UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Mémoire de Maîtrise en médecine No 1481

Exploring Brain Inhibition and Facilitation by Transcranial Magnetic Stimulation

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Lausanne, November 2014

Abstract

Background and Question

Paired-pulse TMS (Transcranial Magnetic Stimulation) paradigms allow explore motor cortex physiology. The Triple Stimulation Technique (TST) improves conventional TMS in quantifying cortico-spinal conduction. The objective of our study was to compare both methods in paired-pulse paradigms of inhibition and of facilitation.

Method

We investigated paired pulse paradigms of 2 ms (short intra-cortical inhibition) and of 10 ms intervals (intra cortical facilitation) in a randomized order in 22 healthy subjects applying conventional TMS and the TST protocol.

Results

Paired-pulse paradigms by both TMS and the TST yielded comparable results of short intra-cortical inhibition and intra cortical facilitation. However, the coefficient of variation was significantly smaller for SICI paradigm using TST.

Conclusion

These results suggest no greater sensitivity of the TST for quantifying inhibition and facilitation. The utility of TST to better quantify the individual amount of inhibition in SICI paradigms and its clinical utility need further studies.

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Introduction

Transcranial magnetic stimulation (TMS) is an established method to study the excitability of the motor cortex. The paired pulse paradigm allows explore the primary motor cortex, and it has shown that, depending in the interval between a first conditioning stimulus and a second test stimulus, there is a decrease [intra-cortical inhibition (SICI)] or an increase [facilitation (ICF)] of the amplitude of the motor evoked potential (MEP)(Reis et al, 2008). Paired pulse paradigms consist of a conditioning stimulus, "enough to activate cortical neurons, but small enough so that no descending influence on the spinal cord can be detected and there is no MEP"(Hallett et al, 2007), and a test stimulus, supra-threshold, that cause a MEP. If the interval between the two stimuli [interstimulus interval (ISI)] is short, less than 5ms, there is an inhibition (the MEP is decreased). If it is long, between 8 and 30ms, there is a facilitation (the MEP is increased)(Hallett et al, 2007) see Kujirai et al., 1993.

MEPs elicited by TMS are highly variable and there are a number of factors confounding TMS measures. Among these there is the desynchronization of the descending volleys that cause a decrease in amplitude of the MEPs due to 'phase cancellation' in which the negative phases of individual motor unit potentials are cancelled by the positive phases of others (Magistris et al, 1998), and a certain amount of central desynchronization. The triple stimulation technique (TST), originally developed by Magistris (Magistris et al, 1998), corrects for the desynchronization and MEPs evoked are less variable.

Our objective is to study the SICI and ICF using paired-pulse TST to better quantify facilitation and inhibition, which will allow a better understanding of SICI and ICF.

Material and Methods

Subjects

Twenty-two healthy subjects, fifteen males and seven females, aged from 21 to 40 years (mean 27.6 ± 5.2 years) participated in the study. All of them were screened for TMS contraindications and gave their written informed consent prior to their inclusion in the study. The study is conform to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Electrophysiological recordings

For this experiment we use the same electrophysiological recording settings as previously described by Bedulli et al. (2013): A Viking Select IV EMG apparatus (Nicolet, Madison; Wisconsin, USA) recorded and amplified the EMG signal. Surface electrodes were put in a belly-tendon montage on the right Abductor Digiti Minimi (ADM). Band pass filter were set at 1 Hz - 5 kHz (Groppa et al., 2012). The subjects were seated in a comfortable reclining chair with the forearm on a cushion during the procedures. Cable and electrodes were fixed with sufficient tape to avoid artifacts during the measurement. Signal processing was done with LabVIEW software (National Instruments Corporation, LabVIEW 12.0f3, Austin, 2012).

