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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Exploring the relationship between neurophysiological measures and clinical outcomes in persons with MS

Lotte Tans
Julie van Herk

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

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
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Research context

Our master thesis takes place in the perspective of neurological rehabilitation in the category of neurophysiological research. Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. The inflammation can occur throughout the entire central nervous system which is why symptoms are very diverse and widespread. Impairments in hand manipulation or walking ability arise often. In this study we examine whether there is a relation between these impairments and neurophysiological techniques, namely the triple stimulation technique (TST) and transcranial magnetic stimulation (TMS).

There is currently little research into this link, which is why we are comparing different upper and lower limb clinical tests with TST and TMS measurements. This study will be especially attractive to researchers in the neurophysiological domain and to physiotherapists specialized in rehabilitation in persons with MS. Understanding pathophysiology and underlying mechanisms can provide more targeted rehabilitation and thus better help for the patient.

This study is a continuation of our research from the previous year. The recruitment of the participants and the research were performed by Dr. Fanny Van Geel. The tests and measurements were administered at REVAL (UHasselt) and at CHU (Liège) by Dr. Fanny Van Geel, Dr. Dominique Dive and Dr. Xavier Giffroy. We took over these data and performed the research independently. For us as researchers, it is a limitation that we did not collect the data ourselves, which makes it difficult for us to know the details of the executed study procedures. We conducted the data analysis in our study ourselves with additional help from our co-promoter Dr. Lisa Tedesco Triccas and Dr. Fanny Van Geel. Lotte Tans and Julie van Herk wrote the entire thesis together with improvements from Prof. Dr. Peter Feys, Dr. Lisa Tedesco Triccas and Dr. Fanny Van Geel.

1 Abstract

Background: Little is known about the relationship between transcranial magnetic stimulation (TMS) or triple stimulation technique (TST) and multiple clinical tests. Especially TST is not often studied in comparison to TMS.

Objectives: This study aims to investigate the correlation between different TST or TMS parameters and multiple clinical tests in persons with multiple sclerosis (pwMS), including whether there is a difference between the pwMS and healthy controls (HC).

Participants: 24 participants, 16 MS (mean age = 48.3y) and eight HC (mean age = 56.8y), were included in this study. MS had a mean EDSS score of 3.2.

Measurements: All participants performed a six-minute walking test (6MWT), timed 25-foot walk test (T25FW), two nine-hole peg tests (NHPT) and several maximal isometric force (Fmax) tests. TST was measured only in the upper limbs (UL). TMS (latency and amplitude) was applied in both the upper and lower limbs (LL).

Results: Several significant differences were found between MS and HC: in the 6MWT, T25FW and Fmax of the right UL and LL ($p<0.01$) and left UL ($p<0.05$). For TST, the amplitude ratio of the right UL ($p<0.05$) is significantly different and in TMS amplitude-cortex in the left UL, right LL ($p<0.01$) and in the left LL ($p<0.05$). For TST, we found significant correlations between amplitude-ratio left and Fmax left LL ($p<0.01$) and amplitude highest severity and left LL ($p<0.00625$). Several correlations between amplitude or latency and a clinical test ($p<0.05$) were found in TMS. With the Bonferroni correction, one significant correlation in TST and two in TMS ($p<0.00625$) remained.

Conclusion: We observed a difference between MS and HC in different tests. In the MS group, both in TMS and TST, reduced amplitudes reflect motor impairments of which axonopathy is the basis.

Keywords: Multiple Sclerosis, Neurophysiology, Transcranial magnetic stimulation, Triple stimulation technique, Clinical outcomes

2 Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system characterised by inflammation and degeneration of myelin[1]. The underlying cause of MS is uncertain, although complex gene-environment interactions play a significant role[2]. People with MS show several symptoms, but the most common is fatigue. They also experience deterioration of upper and lower limb function[3,4,5,6]. Larocca (2011)[7] found that 41% of MS patients have difficulty walking, of which 13% were unable to walk at least two times per week. Some of the challenges in MS that make walking difficult are fatigue, weakness and spasticity, ataxia, and balance issues[7]. Other signs are sensory disturbances, vision problems, intestinal and urinary dysfunction and cognitive and emotional disturbances[8].

The symptoms related to MS have a major impact on quality of life since they influence activities in daily life. Therefore, the assessment of these impairments plays an important role in treatment strategies. Hand grip strength is a commonly used outcome measure to determine the upper limb at body function level in a standardised manner[9]. The capacity of the upper limb at activity levels is frequently measured using the nine-hole peg test (NHPT)[9]. For the lower limb, the six-minute walk test (6MWT) is often used to assess the walking distance and endurance in MS patients[10].

In addition to a neurological examination[11], MRI is a widely used imaging technique in the diagnosis of pathophysiological processes in MS. It is an essential tool to support diagnosis, longitudinal monitoring, evaluation of therapeutic response and scientific research in MS. Another method for identifying the neural motor system is with a neurophysiological measurement such as transcranial magnetic stimulation (TMS)[12]. In this technique a coil is placed above the skull through which a very high intensity current is conducted. This generates a magnetic field which passes through the skull bone and on his turn induces an electric field in the cortex. When the intensity of the induced current is sufficient this produces action potentials which activate brain networks[13]. This technique is non-invasive, and well tolerated[14]. As a result, from the elicited action potentials a motor evoked potential (MEP) can be visualized[13]. The main MEP parameters are amplitude and latency. Amplitude is the peak to peak and is a representation of the percentage of muscle response evoked by supramaximal stimulation of the target muscle. Latency is the delay time between stimulation and onset of the response in the target muscle. Modifications in MEP latency are related to demyelination whereas amplitude reduction represents axonal loss or conduction block[15].

A derivative of TMS is the triple stimulation technique (TST). TST consists of one transcranial stimulation followed by two stimuli on the peripheral nerve[17]. These three stimuli are appropriately timed to allow collisions of the evoked action potentials at the desired locations[18]. TST is a

neurophysiologic manner of measuring deviations in persons with MS (pwMS). It quantifies findings on a neuronal level and is able to detect abnormalities in conductibility[19] and axonopathy[21].

TST can serve as an additional value for accurate and functional quantification of central motor axonal loss. Moreover, abnormal TST values in MS are very reliable in long-term follow-up[20,21,22,23]. Nevertheless, previous studies often only look at one clinical test and its relationship with TST or TMS parameters[20,22,23]. For example, Giffroy et al. (2019)[21] found that there was a high negative, significant correlation between the expanded disability status scale (EDSS) and TST ($R=-0.74$; $p<0.0001$). Meaning that a higher score on the EDSS, reflecting higher disability, is associated with lower TST outcomes. This means that a more deteriorated walking ability is related with worse conduction of stimuli[21]. For TMS it was found that a lower EDSS correlates with more normal values in latency and amplitude. This also indicates that a more normal conduction of stimuli is related with a better walking ability[24]. Only one study examined the correlation between TST or MEP parameters with multiple clinical tests (NHPT, timed 25-foot walk test (T25FW), and the JAMAR) at once in pwMS[21]. Besides, studies where a comparison between TST and TMS measures was made, are very rare.

