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Transcranial Magnetic Stimulation (TMS) and impact on the contraction force

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Abstract

Objectives: First, to measure the contraction force and to correlate these contraction force measures with the motor-evoked potentials (MEP) resulting from TMS, TST, Quadruple and Quintuple stimulation associated with the paired-pulse paradigm of SICI and ICF. Then, to compare the neuromuscular and electrophysiological responses between two groups of subjects according to their current and past physical activity.

Background: Transcranial magnetic stimulation (TMS) causes brain activation which generates repetitive spinal motor neuron discharges (RepMNDs). A paradigm called paired-pulse TMS (PP-TMS) allows inhibit or facilitate the neuromuscular response depending on the inter-stimulus interval (ISI) and the intensity of the two stimuli. The paired-pulse paradigm consists on the combination of a subthreshold conditioning stimulus (CS) preceding a suprathreshold test stimulus (TS) at different intervals. The triple stimulation technique (TST), the Quadruple stimulation (QuadS) and the Quintuple stimulation (QuintS) allow a more precise exploration of the motor conduction and of the RepMND.

Method: Investigation of 17 healthy volunteers in a randomized design study using single pulse and the paired-pulse paradigm of short intracortical inhibition (SICI) with an ISI of 2ms and an intracortical facilitation (ICF) with an ISI of 10ms through TMS, TST, QuadS and QuintS. Measurement of the contraction force of the abduction of the fifth digit corresponding of the Abductor Digiti Minimi muscle (ADM) using a force transducer.

Results: Negative correlation between the physical activity and the amplitude of the contraction force responses for all the stimulation techniques. Paradoxical positive correlation between the physical activity and the amplitude of the MEP response especially concerning QuadS and QuintS. Another founding is that about half of the

subjects have repMNDs following a single pulse TMS in the QuadS and QuintS condition (60% and 40% respectively).

Conclusions: There is an inverse and paradoxical correlation between the contraction force responses and the MEP responses according to the physical activity of the subjects. These results point to potential association between MEP and the contraction force responses. Force contraction response may depend on the physical activity of each volunteer.

Keywords: TMS, TST, PP-paradigms, MEP, repMND, cortico-spinal excitability, strength responses

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Introduction

Transcranial Magnetic Stimulation (TMS) created by Barker et al. (1) corresponds to a pulse generated by electromagnetic induction using a metallic coil which generates muscle response termed motor-evoked potential (MEP). The fast changes of the magnetic field induces an electric current which depolarizes neurons in the magnetic field. The stimulation can excite or inhibit the human brain depending on stimulation parameters such as intensity and repetition. The paired-pulse paradigm (PP paradigm) helps to better understand the different circuits at the origin of facilitation or inhibition in the brain as described by Kujirai et al.(2) It functions by associating two stimuli, a subthreshold conditioning stimulus (CS) and a suprathreshold test stimulus (TS) of variable intensities and separated by a variable inter-stimulus interval (ISI) which determine the effect of facilitation called intra-cortical facilitation (ICF) or inhibition called short intra-cortical inhibition (SICI) of the MEP.

A problem of this paradigm is the variability of the response caused by different factors such as the desynchronization of the discharges or the presence of repetitive motor neuron discharges (repMND). A technique called the Triple Stimulation Technique (TST) using the collision phenomenon (3) permits to correct the desynchronization and to quantify more accurately the corticospinal conduction than with the TMS alone.(4) Extended TST techniques known as quadruple (QuadS) and quintuple (QuintS) stimulation allow the quantification of the RepMND.

This research comes in line with precedent Master theses.(5–7) The general aims of these studies were, first, to explore subthreshold stimulation responses (7), in the second study, to assess whether applying TST enhance diagnostic accuracy and consistency of PP paradigm responses (6), and on the last one, to explore whether repMNDs could contribute to the mechanism of SICI and ICF in the PP paradigm with QuadS and QuintS.(5)
This research was done in a team formed with Eleni Batzianouli. I participated in the execution of the experiment, analysis of results and focused my work and research on possible correlation between force contraction and MEP responses depending on the physical activity of each volunteer.

Objectives

The objectives of the study were to measure contraction force and to try to find a correlation with neuromuscular response to TMS, TST, Quadruple and Quintuple stimulation. Then, to compare these results between two groups of subjects according to their current and past physical activity.

Method

Subjects

Seventeen healthy volunteers participated in the study. Eleven men and six women with a mean age of 23.7 years old (range 22-26 years old). Three subjects were left-handed and the rest were right-handed according to the Edinburgh Inventory of Handedness.(8) The dominant hand of each subject was investigated. All subjects gave written informed consent and the local ethics committee approved the experiment. The exclusion criteria established by international safety standards for TMS were followed.(9)

Questionnaire

Before their participation, the subjects answered to an online questionnaire of 20 questions concerning their current and past physical activity, whether they had consumed before the experiment (tea, coffee and/or alcohol) and their sleeping habits (duration of casual nights and duration of the previous night) that could modify their responses to the stimulation. The participant were then attributed to a high or low physical activity group. These two different groups of subjects have been done according to the frequency of the physical activity in hours per week and to the duration of this activity in months. Finally, their results have been compared to better understand if there is a correlation between the physical activity and the neuromuscular/contraction force responses to TMS.

Electrophysiology and EMG recordings

Recordings were obtained from the Abductor Digiti Minimi muscle (ADM) using the muscle belly tendon technique with silver surface electrodes. A ground electrode was placed at the wrist. Two other grounds were placed on the subject, the second one on the sternum and the third one which was a copper plate on the scapula. A Viking Select apparatus was used for the measurement (Nicolet, Madison; WI, USA). Bandpass filter were set at 1 Hz – 5 kHz.(10) Signal acquisition and pre-processing was done with a software called «EMG triggering and acquisition» coded on LabVIEW (National Instrument Corporation, LabVIEW, Austin) by Sci-Consulting. Post processing was done with another software coded on LabVIEW by Nguyet Dang (National Institutes of Health, Bethesda, MD, USA).