Transcranial Magnetic stimulation

Transcranial Magnetic stimulation (TMS) stimuli were applied with a figure-of-eight coil (7mm) over the hand motor cortex, using a Magstim bistim2 stimulator (The Magstim Company Limited, Spring Gardens, Whitland, UK). The localization of the optimal cortical stimulation spot for the ADM was made in accordance with the guidelines of IFCN (International Federation of Clinical Neurophysiology)(Groppa et al., 2012). The coil was kept in the same position, marked on a cap, throughout the experiment.

Triple stimulation technique

Magistris originally described the triple stimulation technique in 1998 (Magistris et al., 1998). This technique consists in a succession of three stimulations that corrects for the phase cancellation phenomena. The first stimulation is a transcranial magnetic stimulation over the motor cortex (1), followed, after a lapse of time sufficient for the action potential to reach the forearm, by an electrical stimulation of the wrist (2) and finally by an electrical stimulation at Erb's point (3). These three stimulations cause two collisions that lead a re-synchronisation of the action potentials (Figure 1). The Viking Select IV EMG apparatus has a specific TST

program that triggers the stimulators with the pre-set delays calculated for each subject between the stimulations, the stimulations at the wrist and Erb's point are given at a supra-maximal intensity.

The control condition consists of an electrical stimulation of the Erb's point (Erb's – wrist – Erb's stimulations) instead of the motor cortex. The MEPs generated with the test stimuli are compared with the one generated with the control stimuli, the difference in amplitude quantifies the integrity or eventual loss in the corticospinal conduction.