Therefore, our research is of added value to current findings. A comprehensive study using several neurophysiological techniques can explain more precisely the underlying mechanisms for symptoms found by clinical outcome measures. Since both TMS and TST have high temporal and spatial resolution, we would like to investigate whether a causal link can be made between functional and structural loss in pwMS. The present study therefore focuses on the correlation between TST or MEP parameters and multiple clinical outcome measures of the upper and lower limbs.

Based on these findings, we generally hypothesise that a correlation will be present between lower amplitudes and higher latencies and reduced performance on clinical outcomes. In detail, for the 6MWT and maximal isometric force (Fmax) this means less distance covered and less force and thus a negative correlation with latency and positive with amplitude. For the NHPT and T25FW it means more time was needed to fulfil the task and thus a positive correlation with latency and negative correlation with amplitude will be found. We also expect to find a moderate to strong correlation between the latencies and amplitudes taken from the upper limb in both TST and TMS and the NHPT and Fmax of the upper limb muscles. A moderate to strong correlation will be found between the latencies and amplitudes taken from the lower limb in TMS and the T25FW, 6MWT and Fmax of the lower limb muscles. If we look at the difference between the MS and HC group, we hypothesise that the HC group achieves better scores on all clinical outcomes and neurophysiological parameters compared to pwMS.

3 Methods

This clinical trial was set up as a collaboration between Centre Hospitalier Univeristaire Liège (CHU) Liège, the Rehabilitation MS Centrum in Pelt and the University of Hasselt and was approved by the Comité d'Éthique Hospitalo-Facultaire Universitaire de Liège, Medical Ethics Committee of UHasselt and Overpelt (B707201835771).

3.1 Participants

The recruitment of outpatients with MS was done in the Rehabilitation and MS Centrum Pelt, the University of Hasselt and through flyers and posters. The inclusion criteria were (1) age between 18-70 years, (2) confirmed diagnosis according to the McDonald criteria[25] and (3) able to walk independently or with unilateral support for six minutes without rest. Participants were excluded if there was an (1) exacerbation or relapse in the last three months before study and (2) other medical conditions interfering with walking ability (e.g., cardiac, or respiratory diseases, arthritis and fibromyalgia, stroke, Parkinson's disease).

3.1.1 Participant characteristics

From all participants, data was collected by Dr. Fanny Van Geel about their age, gender, height, and weight. Only the pwMS provided additional information about disease duration and MS-type. The EDSS score was also determined in this group. Finally, it was assessed which body side was strongest in both the MS and HC groups. We determined this by counting how many patients had the highest Fmax on the right bodyside and the dividing this by the number of participants in a group. To become a percentage, we multiplied this by 100. We have acquired these data for this study.

3.2 Procedure

During TMS and TST testing, participants were sitting in a chair with backrest and arms supported.

3.2.1 Neurophysiologic measures

3.2.1.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was performed by Dr. Xavier Giffroy and Dr. Dominique Dive bilaterally in both the upper limb (UL) and lower limb (LL). They used a six-channel Keypoint G4 apparatus (Natus Medical Incorporated) and a Magstim 200 device (The Magstim Company Ltd., Whitland, UK) with a circular (70mm inner diameter) hand-held coil (maximal output 2.2T). Pre-gelled disposable surface electrodes (Alpine Biomed) were used for recording. A corresponding ground electrode was taped to the forearm and lower leg. For the UL, a bandpass filter setting was set from 0.5 kHz to 2 kHz while for the LL this was 0.5 kHz to 3kHz.

Motor evoked potential (MEP) parameters were measured from the first dorsal interosseus (FDI) muscle for the UL by stimulation of the ulnar nerve, the motor cortex, and the cervical root at C8. For the LL, stimulation of the peroneal nerve, motor cortex and lumbar root at L4-L5 was applied for monitoring motor responses at the tibialis anterior (TA) muscle. First a supramaximal electrical stimulation was applied to the ulnar nerve at the wrist and common peroneal nerve at the knee to record the compound muscle action potential (CMAP). Second, three TMS were given at the motor cortex in the hand and leg areas. Motor threshold intensity was set at 130% for stimulation of the motor cortex and at 80% and 100% for foraminal electromagnetic stimulation of C8 and L4-L5, respectively. The best MEP recording, thus shortest latency and highest amplitude was selected out of five trials for each limb. In this study the parameters derived from MEP measures were peripheral, radicular, and cortical latencies (msec). Absolute baseline-to-peak amplitudes (µV) from the peripheral and cortical stimulations were also considered (Figure 1).

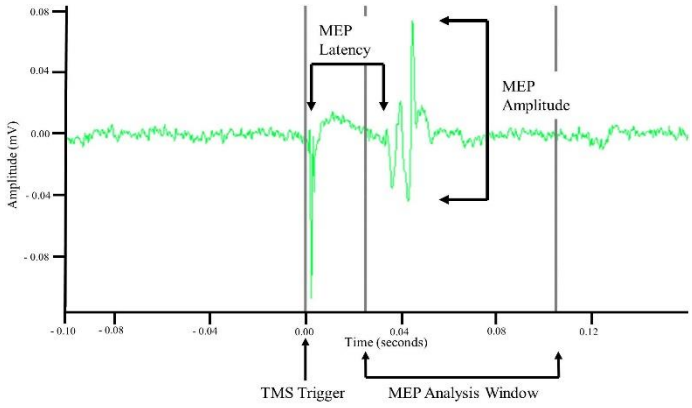

Figure 1: *Example of recorded MEP via surface electromyography[16].*

3.2.1.2 Triple stimulation technique

A specific triple stimulation technique (TST) software (Natus Medical Incorporated) was added to the MEP equipment for TST measurements (Figure 2). The TST test (TSTT) is compared to a TST control (TSTC) which is illustrated on figure 3. Peripheral collisions were obtained by consecutively applying three stimuli with specific delays. The first stimulus was given at the cortex (1) at 130% above motor threshold by TMS. This supramaximal stimulation caused a depolarisation of the cortical motor neurons of the target muscles, namely de FDI and abductor digiti minimi (ADM) (b). A second stimulus was given, after a first delay, to the ulnar nerve at the wrist (2) for the UL. The ascending action potentials from the wrist and the descending discharges from the cortex result in a first collision. This collision does not elicit a response (a*b). After a second delay, the last stimulus (100%) was applied to Erb's point (3) which resulted ultimately in a second motor response in the target muscles (c). The collision occurs between descending and ascending discharges in case of central conduction failure

(c**b). Due to the proportion of conduction failures, there is a size reduction in the second response[21]. This procedure was performed for both left and right UL.

