more comparable between studies.

5.2 Reflection about findings relating to the research question

Many factors of variability are repeatedly researched throughout the studies. There is a shortcoming of other, and maybe unknown physical influencing factors, such as temperature, humidity, and more related factors. A remarkable flaw amongst findings is the lack of research regarding pulse duration. One study searches for differences in variability between two pulse durations, in contrary to other studies which do not, or merely briefly, address this when describing the TMS procedure.

5.3 Recommendations for future research

Lack of uniformity in the TMS protocol seems to be a reoccurring problem in current research. This leads to contradicting results amongst the studies. Although some studies make good attempts to establish a generally accepted protocol, there still is no consensus regarding the standard procedure on which research should be based. There is a strong need for an evidence-based protocol utilized by all TMS studies, to compare the variability-related findings to. In the same way that Cuypers (2014) suggests a reliable CSE estimate, studies need to be done regarding stimulus characteristics, coil shape, and other factors to define the most beneficial protocol for all (Cuypers et al., 2014).

5.4 Reflections about strengths and weaknesses of the literature study

The broad spectrum of this literature study makes it difficult to pinpoint small and subtle, influencing elements next to the substantial, already-known factors. This broad approach will inevitably lower the precision of the study, but is necessary to include articles addressing these less known factors.

Although the researcher has the necessary critical attitude, the lack of experience of the researcher has to be taken into account. The absence of uniformity in methodology makes the quality assessment difficult and needs to be meticulously inspected by a trained eye.

6. Conclusion

Since the introduction of TMS in 1985, research has been performed to evaluate outcome variability and safety of the new technique. Due to lack of proper evidence based scientific research and the novelty of the technique itself, no clear consensus in TMS procedure or indisputable research protocol has emerged since. The scattering of plausible influencing factors has thus led to a myriad of studies where the TMS procedure has been addressed in many different ways. Even though the quality of the results is not necessarily linked to the fact that different approaches are used, it makes the assessment of various influencing factors much more complex. Variability in TMS is found in abundance regarding different factors amongst various articles; however, contradicting outcomes can be explained by the difference in methodology. Although attempts are made to introduce uniformity when adding TMS to a study, a clear protocol has to be made for future studies with inclusion of TMS.