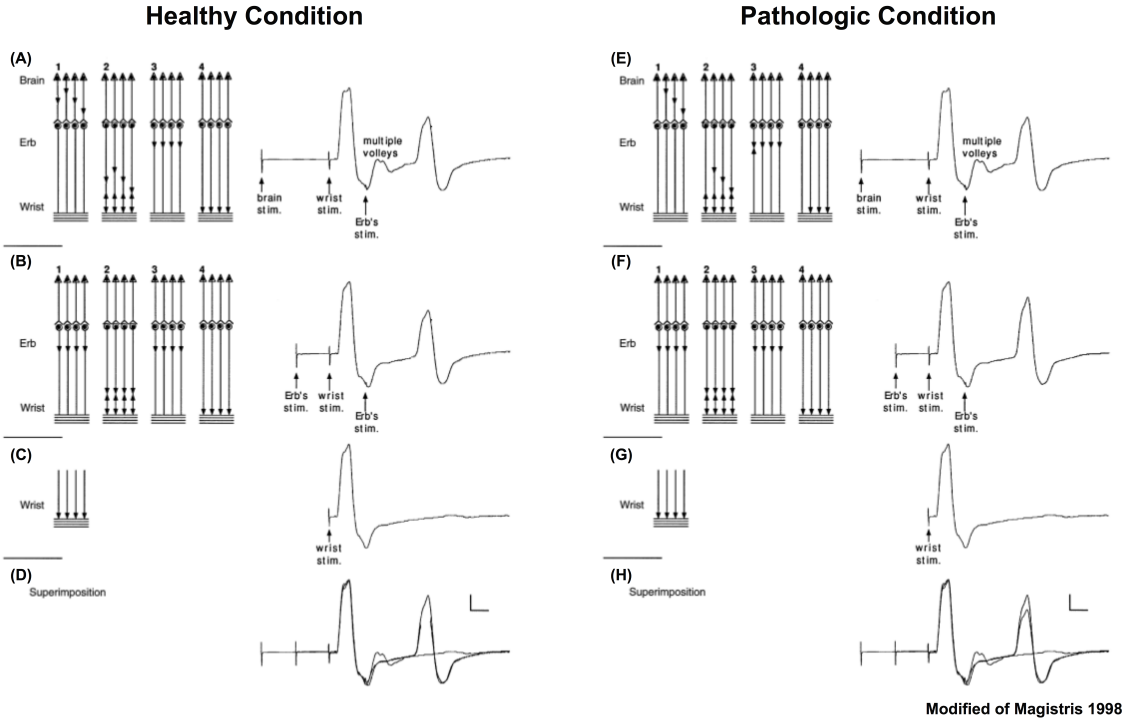


Figure 1: Modified from Magistris et al, 1998. The image in the left (A)(B)(C)(D) represent an healthy condition, in the right (E)(F)(G)(H) a pathologic one. In the left side of each condition nerves are represented and the small black triangles represent the action potentials. A synapse is represented at the level of Erb's point. In the right side there is a representation of the MEP elicited in each situation. (A) Test: a magnetic stimulation generates de-synchronised action potential descending in the arm. A second electrical stimulation at the wrist induce orthodromic and antidromic action potential, the first generates a MEP, the second a collision with the descending actions potential. A third electrical stimulation at Erb's point generates synchronised action potentials that don't collide in a healthy subject and generate a second MEP. (B)(F) Control: The first magnetic stimulation of the Test is replaced with an electrical stimulation at Erb's point creating a control MEPs curve. (C)(G) MEP induced by an electrical stimulation of the wrist. (D) The integrity of the nerves is tested comparing the MEPs generate by the test with the one of the control stimulations; they don't differ in an healthy subject. (E) Test: In a pathologic condition the magnetic stimulation is not able to induce an action potential in each axon where the second stimulation at the wrist is. Therefore the first collision does not occur in each axon. The third stimulation generate action potentials that collide in the axons were the first collision didn't occur and generate a MEP. (H) The integrity of the nerves is tested comparing the MEPs generate by the test with the one of the control stimulations; in this pathologic situation the inability of the first magnetic stimulation to excite each axon is detected by the test MEP who is smaller that the control one.

Paired-pulse paradigms

In 1993 Kujirai (Kujirai and al, 1993) described cortico-cortical paired-pulse paradigms as inhibiting or facilitating motor evoked potential depending on the inter-stimuli interval (ISI). Paired-pulse paradigms consist in a succession of 2 magnetic stimulations. The first (conditioning stimulus, CS) given at 80% of the resting motor threshold (rMT), thus theoretically unable to evoke alone a MEP, followed after an ISI by the second stimulation (test stimulus, TS) given at 120% of the rMT. With cortico-cortical (the CS and the TS are given over the hand motor cortex) paired-pulse paradigms with short ISI (1-5ms) the MEPs evoked are smaller than the one evoked with a single TMS stimuli (SICI: short intra-cortical inhibition) when for longer ISI (10-15ms) the MEPs evoked are bigger (ICF: intra-cortical facilitation).

Procedure

In our study we decided to study the cortico-cortical paired-pulse paradigms using the TST.

For each subject we started by localizing the hotspot for the ADM in accordance with the guidelines of IFCN (International Federation of Clinical Neurophysiology)(Groppa et al., 2012). Then we calculate the resting motor threshold using the maximum likelihood threshold hunting procedure described by Awiszus (Awiszus, 2003). Finally we measured for each subject the intensity of the electrical stimulation at Erb's point and at the wrist able to provoke a supra-maximal response.

The subjects underwent two different phases; first we studied the SICI and the ICF using the TMS. They received 36 stimulations: 12 single pulses, 12 with 2ms of ISI (PP2) and 12 with 10ms of ISI (PP10) in a randomized order.

In the second phase we applied the TST at the paired-pulse stimulation. As for the TMS, they underwent 36 triple stimulations. 12 with the first stimulus of the TST being single, 12 with the first magnetic stimulus replaced with a couple of magnetic stimuli (CS and TS) with an ISI of 2ms (PP2) and 12 with an ISI of 10ms (PP10).

Data Analysis

For each stimulation signal we measured the maximum (Max) and minimum (Min) amplitude of the MEP and the difference between the two of them (MaxMin), the area under the curve (Area) and the root mean square (RMS) using the Nguyet application of LabView (National Instruments Corporation, LabVIEW 12.0.1f5, Austin, 2012). Statistical analysis was made

with IBM SPSS Statistic (IBM Corporation, SPSS Statistic Version 21.0.0.0.0, New York, 2012).