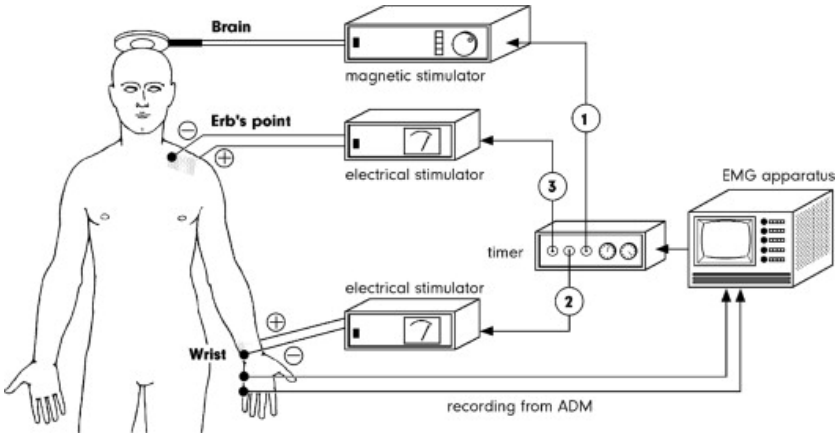

Figure 2: *Set-up of the TST[18].*

The short time periods in between stimuli were adapted to every participant. The difference between minimal MEP latency and CMAP distal latency was fixed as the first delay. The second delay was determined as the difference between CMAP proximal latency and CMAP distal latency. All latencies were rounded up or down the nearest millisecond.

The amplitude ratio between the second response of the TSTT and the TSTC provides the central conduction failure. A percentage < 0 corresponds to an axonal part. The more negative the value, the greater the central motor axonal loss in the corticospinal pathway (linked to the ADM muscle). A TST = 0 corresponds to the absence of axonal loss. If TST > 0 is obtained, it is still identified for technical reasons. TST may be contaminated by muscles other than the ADM muscle explaining a response in which TSTT > TSTC.

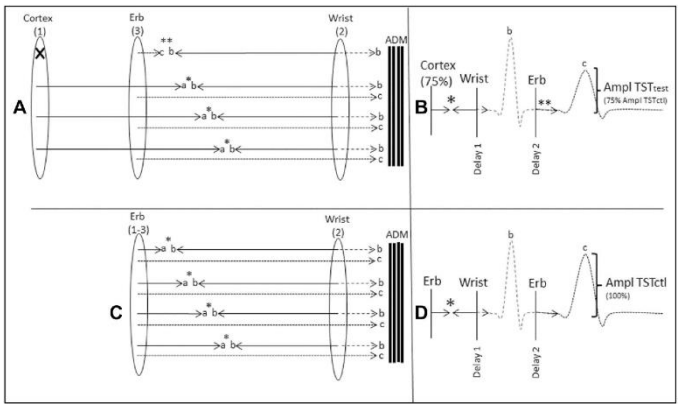

Figure 3: *Illustration of TST[21].*

3.2.2 Clinical outcome measures

Motor outcomes of the LL and UL were examined. Walking endurance was measured by the 6MWT. During the 6MWT the walking capacity was determined as the total amount of distance covered where the patients walked in a 30-m corridor as fast as possible, according to the protocol of Goldman et al[26]. It is a valid and reliable clinical gait performance measure in MS[27]. Walking ability and speed were evaluated by the T25FW. In this test, patients must walk a course of 25 feet, corresponding to 7.62 meters, as fast as possible at a safe pace. The T25FW has strong reliability over both short and long periods of time in MS across a wide range of disability levels. The scores can also be interpreted as a valid measure of walking and its dysfunction in MS[28]. The UL was evaluated for manual dexterity by performing the NHPT for both the dominant and non-dominant side. The patient must take nine pegs from a tray as quickly as possible and insert them into the openings in a plate with one hand. Then the patient must take the pegs out again and put them back in the tray. The NHPT has a high reliability coefficient over a wide range of disability levels, and it shows a high convergent validity[9]. The Fmax of the LL was measured in a static condition using a Datalink system® (Figure 4). This is a Jamar dynamometer adapted for the foot to measure strength of the dorsiflexion of the ankle. For the UL, the overall finger flexion strength was measured using the Jamar dynamometer. Patients were asked to contract for 60 seconds The peak force of handgrip and TA muscle was analysed both left and right.

Figure 4: *Datalink system to measure lower limb strength (CHU Liège).*

3.3 Data-analysis

The characteristics from the participants were collected in an excel file, such as gender, age, height, weight, disease duration, type of MS and the EDSS score. These data were summarised using the means and standard deviations (SD), when appropriate.

In the excel file the clinical measurement outcomes, 6MWT, T25FW, NHPT (dominant and non-dominant) and the Fmax for the LL and UL, and the TST and TMS parameters were processed. For the TST parameters, the percentage of amplitude between the TSTT and TSTC for the right and left UL was presented. In addition, we also evaluated the highest severity amplitude in TST, thus the lowest value. For TMS, the amplitude and latency were analysed for the UL and LL. In the UL, we used the motor response of the FDI muscle to electrical stimulation of the ulnar nerve on the wrist and to magnetic stimulation of the motor cortex and cervical root C8. In the LL, we used the motor response of the TA muscle to electrical stimulation of the common peroneal nerve at the head of the peroneal nerve. The motor response of the TA to the magnetic stimulation of the L4-L5 and the motor cortex was also processed.

The SAS JMP software was used to perform the data analysis. The data was imported into JMP via the excel database. Each group was checked for normality by evaluation of the Q-Q plots. The comparison between the MS and HC group was analysed by using the Wilcoxon Rank Sum test. Non-parametric statistics were performed, based on the low number of participants and not normal distribution of parameters. The different clinical measurement outcomes, TST and TMS variables were compared between both groups. The two-tailed p-values were analysed with significance level $p \leq 0.05$.

The relationship between the different TST or TMS and the clinical measurement outcomes in the MS group was analysed by using Spearman's (rs) correlation for normally and non-normally distributed data. One TST or TMS parameter was correlated with one clinical measurement outcome in JMP. Schober et al. (2018)[29] indicate a correlation between 0.40 and 0.69 for a moderate correlation, a correlation between 0.70 and 0.89 indicates a strong correlation. At first, correlation coefficients above 0.40 were also considered as meaningful even when the p-value did not exceed the significance level of 5%. We did this because these values show a moderate correlation and the bigger the value of a correlation coefficient, the more likely it is that it has occurred because it represents a genuine relationship between two variables. Afterwards, the Bonferroni correction with significance level $p \leq 0.00625$ was applied on the resulting significant p-values to correct for multiple comparisons.