Peripheral nerve stimulation

The peripheral nerve stimulations have been made by a bipolar electrode at the wrist for the ulnar nerve and a monopolar hand-held electrode at Erb's point for the brachial plexus. The intensity of the stimulations were supramaximal to obtain compound muscle action potentials (CMAP).

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation has been made by a Magstim BiStim2 apparatus (Magstim Company Ltd., Spring-Gardens, Whitland, UK) with a figure-of-eight 70mm hand-held coil which was used to obtain MEPs. First of all, the optimal cortical stimulation spot («motor hotspot») has been found in accordance with the IFCN guidelines (10) using a 16-point grid as described by Kimiskidis et al.(11) Minimal displacements were necessary made to find the best position where the lowest threshold was found. The coil was then manually kept in the same position throughout the experiment. The resting (rMT) and active motor threshold (aMT) have been established using a procedure defined by Awiszus et al.(12) We visually assessed and determined a valid MEP response as > 50 µV peak-to-peak amplitude and fed it back to the software.

Triple Stimulation Technique

The TST method consists of a three stimuli sequence with predefined interstimulus intervals which has been developed by Magistris et al. (3); the first stimulus is a TMS at the level of the motor cortex with a figure-of-eight coil, the second one is an electrical stimulation of the ulnar nerve at the wrist and the third one at Erb's point for the brachial plexus. The descending discharges following the TMS collide with ascending depolarization potentials from the ulnar nerve at the wrist which leaves the descending volleys from the brachial plexus stimulation. This technique permits to quantify precisely the number of motor neurons units which are discharging after TMS by comparing TMS_{test} response (Sequence: Brain-Wrist-Erb's point) with $TMS_{control}$ response (Sequence: Erb's point-Wrist-Erb's point).

Quadruple and Quintuple Stimulation

The Quadruple (QuadS) and Quintuple stimulation (QuintS) are extensions to the TST which correspond respectively to fourth and fifth stimulation(s) at the wrist and permits to quantify the number of motor neurons discharging more than once in response to a single TMS which is called repetitive motor neuron discharges (RepMNDs).

QuadS corresponds to an additional stimulation at the wrist which comes after the first stimulus at the wrist and before the stimulus at the Erb's point with an inter-stimulus interval of 3 ms between stimuli at the wrist as described by Z'Graggen et al. (13) (Sequence: TMS - Wrist 1 - Wrist 2 – Erb's point). It allows quantify the number of motor neurons discharging twice after a single stimulation.

QuintS consists of the addition of another stimulation at the wrist (Sequence: TMS – Wrist 1 – Wrist 2 – Wrist 3 – Erb's point). It allows quantify the number of repetitive motor neuron discharges.

Paired-pulse paradigm

The paired-pulse transcranial magnetic stimulation paradigm has been first developed and described by Kujirai et al.(2) and it allows inhibit or facilitate the size of MEPs depending on the inter-stimulus interval (ISI) and the intensity of the two stimuli.

This paradigm resides in the combination of a first stimulus called conditioning stimulus (CS) which is determined to a sub-threshold intensity of 80% of rMT and a second stimulus called test stimulus (TS) which is determined to a supra-threshold intensity of 120% of rMT. When ISI is short (1-5 ms), it causes the Short Intra-Cortical Inhibition (SICI) at the origin of smaller MEPs compared to the ones evoked by single-pulse TMS. On another side, with longer ISI (10-15 ms), it results on the Intra-

Cortical Facilitation (ICF) resulting in larger MEPs compared to those evoked by single-pulse TMS.

In this study, the CS was set at 80% of rMT, the TS at 120% of rMT, the inhibitory ISI at 2 ms (SICI) and the facilitatory ISI at 10 ms (ICF).

Contraction force recording

To measure the contraction force of the abduction of the 5th digit at the level of the Abductor Digiti Minimi muscle (ADM) caused by the stimulations, the dominant hand of the subject was put palm down into a force transducer. The subjects were comfortably seated on a chair with their dominant forearm and hand fastened with Velcro straps to a table next to them. The digits II to IV were scotched together and to the ground and the examinators tried to manually maintain the arm of the subject in the same position during the whole experiment to avoid the possible artefacts movements due to the stimulations.

Procedure

It begins by connecting all the electrodes to the Viking Select ENMG apparatus. Then the determination of the supra-maximal responses at wrist, at Erb's point, a TMS, a control stimulation and then a TST. The Viking Select ENMG apparatus has a specific TST program that triggers the stimulations at appropriate delays previously calibrated as follow:

- Delay I (between stimuli 1 and 2) = minimal MEP latency – $CMAP_{wrist}$ latency.
- Delay II (between stimuli 2 and 3) = $CMAP_{Erb}$ latency – $CMAP_{wrist}$ latency.

However, the Viking Select apparatus cannot apply QuadS and QuintS, therefore another setup was necessary as already used in the last study of Batzianouli et al.(5) We added two stimulators synchronized by a specific software on Labview called: «EMG triggering and acquisition».

The first stimulator assures a series of stimulation at the wrist (Grass S88 – Astro-Med Inc. Grass Instrument Division, West Warwick, RI, USA) and the second to stimulate at the Erb's point (Digitimer DS7AH – Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). We then entered the delays calculated by Viking in the software «EMG triggering and acquisition» which then randomly applied the stimulation paradigms at a specific time and order depending on the condition. We assessed 12 conditions using four technics (TMS, TST, QuadS and QuintS) with three methods (single pulse (SP), inhibitory (PP2) and facilitatory (PP10) paired-pulse). We recorded 12 MEPs and force contraction responses for each stimulus condition for a total of 144 stimulations per subject.