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8. Appendix

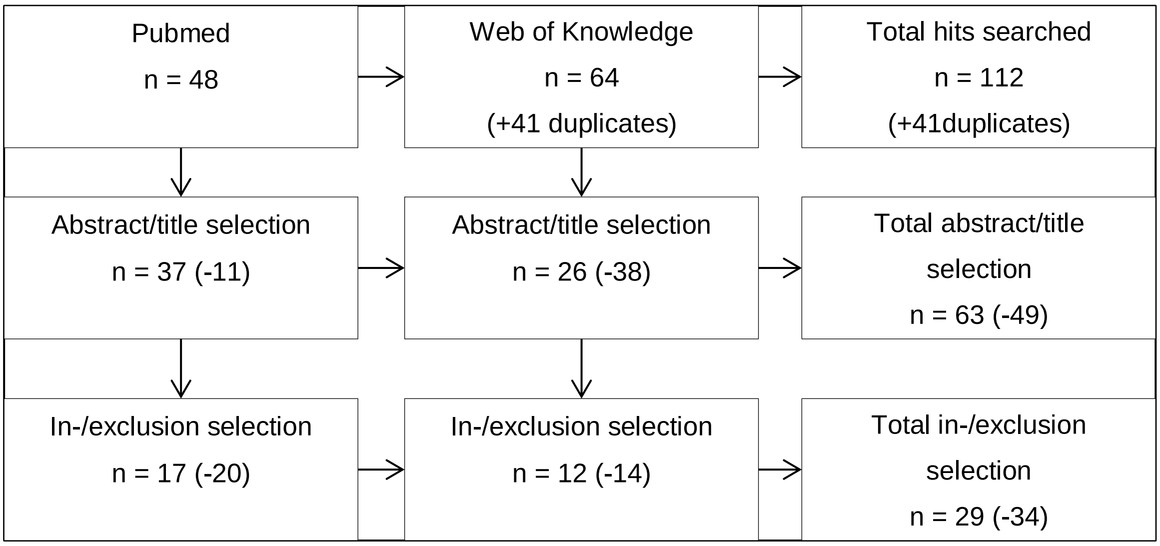
8.1 Pubmed search

Search	Query	Items found
#16	Search **((((("Transcranial Magnetic Stimulation"[Mesh]) OR Transcranial Magnetic Stimulation) OR TMS)) AND ((stimuli) OR stimulus)) AND ((cortical excitability) OR corticospinal excitability)) AND ((Variability) OR Variable)**	48
#15	Search **(Variability) OR Variable**	442101
#14	Search **Variable**	269914
#13	Search **Variability**	187599
#12	Search **(cortical excitability) OR corticospinal excitability**	9449
#11	Search **cortical excitability**	9203
#10	Search **corticospinal excitability**	1057
#9	Search **(stimuli) OR stimulus**	267816
#8	Search **stimuli**	169957
#7	Search **stimulus**	137429
#6	Search **(("Transcranial Magnetic Stimulation"[Mesh]) OR Transcranial Magnetic Stimulation) OR TMS**	14861
#5	Search **TMS**	8249
#4	Search **Transcranial Magnetic Stimulation**	11485
#3	Search **"Transcranial Magnetic Stimulation"[Mesh]**	7256

8.2 Web of knowledge Search

Set	Query	Items found
#5	**#4 AND #3 AND #2 AND #1** Timespan=All years Search language=Auto	**Approximately 156** (107)
#4	TOPIC: (variability) OR TOPIC: (variable) Timespan=All years Search language=Auto	**Approximately 2,104,943**
#3	TOPIC: (cortical excitability) OR TOPIC: (corticospinal excitability) Timespan=All years Search language=Auto	**Approximately 12,557**
#2	TOPIC: (stimuli) OR TOPIC: (stimulus) Timespan=All years Search language=Auto	**Approximately 513,834**
#1	TOPIC: (Transcranial Magnetic Stimulation) OR TOPIC: (TMS) Timespan=All years Search language=Auto	**Approximately 35,911**

8.3 Flowchart



8.4 Data extraction table

Article; Author (Year)	Aim of study	Population	Method	Main results	Category
Crupi D, (2013) Protracted exercise without overt neuromuscular fatigue influences cortical excitability	Determine the cortical mechanisms that underlie the transition from effective performance to its disruption	44 healthy right-handed adult subjects (30 men)	TMS at rest and during motor response preparation (5-10 min) with stimulus intensity set at baseline (MEP with 0.7mV)	Protracted exercise induces significant decrements in corticospinal excitability with initial impairment of the phasic motor neurons that are recruited at higher stimulus intensities	• (Neuro)physiological differences
Cuypers K. (2014) Optimization of the Transcranial Magnetic Stimulation Protocol by Defining a Reliable Estimate for Corticospinal Excitability	To optimize TMS-protocol for a reliable CSE estimate using single-pulse TMS. Minimal number of stimuli required for a reliable CSE estimate.	36 healthy young subjects. 18 males and 18 females.	Using a double-blind crossover procedure, 2 blocks of 40 stimuli (110% or 120% rMT) where given in randomized order.	• At least 30 consecutive stimuli for the most reliable CSE estimate. • No significant influence on CSE estimation from stimulus intensity or gender. • Subject with higher rMT need fewer stimuli for CSE estimation.	• Stimulus characteristics • (Neuro)physiological differences
Darling W.G., (2006) Variability of motor potentials evoked by transcranial magnetic stimulation depends on muscle activation	Determine whether motor cortex excitability assessed using TMS is less variable when subjects maintain a visually controlled low-level contraction of the muscle of interest	8 healthy adult male subjects	Two sets of five single pulse TMS stimuli with intensity increasing from 0.9 - 1.6 x RMT	• Stable low intensity contraction helps stabilize cortical and spinal excitability • Individual MEP amplitudes depended on the combined influence of stimulus intensity and pre-stimulus EMG activation level	• (Neuro)physiological differences