4 Results

4.1 Participants

A detailed overview of the participants is provided in table 1. A total of 16 MS patients and eight age- and gender-related healthy controls (HC) were recruited into the study. In the HC group, five women and three men participated with a mean age of 56.8 years (SD= ±14.1) and in the MS group, 15 women and one man participated with a mean age of 48.3 years (SD= ±9.4). The EDSS varied between zero and six, with a mean of 3.2 (SD= ±1.6). In the MS group 56.25% of the participants were stronger in the right upper limb (UL). For the lower limbs (LL) this was equally divided in 50% right and 50% left. The right body side was strongest in both the UL and LL for 62.5% of the HC.

Table 1: *Descriptive characteristics and the clinical outcomes in MS and HC (data is presented as mean ± SD)*

	MS patients (n = 16)	**HC patients (n = 8)**
Descriptive characteristics		
Type of MS (RR/SP)	13/1	/
Gender F/M (n)	15/1	5/3
EDSS (0-10)	3.2 ± 1.6	/
Disease duration (years)	14.1 ± 6.0	/
Age (years)	48.3 ± 9.4	56.8 ± 14.1
Height (cm)	165.7 ± 7.1	166.4 ± 5.0
Weight (kg)	71.9 ± 13.7	72.7 ± 12.0
Clinical outcomes		
6MWT (m)	466.4 ± 120.9	607.0 ± 51.9
T25FW (s)	5.0 ± 1.8	3.3 ± 0.4
NHPT dominant (s)	20.2 ± 3.9	21.6 ± 4.4
NHPT non-dominant (s)	22.7 ± 4.3	23.1 ± 3.4
Fmax (datalink)		
Upper Limb Right	23.6 ± 7.3	31.9 ± 6.7
Upper Limb Left	23.0 ± 7.5	31.0 ± 7.7
Lower Limb Right	13.0 ± 4.0	18.6 ± 3.5
Lower Limb Left	14.7 ± 4.4	18.7 ± 4.6

HC: healthy controls; MS: multiple sclerosis; RR: relapsing remitting; SP: secondary progressive; F: female; M: man; EDSS: expanded disability status scale; 6MWT: six minute walking test; T25FW: timed 25 foot walk test; NHPT: nine hole peg test; Fmax: maximum isometric force

4.2 Study results: Comparison of MS and HC groups

The mean and p-values of the MS and HC groups are listed in table 2 and 3.

There were several significant differences between the MS and HC group for the clinical outcomes. Groups differed on tests for the lower limb (LL), namely 6MWT (p=0.0036) and T25FW (p=0.0011). For the functional test of the upper limb (UL), NHPT dominant and non-dominant, we observed no significant difference in mean outcome between the two groups. The results of the maximum isometric force (Fmax) show a significant difference in the right UL (p=0.0093), the right LL (p=0.0077) and in the left UL (p=0.0353).

For the TST parameters, the mean amplitude ratio for both the right and left UL was <0 in pwMS. However, we observed only one significant difference, namely for the amplitude ratio in the right UL (p=0.0155). In the TMS parameters, we see a significant difference in the $amplitude_{cortex}$ in the left UL (p=0.0077), in the left LL (p=0.0251) and in the right LL (p=0.0092). Latency in the UL and LL did not show any significant difference in both groups.

Table 2: *Results of Wilcoxon rank sum test of the clinical outcomes*

	MS patients (mean)	HC patients (mean)	P-value
6MWT	466.44	607.00	**0.0036 ****
T25FW	5.05	3.29	**0.0011 ****
NHPT dominant	20.20	21.61	0.6460
NHPT non-dominant	22.66	23.11	0.9025
Fmax upper limb right	23.62	31.86	**0.0093 ****
Fmax upper limb left	22.98	31.03	**0.0353 ***
Fmax lower limb right	12.95	18.61	**0.0077 ****
Fmax lower limb left	14.68	18.66	0.1925

MS: multiple sclerosis; HC: healthy controls; NHPT: nine-hole peg test; 6MWT: six-minute walking test; T25FW: timed 25-foot walk test; Fmax: maximum isometric force; * (p<0.05); ** (p<0.01)

Table 3: *Results of Wilcoxon rank sum test of the TST and TMS parameters*

	MS patients (mean)	HC patients (mean)	P-value
TST – Upper Limb			
%Amplitude right	-12.27	4.48	**0.0155 ***
%Amplitude left	-9.70	3.40	0.1046
TMS - Upper Limb Right			
Amplitude$_{wrist}$	17.93	16.76	0.2321
Amplitude$_{cortex}$	3.14	4.30	0.0920
Latency$_{C8}$	12.94	13.48	0.7361
Latency$_{cortex}$	21.44	20.79	0.2837
TMS - Upper Limb Left			
Amplitude$_{wrist}$	17.65	16.70	0.6025
Amplitude$_{cortex}$	3.21	5.29	**0.0077 ****
Latency$_{C8}$	12.71	13.36	0.5199
Latency$_{cortex}$	21.41	20.31	0.4082
TMS - Lower Limb Right			
Amplitude$_{peroneus}$	5.61	5.65	0.7360
Amplitude$_{cortex}$	1.44	2.56	**0.0092 ****
Latency$_{L4}$	12.51	12.96	0.6457
Latency$_{cortex}$	33.64	28.14	0.1182
TMS - Lower Limb Left			
Amplitude$_{peroneus}$	5.28	5.63	0.7821
Amplitude$_{cortex}$	1.60	2.49	**0.0251 ***
Latency$_{L4}$	12.74	13.84	0.5198
Latency$_{cortex}$	33.35	29.18	0.3912

MS: multiple sclerosis; HC: healthy controls; TST: triple stimulation technique; TMS: transcranial magnetic stimulation; * ($p<0.05$); ** ($p<0.01$)

4.3 Study results: Correlations

4.3.1 Triple stimulation technique

Table 4 is a more detailed overview of TST correlation coefficients. Figure 5A is a schematic overview of the correlations we found between TST parameters and clinical outcomes.

Two significant correlations can be found. The amplitude ratio of the left UL shows a positive and moderate correlation with the Fmax of the left LL (rs=0.50; p=0.0094). Fmax of the left LL also shows a positive, moderate significant correlation with the TST amplitude of the highest severity (rs=0.60; p=0.0011). However, when we apply the Bonferroni correction, only this latter correlation remains significant (rs=0.60; p<0.0062).