Analysis

For each signal of the EMG recordings, the Nguyet Dang's application of LabVIEW has been used to visually inspect the correct response, adapt the time window for the analysis and finally measure the peak-to-peak amplitude of the MEP, the difference between the two (MaxMin), the area under the curve (Area) and the root mean square (RMS). The mean, median and the standard deviation (SD) for each of the 12 conditions has been calculated too. To compare the variability of the different measures, we applied the coefficient of variation (CV), defined as the standard deviation divided by the mean, as previously described by Kiers et al.(14). For the measurement of the contraction force, the AcqKnowledge 4.2 software of BIOPAC System was used to visualize the number of response and the peak-to-peak amplitude for each response to the stimulation. We then did the same statistical analysis as for the neuromuscular responses. Still in progress for the moment.

Literature

We performed a literature review using PubMed, Ovid Medline and Embase from 1990 through March 2018. A description of the exact search terms used: *force response, motor fatigue, contraction force, variability, reproducibility, repeatability, reliability, paired-pulse, trial-to-trial, inter-session, inter-individual, intraindividual, between-session, within-session.*

Associated with: *transcranial magnetic stimulation, TMS, TST, ppTMS, ppTST, SICI, ICF, inhibition, facilitation, repetitive motor neuron discharge.*

Results

Subjects

All subjects that completed the study tolerated the measurements well. No adverse effects occurred.

Groups of subjects

The answers to the questionnaire permit to divide the subjects in two groups according to the frequency of the physical activity in hours per week and the duration of this activity in months. We used «4 hours per week» as the median time of physical activity per subject. For the subjects which are exercising exactly 4 hours per week (7/17 subjects), the duration of this physical activity in months permits to sort them this way:

- «Less active» subjects: [≤ 180 months]
- «Most active» subjects: [> 200 months]

There was not any other study that correlate the physical activity of the subjects and used that kind of separation scale. With these conditions of separation, two groups are finally done with 8 subjects which are considered as «most active» subjects and 9 subjects considered as «less active» subjects.

Stimulation parameters

Table 1: Stimulation parameters

	rMT (%MSO)	Wrist stimulus [mV]	Erb's point stimulus [mV]
Mean (+/- SD)	53% (+/- 8,46)	135,9 (+/- 26,18)	220,3 (+/- 84,59)
Minimum	40%	97	112
Maximum	68%	200	400

rMT = resting motor threshold

%MSO = Percentage of the maximal stimulation output of Magstim bistim

In Table 1, the stimulation parameters for each kind of stimulation are presented and it is possible to realize the heterogeneity of the parameters between the subjects.

MEP amplitudes

The mean peak-to-peak MEP amplitudes values for each conditions are shown in table 2. **One subject (S6) got much higher MEP amplitudes than the other subjects so we decided not to use its results in the mean results.**
Prevalence of response stands for the percentage of subjects showing a response out of 17 subjects and *prevalence of trials* stands for the percentage of trials showing responses out of 144 trials.

Table 2: **MEP amplitude mean values**

	TMS			**TST**		
	SICI	SP	ICF	SICI	SP	ICF
Mean (±SD) [mV]	0.8156 (± 0.73)	1.8683 (± 1.71)	1.8226 (± 1.64)	2.7388 (± 3.30)	3.0349 (± 3.30)	3.7148 (± 3.40)
Prevalence of responses	100%			100%		
Prevalence of trials	75%	85%	82%	84%	93%	93%
	QuadS			**QuintS**		
	SICI	SP	ICF	SICI	SP	ICF
Mean (±SD) [mV]	1.2248 (± 1.57)	1.4496 (± 2.04)	1.7735 (± 2.35)	1.2139 (± 2.01)	0.9114 (± 1.71)	0.8051 (± 1.57)
Prevalence of responses	94%	82%	94%	71%	71%	76%
Prevalence of trials	59%	60%	61%	40%	40%	41%

By taking a look at the groups of subjects, the results shows that there is higher MEP responses in the group of the «most active» subjects with ratios of 152% for TMS, 342% for TST, 411% for QuadS and 483% for QuintS. **As written above, one of the subject (S6) of the «most active» group got some very high MEP responses, so without taking its results, the ratios are a bit lower with 137% for TMS, 230% for TST, 199% for QuadS and 178% for QuintS.** These results are shown in table 3.

***Table 3* : MEP amplitude mean values**

	TMS			**TST**		
	SICI	SP	ICF	SICI	SP	ICF
Mean «most active» [mV]	0.892557	1.967219	2.082912	3.693696	4.056305	4.99473
Mean «less active» [mV]	0.656549	1.572824	1.388779	1.585731	1.7898	2.164278
Comparison (most/less) [%]	137 %			230 %		
	QuadS			**QuintS**		
	SICI	SP	ICF	SICI	SP	ICF
Mean «most active» [mV]	1.367284	1.993928	2.316777	1.324625	1.196782	1.066579
Mean «less active» [mV]	0.96206	0.804692	1.093515	0.980575	0.55645	0.48327
Comparison (most/less) [%]	199%			178%		

This table displays the MEP amplitude mean values in each condition for the two groups of subjects and the comparison between these two groups ***without the outlier***

Intra-cortical inhibition and facilitation

SICI and ICF are calculated as a percentage ratio between the conditioned stimulus (paired-pulse) and the test stimulus (single-pulsed) peak-to-peak amplitude. SICI corresponds to a ratio which is < 100% and ICF when the ratio is > 100%.

Concerning TMS, SICI was found, in PP 2ms, in 15/17 subjects with a mean ratio of 58%. Concerning TST, it was found in 10/17 subjects with a mean ratio of 88% (without the outlier). In PP 10ms, ICF was found, concerning TMS, in 10/17 subjects with a mean ratio of 115%. Concerning TST, it was found in 12/17 subjects with a mean ration of 128% (without the outliers). The other subjects were showing inhibition and facilitation when the opposite was expected, with the four methods and with all ISI: 2 subjects with TMS and 7 with TST showed facilitation with ISI of 2ms and 7 subjects with TMS and 5 with TST showed inhibition with ISI of 10ms. Results are presented below in table 4 and in figure 1 and 2.