The first step of the analysis has been to calculate the mean, the median and the standard deviation for the five variables. This calculation was done for each condition (PP2, S, PP10, NA) of each of the 22 subjects. We tested the normality of the distribution using the Shapiro-Wilk test (normal distribution if p> 0.05). Successively we calculated for each subject the ratio between the paired pulse response and the single response. To analyse the variations of the elicited MEP we use the coefficient of variation (CV) of the peak-to-peak amplitude as suggested by Kiers et al. (1993), for both TMS and TST methods. CV consists in the standard deviation divided by the mean. We applied the Shapiro-Wilk statistical analysis to determine the normality of the distribution of the values and then we applied the Related-Samples Wilcoxon Signed Rank test, or the paired samples T-test to test the statistical significance (accepted for p value < 0.05).

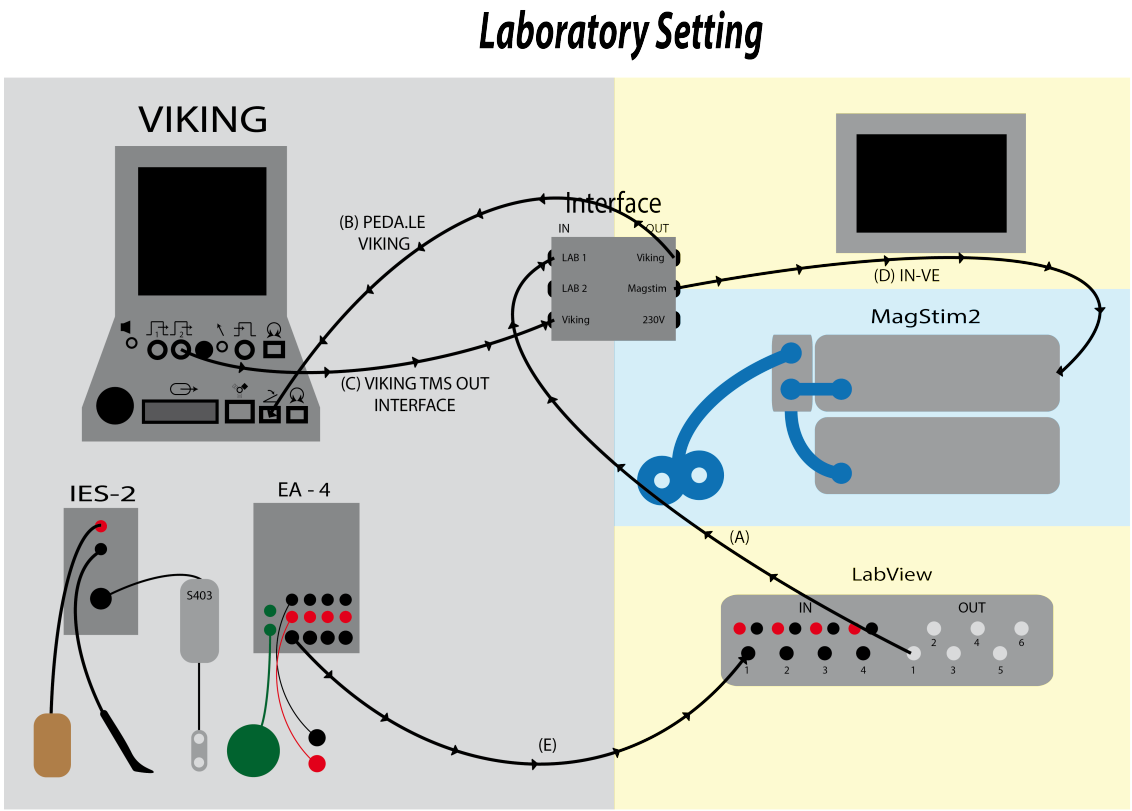


Figure 2 : Laboratory Setting: To perform the TST we used the a Magstim bistim2 (The Magstim Company Limited, Spring Gardens, Whitland, UK) combined with a Viking Select IV EMG apparatus (Nicolet, Madison; Wisconsin, USA) all drived by a LabVIEW software (National Instruments Corporation, LabVIEW 12.0f3, Austin, 2012). The initial trigger is generated by LabView and goes into the interface (A) needed to invert the trigger polarity. Then the signal goes to the Viking select and starts the previously programmed TST protocol. Viking Select sends a signal to the interface (C) and then to the Magstim bistim2 (D) to trigger the magnetic stimulation, and it sends à signal to its IES-2 stimulator to trigger the peripheral stimulations. The MEP's elicited are recorded with the EA – 4 unit of the Viking Select and then send back to LabView (E).