4.3.2 Transcranial magnetic stimulation

The correlation coefficients of the TMS parameters and clinical outcome measures show multiple significant results. Table 5 gives an extensive overview of the correlation coefficients in TMS. Figure 5B is a schematic overview of all correlations we found between MEP and clinical outcomes.

First, we will look at the correlation coefficients of the upper limbs. On the right bodyside we see that the amplitude when giving a stimulation at the cortex ($amplitude_{cortex}$) significantly correlates, positive and moderate, with Fmax of the left LL (rs=0.52). The latency when giving a stimulation at the cortex ($latency_{cortex}$) significantly correlates, moderate and negative, with Fmax of the left UL (rs=-0,49) and Fmax of the right LL (rs=-0,57; p=0.0452). It also shows a moderate but positive significant correlation with T25FW (rs=0.44). On the left UL, we see some similarities. A negative and moderate, significant correlation was also found here between $latency_{cortex}$ and Fmax of the left UL (rs=-0,59). In addition, $amplitude_{cortex}$ shows a positive and moderate correlation with Fmax of the left LL (rs=0.56; p=0.0116). Further, we observed a positive, moderate significant correlation between the amplitude when giving stimulation at the wrist ($amplitude_{wrist}$) and Fmax of the right UL (rs=0.46).

Second, we examined the correlation coefficients of the lower limbs. For the right bodyside we saw two negative, moderate significant correlations between NHPT of the non-dominant side: with $latency_{L4}$ (rs=-0.42) and $latency_{cortex}$ (rs=-0.47). Moreover, $latency_{L4}$ also showed a negative, moderate significant correlation with NHPT of the dominant side (rs=-0.55; p=0.0275) and with Fmax of the right LL (rs=-0.48). $Latency_{cortex}$ also correlated negatively and moderately with Fmax of the right UL (rs=-0.51). Fmax of the left UL, on the other hand, showed a positive and low significant correlation with $amplitude_{cortex}$ (rs=0.25; p=0.0426). When giving stimulation at the peroneus, the amplitudes ($amplitude_{peroneus}$) correlated moderately and significantly with both walking tests: 6MWT (rs=0.53; p=0.0244) and T25FW (rs=-0.56; p=0.0045). For the left LL, we observed the following correlation coefficient. $Latency_{L4}$ showed a negative and moderate significant correlation with Fmax of the right LL (rs=-0.59). It also significantly correlated with T25FW but in a moderate and positive manner (rs=0.49). $Latency_{cortex}$ correlated negatively and moderately with Fmax of both the right and left UL (rs=-0.46 and rs=-0.44 respectively). Fmax of the left UL showed another moderate significant correlation, namely with $amplitude_{cortex}$ (rs=0.51; p= 0,0478). $Amplitude_{cortex}$ also correlated positively, moderately, and significant with Fmax of the left LL (rs=0.63; p=0.0043). Lastly, $amplitude_{peroneus}$ showed two moderate, significant correlations with walking tests: 6MWT (rs=0.66; p=0.0154) and T25FW (rs=-0.61; p=0.0141).

When applying the Bonferroni correction, we see that two correlation coefficients remain significant. The $amplitude_{peroneus}$ for the right LL is significantly correlated with the T25FW ($p<0.0045$). The $amplitude_{cortex}$ of the left LL is significantly correlated with the Fmax of the left LL ($p<0.0043$).

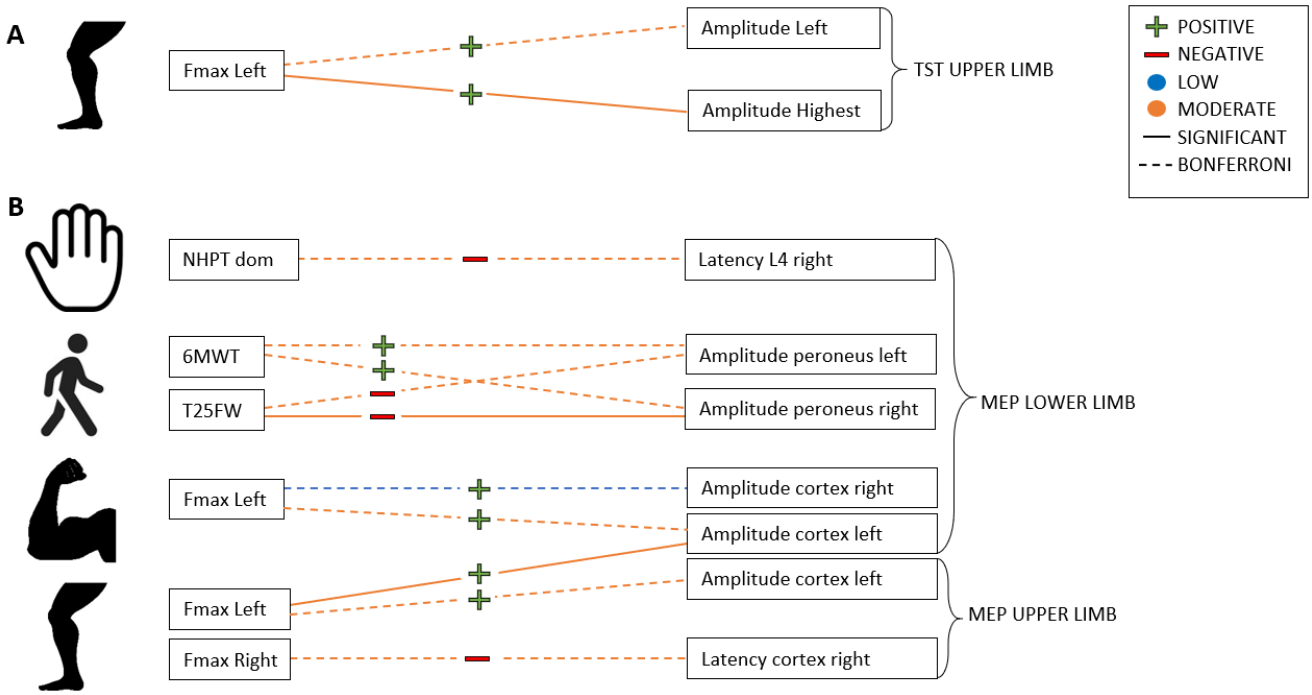

Figure 5: *Schematic overview of the results of the TST and TMS correlations. A line was drawn between clinical outcomes and (A) TST parameter from the UL or (B) MEP parameters from the UL or LL that correlate with each others. The dotted lines show a correlation were the p-value was less than the significance level. The solid lines represent the correlations that remained after applying the Bonferroni correction ($p<0.00625$). The sign in the middle of the line determines whether the correlation was positive or negative and the colour shows the strength (e.g. Figure 5B: The correlation between NHPT of the dominant hand and $latency_{L4}$ of the right LL was significant, moderate and negative.).*