***Table 4* : TMS & TST MEP amplitude [mV] with SICI and ICF results [%]**

Subject	TMS					TST				
	PP 2ms	SP	PP 10ms	SICI	ICF	PP 2ms	SP	PP 10ms	SICI	ICF
1	0.6867	1.1294	2.0720	**61%**	**183%**	3.2292	2.4237	3.6934	133%	**152%**
2	0.4152	1.0239	1.6330	**41%**	**159%**	0.3860	1.7152	3.2425	**23%**	**189%**
3	1.9291	2.6566	3.2490	**73%**	**122%**	1.6107	1.9527	2.8245	**82%**	**145%**
4	0.3053	2.9217	0.9604	**10%**	33%	0.6700	1.2869	0.4996	**52%**	39%
5	0.3054	0.7003	1.0454	**44%**	**149%**	10.8136	12.346	11.0659	**88%**	90%
6	0.8855	1.4142	2.1667	**63%**	**153%**	16.4908	16.5547	16.3458	100%	99%
7	0.2159	0.5715	0.4913	**38%**	86%	2.7662	4.6230	3.5489	**60%**	77%
8	0.2828	2.1717	1.9161	**13%**	88%	1.0846	3.1140	5.1343	**35%**	**165%**
9	1.9994	4.2261	4.3730	**47%**	**103%**	1.9173	3.4972	4.4856	**55%**	**128%**
10	1.1788	5.2144	4.5469	**23%**	87%	1.9512	2.9549	4.3750	**66%**	**148%**
11	2.2342	1.9737	1.7249	113%	87%	2.2723	2.1022	1.1344	108%	54%
12	1.6089	5.1201	5.1450	**31%**	**100%**	10.9415	9.1598	12.0680	119%	**132%**
13	0.4261	0.7011	0.3931	**61%**	56%	2.1004	0.3337	2.0252	629%	**607%**
14	0.8467	0.6648	0.5887	127%	89%	0.7086	0.8019	1.9652	**88%**	**245%**
15	0.2936	0.4461	0.4821	**66%**	**108%**	0.8348	0.6097	0.6499	137%	**107%**
16	0.1533	0.1738	0.1954	**88%**	**112%**	0.0616	0.059	0.3097	104%	**525%**
17	0.1682	0.1983	0.3461	**85%**	**175%**	2.4732	1.5788	2.4144	157%	**153%**

In **bold** and coloured are the expected results for each method (SICI < 100% and ICF > 100%)

Figure 1

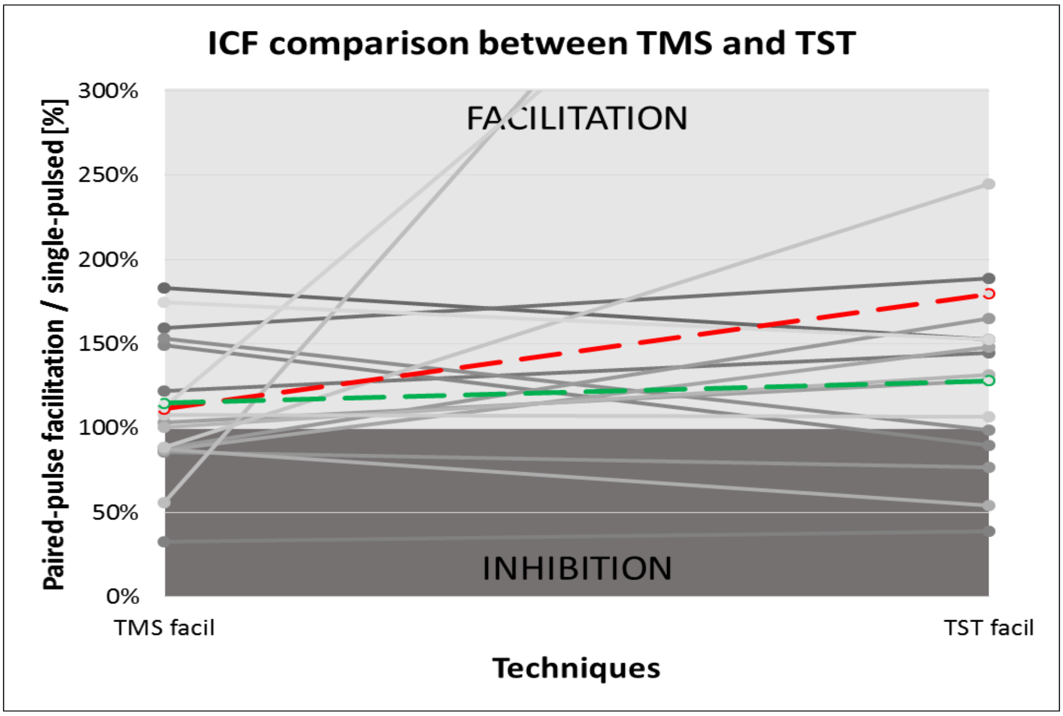
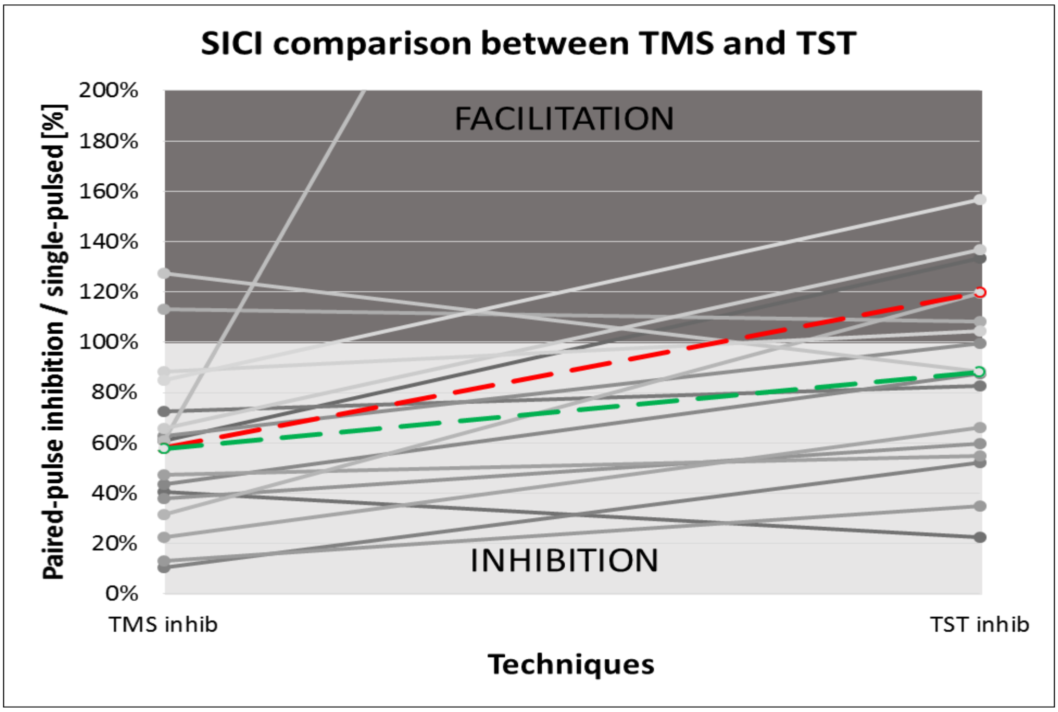