Article; Author (Year)	Aim of study	Population	Method	Main results	Category
Ellaway P.H., (1998) Variability in the amplitude of skeletal muscle responses to magnetic stimulation of the motor cortex in man	Assessment of variability in cMEP amplitude in response to synchronous bilateral tms	5 normal healthy subjects (4 male)	50 paired stimuli with intensity to produce cMEPs of similar amplitudes bilateral	No effect on variability by clamping coil or altering orientation of the coil	• Coil positioning and orientation
Fleming M.K. (2012), The Effect of Coil Type and Navigation on the Reliability of Transcranial Magnetic Stimulation. *ABSTRACT*	To investigate reliability of transcranial magnetic stimulation parameters for three coil systems.	10 healthy subjects.	Stimulus response curves, intracortical facilitation & inhibition tested in right FDI. Per subject, each coil is tested twice. Navigation through a custom build system.	• Moderate-to-good reliability for hand-held and navigated figure-of-eight coils. • Poor reliability for MEP amplitude at 120% rMT for circular coils. • Good SICI, bad ICF reliability for al coil systems. • Higher MEP(120rMT) for circular coil than figure-of-eight coil. • Figure-of-eight coils for a confident over-time investigation of CSE.	• Coil shape • Coil positioning and orientation
Fox P.T., (2006) Intensity modulation of TMS-induced cortical excitation primary motor cortex	Characterization of the intensity dependence of the local and remote effects of TMS on human motor cortex	12 normal subjects	3 Hz TMS stimuli to hand region of primary motor cortex with intensity at 75%, 100% and 125% of motor threshold	Stimulus-response functions for PET-measured hemodynamic variables and MEP amplitude were similar non-linearly increasing with stimulus intensity	• Stimulus characteristics
Giovannelli F. (2013) The effect of music on corticospinal excitability is related to the	Influence of emotions, triggered by music listening, on motor cortex activity.	23 healthy volunteers.	MEP response on TMS while listening to music that evokes emotions.	• Fear-related music significantly increases MEP amplitude in comparison to neutral music or the control group.	• Facilitatory / inhibitory effects.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
perceived emotion: a tms study.					
Julkunen P. (2009) Comparison of navigated and non-navigated transcranial magnetic stimulation for motor cortex mapping, motor threshold and motor evoked potentials	To compare accuracy of cortical mapping and the cohorence of motor threshold (MT) and MEP between navigated and non-navigated TMS.	8 volunteers	Two sessions, in which each both hemispheres where tested with and without navigation.	• Similar session-to-session motor MT with no differences between hemispheres or with or without navigation. • In navigated TMS, stimulus location is more spatially discrete; MEP more stable, significantly higher amplitudes and shorter latencies. • Significant differences in MEP whether navigation is used. • MT not significantly dependent on discrete stimulation site.	• Coil positioning and orientation. • (Neuro)physiological differences.
Julkunen P. (2012) Within-subject effect of coil-to-cortex distance on cortical electric field threshold and motor evoked potentials in transcranial magnetic stimulation	To analyze the effect of coil-to-cortex distance (CCD) on motor threshold.	6 volunteers	CCD is increased in 5-7 steps. For every CCD, motor threshold was estimated.	• Stimulus intensity correlates to CCD. • Significant effect of CCD on within-subject variation in stimulus intensity. • Significant, minor within-subject effect of CCD on single-trial MEP induced at different intensities of stimulus. • Maximum cortical electric field at MT level can be used to reduce within-subject variation effect when measuring CSE.	• Coil positioning and orientation.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
Jung N.H. (2010) Navigated transcranial magnetic stimulation does not decrease the variability of motor-evoked potentials	To investigate whether navigation decreases MEP amplitude variability and increase test-retest reliability.	8 healthy subjects (4 male)	Subjects tested in 3 moments, with and without navigation. Recording of input-output curves, motor threshold and MEP.	• No difference in coefficient of variance of MEP between navigated and non-navigated TMS in input-output curves. • No significant difference in MEP amplitude between sessions. • MEP variability probably due to uninfluencable neurophysiologic factors.	• Coil positioning and orientation. • (Neuro)physiological differences.
Kiers L., (1993) Variability of motor potentials evoked by transcranial magnetic stimulation	Determination variables causing variability of MEPs evoked by transcranial magnetic stimulation	5 healthy subjects	30 consecutive stimuli at 4 stimulus intensities in 10% increments above resting motor treshold	Variability of MEP response size was inversely related to stimulus intensity, pre-stimulus voluntary muscle contraction, recruitment of motoneurons and size of field generated by magnetic coil Variability	• Coil shape • Facilitatory / inhibitory effects.
Kobayashi M, (2003) Transcranial magnetic stimulation in neurology	Highlight possibilities and preliminary assessment of clinical value of TMS in neurology	Review	Search for articles in Medline and the references from relevant articles Search terms: “transcranial magnetic stimulation” and “magnetic stimulation”, with several neurological diseases and terms of internationally renowned experts in the use of TMS	• No clear clinical indication for application of TMS as a diagnostic or therapeutic tool in any neurological or psychiatric disease • Exciting capabilities for clinical trials	• None