Table 4: *Spearman (rs) correlation coefficients and Bonferroni correction between the TST parameters and clinical outcomes in MS patients*

	NHPT (non-dom)	NHPT (dom)	6MWT	T25FW	Fmax right UL	Fmax left UL	Fmax right LL	Fmax left LL
%Amplitude right UL	-0.11	-0.19	0.08	-0.13	-0.07	-0.14	0.11	0.37
%Amplitude left UL	-0.24	-0.18	0.24	-0.03	-0.39	-0.02	-0.20	**0.50 ****
%Amplitude highest severity	-0.15	-0.36	-0.06	0.16	-0.06	-0.06	-0.26	**0.60 *****

MS: multiple sclerosis; TST: triple stimulation technique; NHPT: nine-hole peg test; non-dom: non-dominant; dom: dominant; 6MWT: six-minute walking test; T25FW: timed 25-foot walk test; Fmax: maximum isometric force; UL: upper limb; LL, lower limb; * ($p<0.05$); ** ($p<0.01$); Bonferroni *** 0.05/8 = 0.00625

Table 5: *Spearman (rs) correlation coefficients and* Bonferroni *correction between the TMS parameters and clinical outcomes in MS patients*

	NHPT (non-dom)	NHPT (dom)	6MWT	T25FW	Fmax right UL	Fmax left UL	Fmax right LL	Fmax left LL
Upper Limb Right								
Amplitude$_{wrist}$	-0.13	-0.03	-0.07	-0.01	-0.14	-0.10	-0.04	-0.31
Amplitude$_{cortex}$	0.14	-0.03	0.28	-0.28	0.26	0.08	0.30	**0.52**
Latency$_{C8}$	0.05	-0.20	-0.24	0.34	-0.09	-0.31	-0.38	0.16
Latency$_{cortex}$	-0.16	-0.14	-0.31	**0.44**	-0.38	**-0.49**	**-0.57 ***	-0.38
Upper Limb Left								
Amplitude$_{wrist}$	0.31	0.37	-0.37	0.37	**0.46**	0.16	-0.01	-0.27
Amplitude$_{cortex}$	0.03	0.09	0.22	0.02	-0.03	0.30	-0.03	**0.56 ***
Latency$_{C8}$	-0.13	-0.31	-0.28	0.28	-0.23	-0.39	-0.30	0.16
Latency$_{cortex}$	0.15	-0.17	-0.19	0.09	-0.22	**-0.59**	-0.05	-0.18
Lower Limb Right								
Amplitude$_{peroneus}$	-0.20	-0.02	**0.53 ***	**-0.56 *****	-0.12	0.16	0.21	0.10
Amplitude$_{cortex}$	-0.01	-0.12	0.33	-0.21	0.38	**0.25 ***	0.14	0.35
Latency$_{L4}$	**-0.42**	**-0.55 ***	0.12	0.02	-0.14	-0.04	**-0.48**	0.19
Latency$_{cortex}$	**-0.47**	-0.18	0.11	-0.05	**-0.51**	-0.33	-0.20	-0.27
Lower Limb Left								
Amplitude$_{peroneus}$	-0.32	-0.01	**0.66 ***	**-0.61 ***	-0.35	0.19	0.09	0.07
Amplitude$_{cortex}$	-0.10	-0.02	0.37	-0.22	0.07	**0.51 ***	0.03	**0.63 *****
Latency$_{L4}$	-0.13	-0.34	-0.39	**0.49**	0.07	-0.20	**-0.59**	-0.08
Latency$_{cortex}$	-0.37	-0.22	-0.04	-0.01	**-0.46**	**-0.44**	-0.09	-0.34

MS: multiple sclerosis; TMS: transcranial magnetic stimulation; NHPT: nine-hole peg test; non-dom: non-dominant; dom: dominant; 6MWT: six-minute walking test; T25FW: timed 25-foot walk test; Fmax: maximum isometric force; UL: upper limb; LL: lower limb; * ($p<0.05$); ** ($p<0.01$); Bonferroni *** 0.05/8 = 0.00625

5 Discussion

5.1 Reflection of the results

As we expected, the HC performed better on clinical outcomes than pwMS. However, this is only the case in the walking tests. This means that pwMS have worse lower limb (LL) but not upper limb (UL) function than HC. This can be explained on the basis of an earlier study by Bertoni et al.[30] stating that manual dexterity decreases with higher EDSS scores (EDSS>6.5). On the other hand, reductions in walking speed are already present at low levels of EDSS (EDSS<4)[31]. This implies that we would probably have found other correlations if the EDSS were higher in our MS group (mean= 3.2). There is a gap between low and moderate-severe EDSS because less research has been done in the latter group. Our results are also only applicable for pwMS with low EDSS. As far as strength is concerned, we see that pwMS have lower force than HC in three out of four body sides. However, the deficits in muscle force are not explicit enough to show correlations in our MS group. The same applies for the UL function. Impairments are not picked up by the NHPT in our patient population. A possible explanation might be that the muscle mechanical function of the LL is more affected than the UL because UL is more frequently used during daily activities[32,33]. Moreover, UL are used to perform complex multidimensional tasks such as reaching, grasping and manipulating objects. Therefore, multiple clinical outcomes are necessary to evaluate UL dysfunctions more completely[34]. Another possibility might be that there simply were no UL impairments present in our MS population.

When we discuss the results, it is interesting to present all correlations. However, the Bonferroni correction gives us the most trustworthy results. That is why we will only discuss these correlations here. No correlation was found between MEP latencies and clinical outcomes[35]. This can be explained by the fact that there was no difference in latencies between HC and MS. Previous studies suggest that abnormal MEP latencies are correlated with higher EDSS in pwMS[24,36]. Again, our population had rather low EDSS, so MEP latencies are expected to be normal.

We found a positive correlation with TST amplitude of the highest severity and Fmax of the left LL. This means that when amplitude ratio is more severe and thus lower, a lower force can be found in the left LL. The link between the proportion of central motor neurons that could not be activated, and the limited muscle force was previously demonstrated by Magistris and Rosler (2003)[19]. Although TST was taken from the UL, it shows a correlation with force in the LL. Besides, the right body side was the body side with highest severity for most participants. We would therefore expect a correlation with clinical outcomes of the right body side. Nonetheless, it has been proven earlier by Giffroy et al. (2019)[21] that TST reflects a global and degenerative process even when TST focused on assessment of

the corticospinal tract (CST) in the UL. In addition, they suggest that a more negative amplitude ratio represents central motor axonal loss in the CST. This indicates that the right UL suffers more axonal loss for most pwMS in this study since this was the bodyside of highest severity for most of them. Besides, the mean amplitude ratio was more negative for the right UL.