Figure 2



In **light grey area** are the expected results. In **dark grey area** are the unexpected results.

Red dotted line corresponds to the mean result with the outliers.

Green dotted line corresponds to the mean result without the outliers.

QuadS and QuintS

The prevalence of MEP responses and the prevalence of trials showing MEP response to QuadS or QuintS for each condition are presented above in table 2. Concerning the force contraction responses to QuadS and QuintS, the results are presented below in table 5.

Contraction force responses

The mean peak-to-peak contraction force responses amplitudes values for each conditions are shown in table 5. *Prevalence of responses* stands for the percentage of subjects showing a response out of 17 subjects and *prevalence of trials* stands for the percentage of trials showing responses out of 144 trials.

Table 5 **: Force amplitude mean values and prevalence of responses/trials**

	TMS			**TST**		
	SICI	SP	ICF	SICI	SP	ICF
Mean (±SD) [N]	0.96481 (±1.759)	1.27665 (±2.596)	1.18922 (±2.377)	2.09286 (±2.442)	2.08673 (±2.279)	1.86871 (±2.474)
Prevalence of responses	53%	59%	47%	82%	82%	82%
Prevalence of trials	33%	34%	34%	59%	58%	61%
	QuadS			**QuintS**		
	SICI	SP	ICF	SICI	SP	ICF
Mean (±SD) [N]	2.11453 (±2.622)	1.78200 (±1.837)	2.52705 (±3.246)	2.46729 (±2.998)	2.30662 (±2.923)	2.77936 (±3.415)
Prevalence of responses	82%	76%	71%	82%	71%	88%
Prevalence of trials	64%	62%	62%	64%	61%	63%

The comparison of the contraction force of the Abductor Digiti Minimi (ADM) muscle which have been measured by the force transducer between the two groups of subject according to their physical activity show that there is higher responses for each method in the group of «less active» subjects and by far. For TMS, the responses were 1127% higher in the «less active» group than in the «most active» groups, 256% for TST, 322% for QuadS and 294% for QuintS. These results are presented in table 6.

Table 6 : **Contraction force mean values**						
	TMS			**TST**		
	SICI	SP	ICF	SICI	SP	ICF
Mean «most active» [N]	0.22210	0.10811	0.19157	1.18023	1.32488	0.77457
Mean «less active» [N]	1.59025	2.26067	2.02935	2.86946	2.72828	2.79008
Comparison (less/most) [%]	1127%			256%		
	QuadS			**QuintS**		
	SICI	SP	ICF	SICI	SP	ICF
Mean «most active» [N]	0.98037	0.96629	0.96682	1.04659	1.16280	1.47218
Mean «less active» [N]	3.06961	2.46892	3.84092	3.66366	3.26983	3.88015
Comparison (less/most) [%]	322%			294%		

This table displays the contraction force mean values in each method for the two groups of subjects and the comparison between these two groups

Correlation between contraction force and MEP responses

Concerning the correlation analysis between the two types of responses in the two groups, the p-value and the Pearson's correlation coefficient (PCC) have been used to initially see if there was a statistically significant correlation between the activity of the subject and its responses. For the MEP responses, these two tests show that there is a positive correlation (if PPC > 0) according to the activity which means that more active is the subject, higher its MEP response to the stimulation will be except for TMS SP and TMS PP10. But, these tests didn't show any statistically significant results (significant if p-value < 0.05) (see Figure 3 and Table 7).