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
Kotb M.A., (2005) Effect of spatial attention on human sensorimotor integration studied by transcranial magnetic stimulation	Investigation of effect of spatial attention on afferent inhibition	9 right-handed healthy subjects (7 males)	Pulse configurations 3 s apart of TS alone, and 11 pulses with MNS preceding the TS, with stimulus intensity set at 3 x sensory threshold	Enhancement of the afferent inhibition induced by spatial attention to the stimulated side is likely to reflect the interaction between attention and sensorimotor integration	• Facilitatory / inhibitory effects.
Littmann A.E., (2013) Variability of motor cortical excitability using a novel mapping procedure	Assess reliability of a novel TMS motor cortex mapping procedure	6 healthy adult volunteers (5 male)	5 stimuli per intensity at 80, 100, 120, 140, and 160% RMT in pseudorandom order at a frequency ≤ 0.1 Hz	Reliable mapping procedure: • Reproducibility of MEPs was highest along an axis approximately 45◦ to the nasion–inion. • Stimulus–response MEP amplitudes showed moderate to high reliability (ICC 0.54–0.95). • Mean CoG shift between sessions was 2.79 ± 1.2 mm.	• Coil positioning and orientation.
Müller-Dahlhaus J.F., (2008) Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation	Assess interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation	27 healthy adult subjects	225 pairs of electrical stimulation of the right median nerve at the level of the wrist and a single TMS pulse over the hot spot of the APB motor representation of the left primary motor cortex at a rate of 0.25 Hz	Measures of motor cortical excitability (RMT, MEP1 mV) and age determine direction and magnitude of PAS eVects in individual subjects	• (Neuro)physiological differences.