The correlation between T25FW and MEP amplitude of the right LL when giving stimulation to the peroneus muscle is negative. This means when the MEP amplitude is lower, the time needed to walk 25 foot will be higher. Axonal loss may be the reason behind reduced gait. Strik et al.[37] reported a correlation between gait impairments and axonal loss in sensorimotor pathways of the brain. However, this says little to nothing about peripheral pathways. Their study also showed a correlation with LL motor control impairments and axonal loss. This supports the correlation we found between the MEP amplitude of the left LL when giving stimulus at the cortex and Fmax of the left LL. Several other studies also indicated that motor disability is related to axonal loss in motor tracts[38]. More specifically, demyelination in the CST causes signal leakage which results in reduced amplitudes. This reduction in amplitude is on his turn correlated with disability in pwMS[39]. Besides, Comi et al.[15] claimed that demyelination is related to modifications in MEP latency whereas axonal loss or conduction block are represented by amplitude reduction. Therefore, we suggest that axonal loss lays at the basis of our findings since we found no abnormalities in latency.

Nonetheless, axonal loss develops at different stages of the disease course[40]. This might also be the reason we found so little correlations in this study. Demyelination and inflammation result in axonal changes but it is not yet clear how[41]. There is discussion about the evolving pattern of pathology in MS. Bjartmar et al. (2003)[40] suggest that axonal injury already starts at onset of the disease. Unlike Vickers et al. (2009)[41], who state that axonal pathology is the final stage. On the other hand, Bjartmar and Trapp (2001)[42] suggest that neurodegenerative mechanisms other than axonopathy contribute to neuronal decline at more severe stages of the disease. Anyway, they all agree that eventually neurodegeneration will be the major cause of permanent neurological disability in MS[43]. Progression to permanent loss of connections leading to disability is inevitable in MS[41]. Cumulative axonal loss provides the pathological substrate for permanent disability in MS[40]. TMS may even predict further progression in MS since it correlates with disability[24]. Moreover, MEP parameters assess dysfunctions of motor pathways independent of its pathogenesis[44].

The reason we found more correlations in the LL, compared to UL, might be because axonal loss in the lumbar regions of the CST have a more significant impact on the LL motor function[45]. In addition, axonal loss is length dependent[46]. Therefore, there is a minor risk of pyramidal tract damage on shorter

axons supplying the UL[32,33]. Nonetheless, demyelination was found more often in the UL nerves. It is suggested by Van Asseldonk et al. (2003)[46] that the random distribution of demyelination lesions in longer nerves lead to axonal degeneration and axonal loss is due to this.

In conclusion, we found that altered amplitudes in MS patients explain the reduced performances in clinical tests. In both TMS and TST, reduced amplitudes reflect motor impairments of which axonal loss is the basis. For future research, an interesting train of thought might be whether axonal loss is reversible due to rehabilitation strategies and if this implies that amplitudes will increase again and in turn also resolve disability.

5.2 Reflection on the strength and weakness

The strengths of this study include that Xavier Giffroy[21] has already conducted many studies with TST, making him very skilful in performing these neurophysiological techniques. Furthermore, different measuring tests are used such as the 6MWT, NHPT, T25FWT and the maximum isometric force with the Datalinks system. These tests give objective results that can be more confident than when subjective tests are used[47]. They are also valid and reliable, which reduces the chance of measuring errors and increases the quality of the study[48]. The clinical measures are also quite standardised. Therefore, the influence of performing all tests in different rehabilitation centres is rather small. Furthermore, the tests were carried out by the same examiner in Liège . For the analysis of the TMS, we used amplitude and latency because our research of last year showed that these MEP parameters are the most useful to predict the prognosis in motor disorders, both in UL and LL[24,36,49]. We also gained ethical approval, which is an additional strength for this research[50]. This means that the study was conducted in a quality way that meets the legal requirements. Another asset is that the participants come from different rehabilitation centres, which reduces the chance of selection bias[51]. Finally, this study is one of the first studies that examined the correlation between TST or TMS parameters with different clinical outcome measurements at once (6MWT, T25FW, NHPT dominant, NHPT non-dominant and Fmax). We obtained a few significant results which makes this a good basis for further research on a larger scale.

However, this study has limitations that should be taken into account for future studies. Quality is also characterised by the number of participants. A larger sample is more representative of the population and limits the influence of outliers or extreme observations[52]. A larger sample also gives a better picture of the analysis[53]. We have a smaller sample in both the MS and the HC group which is a qualitative limitation for our study[54]. If we had a larger sample size, we could perform parametric tests

and thus more advanced statistics like the Pearson correlation or regression. Moreover, there was no equal distribution of both groups, 16 MS participants and eight HC participants, which can be considered as a weakness of the study. Likewise, there was no equal distribution between gender, four men and 20 women. This does not show a perfect representation which makes it difficult to generalise the results. However, there is a 1:2 ratio when looking at male/female so the distribution in gender in this study is not a major limitation. The clinical tests in our study were performed on different days which can slightly distort the results.

Recommendations for future research could be to focus on a larger sample size and to include participants with higher EDSS so that the results are more applicable on a larger population. There should also be an equal distribution among the MS and HC participants so that the results would be less biased, and the quality of the study would improve. In our opinion, the use of TMS is superior to TST for the functional quantification of central motor axonal loss. TST is a complex method to apply in comparison to TMS and it does not show as many correlations with clinical outcomes since there are less TST parameters available. Therefore, we are concluding that TMS is more adequate to use in pwMS for the present research questions. Moreover, we suggest the use of TMS to estimate primarily walking disabilities and secondary loss of strength.

6 Conclusion

Persons with MS perform worse on clinical outcome measures for the lower limb, namely walking tests, in comparison to HC. A correlation exists between Fmax of the left LL and the reduced amplitudes monitored for the UL by TST. Reduced MEP amplitudes monitored for the LL show correlations with T25FW and Fmax of the left LL. A recommendation for future research is to include a larger sample size of both persons with MS and matched HC for a widespread generalisation of both the upper and lower limb impairments monitored by TMS or TST.