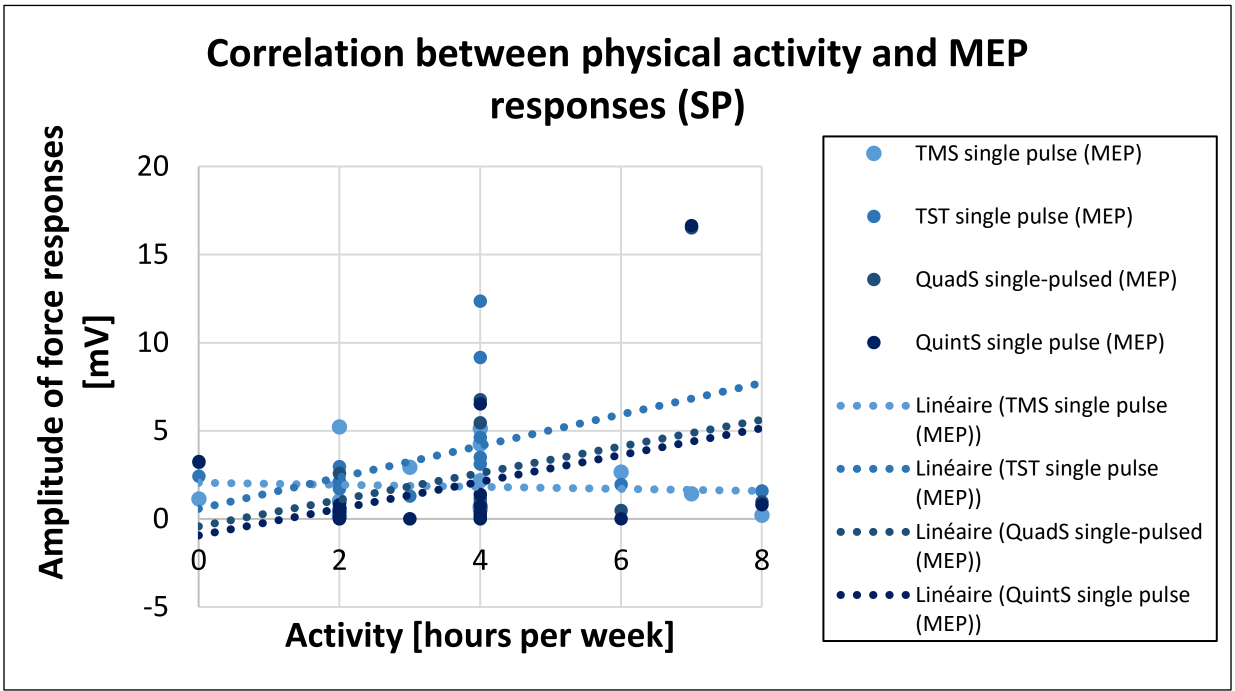


Figure 3: Positive correlation between physical activity and MEP responses amplitude

Table 7 **: Activity & MEP responses**						
	TMS			**TST**		
	Single-pulse	SICI	ICF	Single-pulse	SICI	ICF
P-value	0.79	0.933	0.942	0.122	0.11	0.119
Pearson's correlation coefficient (PCC)	-0.07	**0.022**	-0.019	**0.389**	**0.401**	**0.392**
	QuadS			**QuintS**		
	Single-pulse	SICI	ICF	Single-pulse	SICI	ICF
P-value	0.151	0.16	0.171	0.15	0.237	0.168
Pearson's correlation coefficient (PCC)	**0.364**	**0.357**	**0.348**	**0.365**	**0.303**	**0.351**
This table display the statistical correlation analysis (p-value and PCC) between the physical activity and the MEP responses in all the different conditions of stimulation						

Concerning the contraction force responses, these tests show that there was a negative correlation (if PCC < 0) in all the techniques which means that more active is the subject, lower its contraction force response to the stimulation will be. With TMS, a significant negative correlation has been found with p-value of 0.049 (significant if <0.05) and PCC of -0.485 for PP2 and PP10 and p-value of 0.035 and PCC of -0.514 for SP. No other statistically significant correlation have been found for the other techniques (see Figure 4 and Table 8)

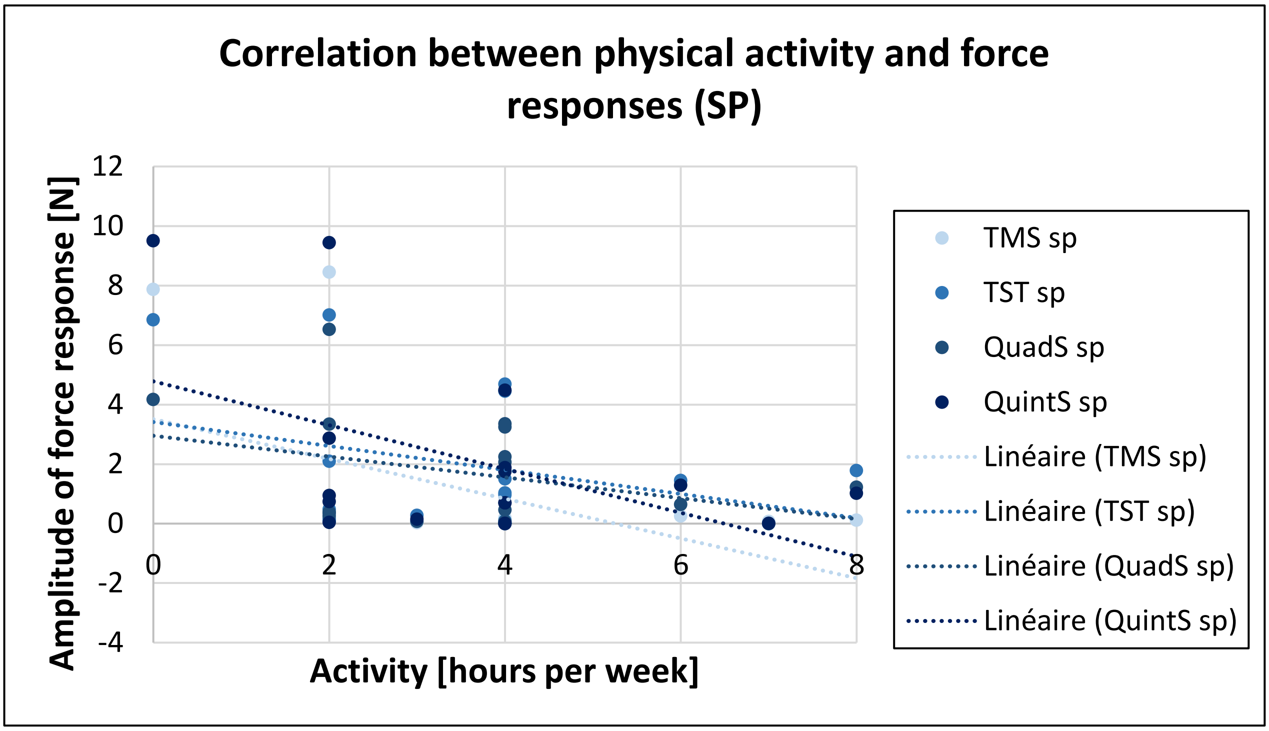


Figure 4: Negative correlation between physical activity and contraction force responses amplitude