Article; Author (Year)	Aim of study	Population	Method	Main results	Category
Pitcher J.B. (2003) Age and sex differences in human motor cortex input-output characteristics *ABSTRACT*	To investigate age and gender on stimulus-response curves for MEP by TMS.	42 subjects		• No effect of age on rMT, maximal MEP amplitude or maximal slope of stimulus-response curve, although higher intensities where needed in older subjects. • Greater trial-to-trial variability in older subjects • Significant interaction between age, threshold and trial-to-trial variability of MEP amplitude. • Overall MEP variability decreases when stimulus intensity increases above threshold, but less rapidly in older than younger subjects. • Larger MEP variability in women, but age and threshold are stronger modulators than gender.	• Stimulus characteristics. • (Neuro)physiological differences.
Poh E, (2013) Ipsilateral corticospinal responses to ballistic training are similar for various intensities and timings of TMS	Investigate ipsilateral corticospinal responses to ballistic training	18 healthy right-handed adult subjects (12 men)	Stimulation of ipsilateral cortex at high intensitiy (70% MEP) and low intensity (20% MEP) at specific time-points after 300 ballistic movements	• Ballistic practice significantly facilitated MEP size for high-intensity stimuli • No tendency towards depression of MEP amplitude at any point post-exercise for both testing intensities	• Stimulus characteristics. • Facilitatory / inhibitory effects.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
Rossi S., (1998) Modulation of Corticospinal Output to Human Hand Muscles Following Deprivation of Sensory Feedback	Excitability and conductivity of corticospinal tracts	10 healthy adult subjects (5 male)	MEPs were simultaneously recorded from two ulnar-supplied muscles during full relaxation and voluntary contraction	physiological latency ‘‘anticipation’’ of • MEPs recorded during active contraction versus relaxation was reduced in the FDI, but not in ADM • FDI cortical representation was significantly reduced, while ADM representation remained unchanged or enlarged • MEP and F-wave variability significantly decreased in the FDI but not in theADM	• Facilitatory / inhibitory effects.
Rothkegel H. (2010) Impact of pulse duration in single pulse TMS.	The influence of pulse duration on (neuro)physiological parameters of CSE using single pulse TMS.	12 healthy right-handed, non-smoking subjects (6 men).	rMT, aMT, recruitment curves, MEP in contracting and relaxing hand muscles, contralateral and ipsilateral silent periods on TMS of 2 durations.	• 20% decrease of motor thresholds when using a 1.4x longer pulse. • No significant effect on threshold adjusted measurements of CSE. • Reduction of pulse-to-pulse variabiliaty in contralateral cortical silent period when using the longer pulse.	• Pulse characteristics • (Neuro)physiological differences.
Saisanen L. (2008) Motor potentials evoked by navigated transcranial mganetic stimulation in healthy subjects *ABSTRACT*	To provide normative values for clinically relevant TMS parameters.	65 healthy volunteers, (22-81 years).	Focal TMS pulses on primary motor area, recording of muscle response, motor threshold, latencies and amplitudes of MEP and silent period duration.	• No results in abstract.	• None