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8 Attachments

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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
14/10/2020	Discussion master's thesis: Part 2	Promotor: Copromotor/Begeleider: Student(e): Student(e):
30/11/2020	Discussion of introduction	Promotor: Copromotor/Begeleider: Student(e): Student(e):
17/12/2020	Discussion of introduction + method	Promotor: Copromotor/Begeleider: Student(e): Student(e):
04/03/2021	Discussion of procedures	Promotor: Copromotor/Begeleider: Student(e): Student(e):
29/03/2021	Discussion of data analysis + results section	Promotor: Copromotor/Begeleider: Student(e): Student(e):
22/04/2021	Discussion of data analysis + results	Promotor: Copromotor/Begeleider: Student(e): Student(e):
11/05/2021	Discussion of data, results and discussion	Promotor: Copromotor/Begeleider: Student(e): Student(e):
20/05/2021	Discussion full thesis	Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1642959 Tans Lotte**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine musc.**

INSTRUCTIES - *INSTRUCTIONS*

Neem onderstaande informatie grondig door.

Print dit document en vul het aan met DRUKLETTERS.

In tijden van van online onderwijs door COVID-19 verstuur je het document (scan of leesbare foto) ingevuld via mail naar je promotor. Je promotor bezorgt het aan de juiste dienst voor verdere afhandeling.

Vul luik A aan. Bezorg het formulier aan je promotoren voor de aanvullingen in luik B. Zorg dat het formulier ondertekend en gedateerd wordt door jezelf en je promotoren in luik D en dien het in bij de juiste dienst volgens de afspraken in jouw opleiding.
Zonder dit inschrijvingsformulier krijg je geen toegang tot upload/verdediging van je masterproef.

Please read the information below carefully.

Print this document and complete it by hand writing, using CAPITAL LETTERS.

In times of COVID-19 and during the online courses you send the document (scan or readable photo) by email to your supervisor. Your supervisor delivers the document to the appropriate department.

Fill out part A. Send the form to your supervisors for the additions in part B. Make sure that the form is signed and dated by yourself and your supervisors in part D and submit it to the appropriate department in accordance with the agreements in your study programme.
Without this registration form, you will not have access to the upload/defense of your master's thesis.

LUIK A - VERPLICHT - IN TE VULLEN DOOR DE STUDENT
PART A - MANDATORY - TO BE FILLED OUT *BY THE STUDENT*

Titel van Masterproef/*Title of Master's thesis:* EXPLORING THE RELATIONSHIP BETWEEN NEUROPHYSIOLOGICAL MEASURES AND CLINICAL OUTCOMES IN PERSONS WITH MS

◉ behouden - *keep*

○ wijzigen - *change to*:

/:

O behouden - *keep*

O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: JULIE VAN HERK

● behouden - *keep*

O wijzigen - *change to:*

LUIK B - VERPLICHT - IN TE VULLEN DOOR DE PROMOTOR(EN)
PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

Wijziging gegevens masterproef in luik A/*Change information Master's thesis in part A:*

O goedgekeurd - *approved*

O goedgekeurd mits wijziging van - *approved if modification of:*

Scriptie/*Thesis:*

O openbaar (beschikbaar in de document server van de universiteit)- *public (available in document server of university)*

O vertrouwelijk (niet beschikbaar in de document server van de universiteit) - *confidential (not available in document server of university)*

Juryverdediging/*Jury Defense:*

De promotor(en) geeft (geven) de student(en) het niet-bindend advies om de bovenvermelde masterproef in de bovenvermelde periode/*The supervisor(s) give(s) the student(s) the non-binding advice:*

O te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

O de verdediging is openbaar/*in public*

O de verdediging is niet openbaar/*not in public*

O niet te verdedigen/*not to defend the aforementioned Master's thesis within the aforementioned period of time*

LUIK C - OPTIONEEL - IN TE VULLEN DOOR STUDENT, alleen als hij luik B wil overrulen
PART C - OPTIONAL - TO BE FILLED OUT BY THE STUDENT, only if he wants to overrule part B

In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/*In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:*

O niet te verdedigen/*not to defend the aforementioned Master's thesis within the aforementioned period of time*

O te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

LUIK D - VERPLICHT - IN TE VULLEN DOOR DE STUDENT EN DE PROMOTOR(EN)
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

24/05/2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1438459 van Herk Julie**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine neuro**

INSTRUCTIES - *INSTRUCTIONS*

Neem onderstaande informatie grondig door.

Print dit document en vul het aan met DRUKLETTERS.

In tijden van van online onderwijs door COVID-19 verstuur je het document (scan of leesbare foto) ingevuld via mail naar je promotor. Je promotor bezorgt het aan de juiste dienst voor verdere afhandeling.

Vul luik A aan. Bezorg het formulier aan je promotoren voor de aanvullingen in luik B. Zorg dat het formulier ondertekend en gedateerd wordt door jezelf en je promotoren in luik D en dien het in bij de juiste dienst volgens de afspraken in jouw opleiding.
Zonder dit inschrijvingsformulier krijg je geen toegang tot upload/verdediging van je masterproef.

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Fill out part A. Send the form to your supervisors for the additions in part B. Make sure that the form is signed and dated by yourself and your supervisors in part D and submit it to the appropriate department in accordance with the agreements in your study programme.
Without this registration form, you will not have access to the upload/defense of your master's thesis.

LUIK A - VERPLICHT - IN TE VULLEN DOOR DE STUDENT
PART A - MANDATORY - TO BE FILLED* OUT *BY THE STUDENT

Titel van Masterproef/*Title of Master's thesis:* Exploring the relationship between neurophysiological measures and clinical outcomes in persons with MS

● behouden - *keep*

O wijzigen - *change to*:

/:

O behouden - *keep*

O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*: Lotte Tans

[redacted]behouden - *keep*

O wijzigen - *change to:*

LUIK B - VERPLICHT - IN TE VULLEN DOOR DE PROMOTOR(EN)
PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

Wijziging gegevens masterproef in luik A/*Change information Master's thesis in part A:*

O goedgekeurd - *approved*

O goedgekeurd mits wijziging van - *approved if modification of:*

Scriptie/*Thesis:*

O openbaar (beschikbaar in de document server van de universiteit)- *public (available in document server of university)*

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Juryverdediging/*Jury Defense:*

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O niet te verdedigen/*not to defend the aforementioned Master's thesis within the aforementioned period of time*

LUIK C - OPTIONEEL - IN TE VULLEN DOOR STUDENT, alleen als hij luik B wil overrulen
PART C - OPTIONAL - TO BE FILLED OUT BY THE STUDENT, only if he wants to overrule part B

In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/*In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:*

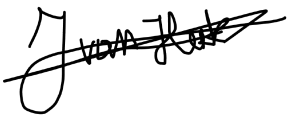
O niet te verdedigen/*not to defend the aforementioned Master's thesis within the aforementioned period of time*

O te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

LUIK D - VERPLICHT - IN TE VULLEN DOOR DE STUDENT EN DE PROMOTOR(EN)
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

24/05/2021



Datum en handtekening promotor(en)
Date and signature supervisor(s)

29/05/2021