Table 8 **: Activity & Contraction force responses**						
	TMS			**TST**		
	Single-pulse	SICI	ICF	Single-pulse	SICI	ICF
P-value	**0.035**	**0.049**	**0.049**	0.146	0.234	0.104
Pearson's correlation coefficient (PCC)	**-0.514**	**-0.485**	**-0.485**	**-0.368**	**-0.305**	**-0.407**
	QuadS			**QuintS**		
	Single-pulse	SICI	ICF	Single-pulse	SICI	ICF
P-value	0.135	0.086	0.16	0.083	0.052	0.085
Pearson's correlation coefficient (PCC)	**-0.378**	**-0.428**	**-0.357**	**-0.432**	**-0.479**	**-0.43**
This table display the statistical correlation analysis (p-value and PCC) between the physical activity and the strength responses in all the different conditions of stimulation						

By looking at these results after the separation of the subject in the two groups according to the physical activity, the results seem to be the same with contraction force responses that are lower in the «most active» subjects than in the «less active» subjects (See Figure 3) and MEP responses that are higher in the «most active» subjects than in the «less active» subjects. (See Figure 4)

Figure 3

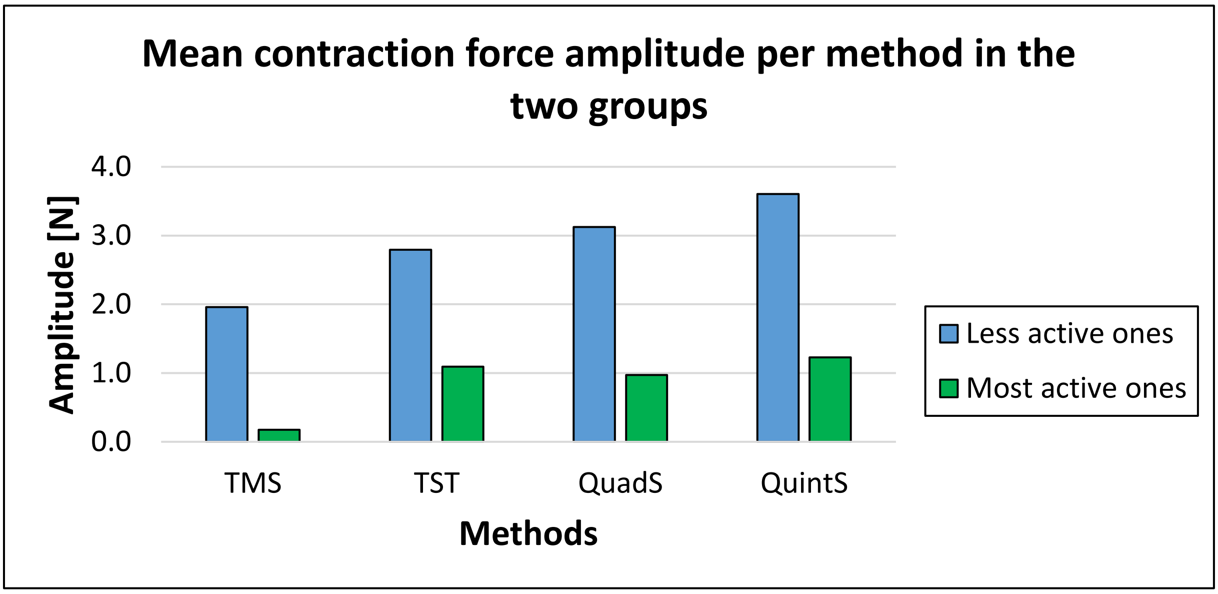
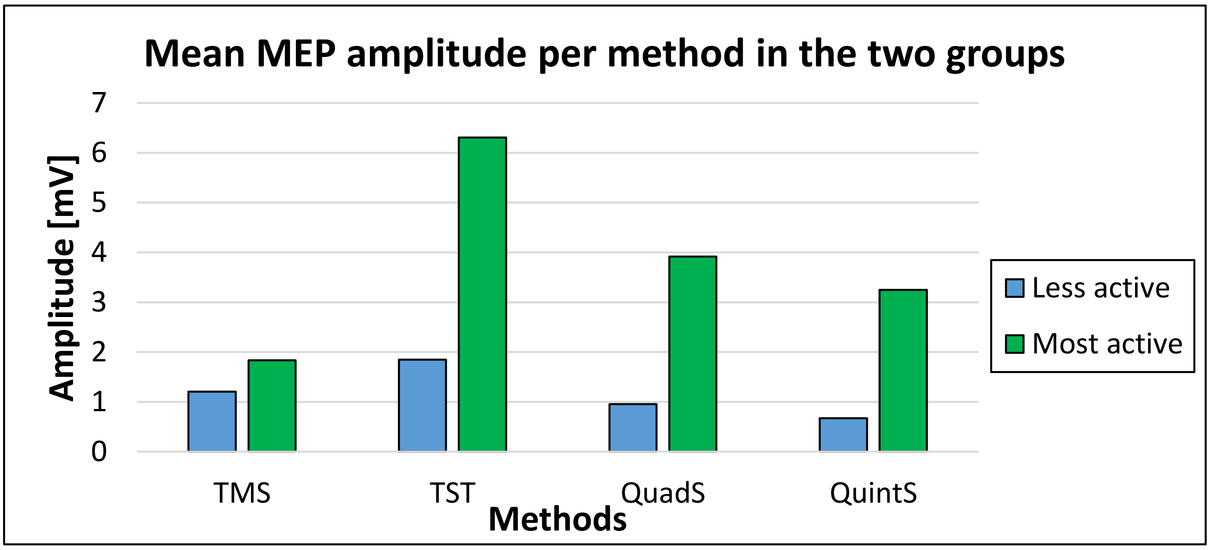


Figure 4



As shown in Figure 3 and 4, the difference of contraction force and MEP amplitude between the different methods and the two groups of subjects are very explicit. As expected, concerning the force amplitude, the responses grow up in correlation with the number of (peripheral) stimulations the subjects are dealing with. In another way, concerning the MEP amplitude, the results are different with higher responses for TST in the two groups, but different results for the other methods according to the group of subject. For the «less active» subjects, TMS got higher responses than