Article; Author (Year)	Aim of study	Population	Method	Main results	Category
Sale M.V., (2007) Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation	Effectiveness and reproducibility of two PAS paradigms, and neurophysiological and experimental variables that may influence this	20 healthy adult subjects	• 132 paired stimuli at 0.2 Hz (short protocol) or 90 paired stimuli at 0.05 Hz (long protocol) • 11 tested in morning, 9 in afternoon	• The short PAS protocol produced greater APB MEP facilitation (51%) than the long protocol (11%), and this did not differ between • sessions • Both PAS protocols induced more APB MEP facilitation, and greater reproducibility between sessions, in experiments conducted in the afternoon	• (Neuro)physiological differences.
Schmidt S. (2015) Nonphysiological factors in navigated TMS studies - Confounding covariates and valid intracortical estimates	Variance dissociation from physical and physiological factors for CSE estimation. To establish a predictive intracortical electric field estimation from spherical head models.	22 healthy volunteers (11 males)	Stepwise regression of event-related physical parameters measurements. Comparing of predictive validity and partitioned parameter variance for a target-controlled and a nontarget-controlled experiment.	• CSE variability is reduced if physical parameters variance is partitioned. • Physiological and physical variance has to be partitioned in TMS studies to make confounded data interpretable.	• (Neuro)physiological differences.
Smith A.E. (2009) Age-related changes in short-latency motor cortex inhibition	Ageing effect on short-interval intracortical inhibition (SICI) and/or facilitation (ICF).	17 old and 13 young males.	Paired-pulse TMS at intervals of 1, 3, 10 and 12ms, using a 95% aMT pulse as conditioning intensity resulted in MEP.	• Greater SICI in left hemisphere, regardless of age. • At 3ms is SICI increased in old men in left hemisphere. At 1ms in both hemispheres. • Higher aMT in old men. • Men with same aMT and relative to aMT SICI constructed curves, fail to show age-related sici increasement. • Less than 20% variability is due to	• (Neuro)physiological differences.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
				age-related changes in aMT.	
Smith A.E., (2011) Male human motor cortex stimulus-response characteristics are not altered by aging	Evaluation of male human motor cortex stimulus-response in relation to aging	13 young healthy male subjects, 18 old healthy male subjects; all right-handed	Ten stimuli were delivered at each intensity, beginning 10% below rMT and increasing in 5% steps either to 100% of stimulator output or to a stimulus intensity at which MEP amplitude had reached a plateau	• There was no effect of age group or hemisphere on MEP amplitude or any other stimulus-response characteristic • MEP variability was strongly modulated by resting motor threshold but not by age	• Stimulus characteristics. • (Neuro)physiological differences.
Temesi J. (2014) Resting and active motor thresholds versus stimulus-response curves to determine transcranial magnetic stimulation intensity in quadriceps femoris	To find an appropriate stimulus intensity (SI) to evaluate variables in muscle fatigue.	8 healthy active men.	Determining of stimulus intensity by rMT, aMT and maximal MEP amplitude from stimulus-response curves.	• SI from contractions of 10% maximal voluntary force (MVC) was higher than SI at 120% aMT and from MVC stimulus-response curve. • 20% MVS stimulus-response curve is appropriate for TMS determination in quadriceps femoris. • 120-130% rMT have the potential to cause discomfort and increased coactivation.	• Stimulus characteristics.
Tranulis C., (2006) Motor threshold in transcranial magnetic stimulation - comparison of three estimation methods	Comparison of three methods to estimate MT in a clinical setting	10 healthy adult subjects	6 MT estimates (2 per method)	No significant differences in variability of MT estimation were found between the methods, but the Rossini-Rothwell method was significantly shorter (half the number of stimuli).	• Stimulus characteristics. • (Neuro)physiological differences.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
van de Ruit M., (2015) TMS Brain Mapping in Less Than Two Minutes	To reduce the time needed to create a reliable brain map	12 healthy adult subjects	Frameless stereotaxy was used to monitor coil position as the coil was moved pseudorandomly within a 6 6 cm square. Maps were acquired using 1e4 s ISIs	Reliable maps could be created with 63 stimuli recorded with a 1 s ISI. Maps created acquiring data using the pseudorandom walk method were not significantly different from maps acquired following the traditional method	• Stimulus characteristics. • (Neuro)physiological differences.
van der Kamp W., (1996) Cortical excitability and response variability of transcranial magnetic stimulation	Assessment of relationships between stimulus intensity and MEP latency, amplitude, duration, and area of the hypothenar muscles	12 right- and 14 left-handed subjects	Intensity of stimulation was increased in 5% steps up to 100%, four stimuli were given per intensity at 20-s intervals	• The mean response threshold was significantly lower for preferential stimulation (32%) than for nonpreferential stimulation (45%) • With increasing stimulus intensities, MEP amplitudes still increased at 100% intensity in some subjects while in others the stimulus response-relations saturated • MEP amplitudes at an intensity of 20% above threshold ranged between 6 and 100% of MEP amplitude at maximum intensity • Differences between dominant and non-dominant hands were not seen, regardless of handedness • The SD of latency, amplitude, duration, or area depended on stimulus intensity	• Stimulus characteristics. • (Neuro)physiological differences.

Article; Author (Year)	**Aim of study**	**Population**	**Method**	**Main results**	**Category**
Weier A.T., (2012) Strength training reduces intracortical inhibition	Investigation of influence of 4 weeks of heavy load squat strength training on corticospinal excitability and short-interval intracortical inhibition	12 healthy adult subjects	Shortinterval intracortical inhibition was assessed using a subthreshold (0,7x AMT) conditioning stimulus, followed 3 ms later by a supra-threshold (1.2x AMT) test stimulus	The strength training group attained 87% increases in 1RM squat strength, significant increases in measures of corticospinal excitability, and a 32% reduction in short-interval intracortical inhibition following the 4-week intervention compared with control.	- Facilitatory / inhibitory effects.