Results

Stimulation parameters

The determined stimulation parameters are shown in the Table 1.

Table 1: Stimulation parameters

	rMT (%MO)	Conditioning Stimulus (%MO)	Test Stimulus (%MO)	Wrist Stimulus (mV)	Erb's point Stimulus (mV)
Mean (±SD)	46.82 (±1.888)	37.68 (±1.485)	56.27 (±2.253)	121.77 (±8.431)	160.18 (±15.700)
Minimum	33	26	40	72	90
Maximum	68	54	82	229	370

rMT = resting Motor Threshold; %MO = percentage of the maximum output of the Magstim bistim2; Conditioning and Test stimulus are transcranial magnetic stimulations, Wrist and Erb's stimulations are electrical stimulations.

MEP Amplitudes

The distributions of the mean values of peak-to-peak MEP amplitudes are not normal for both methods and all the conditions. The Shapiro-Wilk test value are p=0.001 for TMS single stimulation, p=0.000 for TMS PP2 stimulations, p=0.010 for TMS PP10 stimulations, p=0.001 for TST single stimulation, p=0.000 for TST PP2 stimulations and p=0.013 for TST PP10 stimulations.

The mean value of peak-to-peak MEP amplitude, for each subject and each condition are shown in the graph 1. There is a significant difference between the means of each condition with both methods.

With TMS, The mean value of peak-to-peak amplitude is (m) = 1.492 ± 0.307 mV,. In the paired-pulse paradigm, the mean value of peak-to-peak TMS PP2 stimulations it is = 0.941 ± 0.254 mV (p=0.004) and with TMS PP10 stimulations it is (m) = 2.306 ± 0.417 mV (p=0.000).

With TST, The mean value of peak-to-peak amplitude is (m) = 1.983 ± 0.308 mV. In the paired-pulse paradigm, the mean value of peak-to-peak TST PP2 stimulations it is = 1.608 ± 0.301 mV (p=0.004) and with TST PP10 stimulations it is (m) = 2.705 ± 0.419 mV (p=0.019). These results are presented in the Figure 2.