QuadS and QuintS (TST>TMS>QuadS>QuintS) and for the «most active» subjects, QuadS and QuintS got higher responses than TMS. (TST>QuadS>QuintS>TMS)

Discussion

The objectives of the study were to explore the contraction force responses in the paired-pulsed paradigms of SICI and ICF using conventional TMS, TST, Quadruple and Quintuple stimulation techniques and then compare the results between two groups of subjects according to their physical activity. **This is the first study which is looking at a correlation between physical activity, MEP responses and strength responses.** The study of Z'Graggen in 2008 (15) already worked on a possible correlation of MEP responses to QuadS, the handedness and the evolution after a precision/force training and they showed that there was a clear positive correlation between the size of MEP responses and the handedness of the subjects with a conclusion of supraspinal origin of RepMNDs.

The results of the study aren't totally in accordance with the first work hypothesis. We first thought that the «most active» subjects will have higher MEP **and** higher contraction force responses to the stimulation due to their higher frequency of training. As described in the results part, it is not the case in this study with a negative correlation between the physical activity and the contraction force responses. Concerning the MEP responses, the correlation with the physical activity of the participant was still a positive one (except for TMS). These results seems to be paradoxical with opposite conclusion in MEP and force contraction responses, but we could suggest the possible reasons of these results. First of all, we suggest that the «most active» subjects with their higher frequency of training got possibly some more precise movement in contrary of the «less active» subjects who got coarser movements induced by other muscles than only ADM and that can product artefacts in their force responses. The second hypothesis is that the «most active» subjects may be more accustomed to the contraction of their muscles than the «less active» subjects and the reaction to the stimulation could be changed that way. As described in Andersen et al. in 2012 (16), we know that the fraction of spinal MNs which are firing more than once in response to TMS increased when the muscle is fatigued and we can interpret this as the reason of higher contraction force responses in the «less active» subjects, because these subjects may have an earlier fatigue mechanism than the «most active» subjects.

In the same way as the last study from Batzianouli et al.(5), we looked after the contribution to SICI and ICF method in the MEP responses, but we add the studying of the contraction force responses to these methods too. In MEP responses, the results are pretty similar with the results of Kujirai et al.(2) with inhibition using an ISI of 2ms and facilitation using an ISI of 10ms. Nevertheless, the utility of these techniques of paired-pulse paradigm is restricted in clinical practice due to an important inter- and intra-individual variability. As described by Du et al. in 2014 (17), there is an important inter-individual variability to the paired-pulse paradigm and this is the case in this study, but there is a still pretty high intra-individual variability too. In that way, we also found some subjects who shows opposite results with inhibition instead of facilitation with ISI of 10ms and facilitation instead of inhibition with ISI of 2ms. Concerning the contraction force response to this paradigm, there is about 50% of facilitation with ICF and the same kind of results with SICI in all the different methods which may let us think that there is no clear influences of the paired-pulse paradigm to the amplitude of the contraction force response to the stimulation.

To evaluate the variability of these results, we measured the coefficient of variation (CV) and found that TST, QuadS and QuintS are pretty more consistent than TMS with contraction force responses, but it is the opposite for the MEP responses in our study.

Limitations

In this study, there is some limitations concerning the measurement of the contraction force responses caused for example by the sensitivity of the force transducer, the stability of the force transducer, the hand position which has to be the same during the whole experiment and the inter-individual variability of the arm length and hand morphology.

Concerning the TMS use, there is always some limitations with the position of the coil which may change during the experiment due to the fact it is hand-held during the whole experiment (18). To minimize this limitation, we have clearly marked the area where the coil should stay during the experiment and we then focused on maintaining it in the same position.

In another way, concerning the different subjects, there is many sources of limitations as the time of the day in which the experiment has been realized or the state of arousal that was different between the subjects and that could be other causes of modification of the response.(19)

Conclusion

In this study, the measurement of the contraction force as well as the MEP responses to TMS, TST, QuadS and QuintS with single-pulse, paired-pulse 10ms (ICF) and paired-pulse 2ms (SICI) were the main measurements to search a correlation between the responses. The comparison of two groups of subjects according to their physical activity shows us the negative correlation between contraction force responses and physical activity and the positive correlation between MEP responses and physical activity which is not totally in accordance with the first hypothesis. We suspected that the «most active» subjects will get higher strength and MEP responses due to their higher frequency of training. We suggest then that the «most active» subjects possessed a more precise strength responses due to their training and the «less active» subjects got a coarser responses with more artefacts due to the arm movement.

The next steps of the study could be to better analyse and understand the mechanism which induces a lowering of the strength responses with the «most active» subjects by making two sessions of stimulation with possible force and/or precision movement training to search a possible evolution of the contraction force responses.

Abbreviation

ADM.. Abductor Digiti Minimi
aMT .... active Motor Threshold
CMAP.. Compound Muscle Action Potentials
CS.. Conditioning Stimulus
CV .... Coefficient of Variation
ICF .... Intra-Cortical Facilitation
ISI .... Inter-Stimulus Intensity
MEP .... Motor-Evoked Potential
MN .... Motor-Neuron
MSO .... Maximal Stimulation Output
PCC .... Pearson's Correlation Coefficient
PP .... Paired-Pulse
PP-TMS .... Paired-Pulse TMS
PP-TST .... Paired-Pulse TST
QuadS .... Quadruple Stimulation
QuintS .... Quintuple Stimulation
RepMND .... Repetitive Motor Neuron Discharges
RMS .... Root Mean Square
rMT .... resting Motor Threshold
SP .... Single-pulse
SD .... Standard Deviation
SICI .... Short Intra-Cortical Inhibition
TES .... Transcranial Electric Stimulation
TMS .... Transcranial Magnetic Stimulation
TS .... Testing Stimulus
TST .... Triple Stimulation Technique

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