8.5 Progress form master thesis part 1

DATE	CONSULTATION	SIGNATURES
24/11/2014	Master thesis explanation and general guidelines (Skype)	Promotor: Prof. dr. Raf MEESEN Student: Lennert GUARRACI
15/12/2014	Practical meeting in the lab	Promotor: Prof. dr. Raf MEESEN Copromotor: dr. Koen CUYPERS Student: Lennert GUARRACI
19/02/2015	Feedback literature research (Skype)	Promotor: Prof. dr. Raf MEESEN Student: Lennert GUARRACI
13/05/2015	General feedback on thesis (Skype)	Promotor: Prof. dr. Raf MEESEN Student: Lennert GUARRACI
09/07/2015	Agreement hand-in thesis and final accents	Promotor: Prof. dr. Raf MEESEN Student: Lennert GUARRACI

Part 2: Research Protocol

1. Introduction

The majority of articles found in the preceding literature study have made it clear that transcranial magnetic stimulation (TMS) used in clinical and research setting still suffers from many known and unknown factors inducing variability. Although some try to introduce uniformity in the TMS protocol (Cuypers et al., 2014; Tranulis et al., 2006), a lot of research still has to be done. Emerged influencing factors can be divided into (technical) variability originating from the TMS device and/or the environment and (physiological) variability due to human diversity. The ambition to reduce variability in the whole TMS procedure can only be fulfilled if known influences are narrowed down to a strict, controllable few. This is why the decision is made to exclude all human variability by removing the TMS device from the clinical setting and reintroducing it into a controlled lab setting. With this setup, experiments can be conducted whilst controlling known influencing factors such as pulse duration (Rothkegel et al., 2010), pulse intensity (Fox et al., 2006), coil to antenna (instead of coil to cortex) distance (Julkunen et al., 2012), coil shape (Fleming et al., 2012; Kiers et al., 1993). In this way, it becomes possible to systematically evaluate factors that have not yet been researched, such as coil temperature, atmospheric humidity, and others.

2. Goal research

In the light of the ambition to reduce variability in the whole TMS procedure, the current main goal is to find the influence of coil temperature and other physical or environmental factors on outcome variability.

3. Methods

3.1 Design

An experimental design is used for this research since the goal is to identify a cause-and-effect relationship between factors. A commercially available TMS device (Magstim 2002, Whitland, Wales, UK) will deliver magnetic stimuli through a number of different coils. The used coil is fixed on a piece of lumber using electrical tape and suspended at one meter above ground level, so air can flow under the stimulating coil. To expedite the temperature regulation, an electrical fan rested below the suspension, is used to cool the coil between experiments. Room temperature is measured before and after the chain of stimuli, and coil temperature is measured directly after each stimulus, as well at five minutes after experiment termination. This is done by the same device using two temperature sensors and is recorded by the researcher.

Next to coil temperature, the induced magnetic field is measured by a separate antenna that has been fixed in place with electrical tape following the shape of the stimulating coil. This coil-to-antenna distance is close to zero since the antenna and coil are touching. The benefit of this setup is that influencing factors can be controlled and kept the same between experiments. 300 consecutive pulses are fired with randomized pulse intensity, ranging from 10% to 100% of the maximum output of the device, with an interstimulus interval time ranging from 5 to 8 seconds between pulses. The signal received by the antenna is recorded through a computer running Windows XP® into software CED Signal (Version 4.03, Cambridge Electronic Design, Cambridge, UK) and stored on a laboratory computer for offline analysis.

3.2 Outcome Measures

Pulse intensity, coil temperature and the signal received will be registered per signal. In this way, it becomes possible to observe the effect of a specific temperature at a specific impulse intensity on the variability of the received signal. Later, room temperature, room humidity and other technical factors can be added to the equation.

3.3 Data-analysis

To determine whether there is a possible interaction effect between temperature and stimulus intensity on variability of the received signal, a two-way-ANOVA will be used, when the assumptions of the two-way-ANOVA are met.

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comparison of three estimation methods. *Neurophysiol Clin, 36*(1), 1-7. doi: 10.1016/j.neucli.2006.01.005

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Variabiliteitsmeting van Transcraniële magnetische stimulatie (14164)

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
Jaar: **2015**

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Guarraci, Lennert

Datum: **17/08/2015**