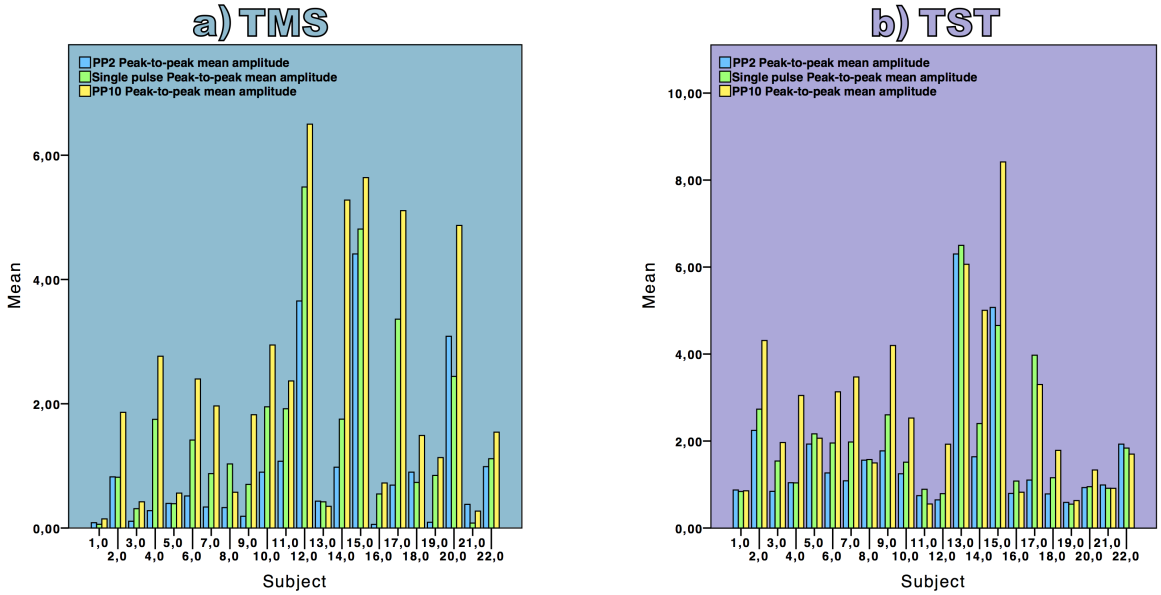
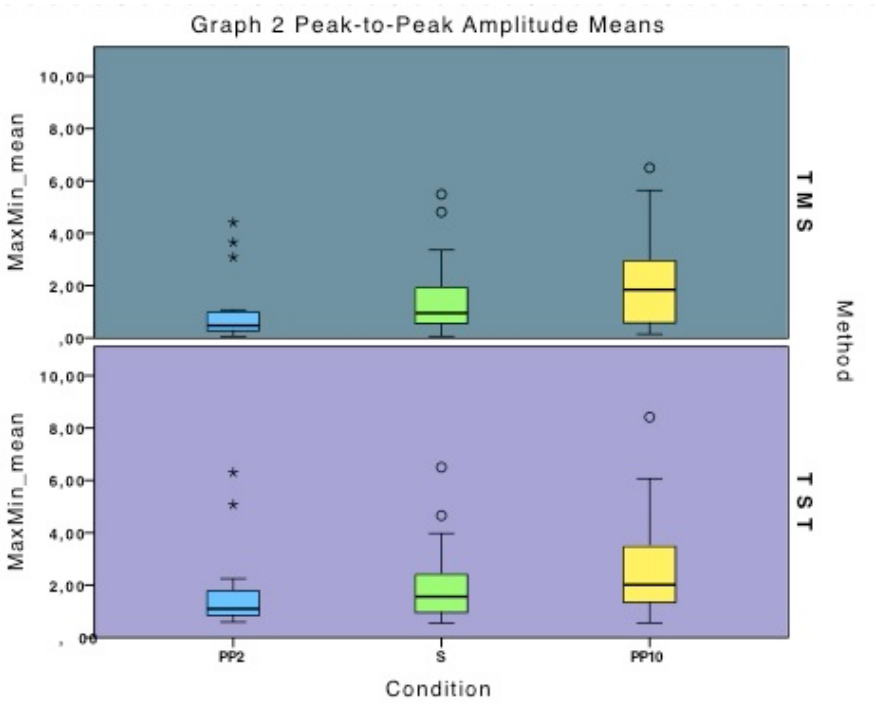


Figure 2: *This figure represents the mean peak-to-peak amplitude for each subject. In the left part a) TMS stimuli are represented and in the right part b) represent TST stimuli. The blue column is for the paired pulse 2 (PP2) stimulations. The green column represent the single pulse stimulations and the yellow column is for the paired pulse 10 (PP10) stimulations.*

Intracortical inhibition and facilitation

Intracortical inhibition and facilitation is determined by the ratios between the peak-to-peak amplitude of the PP2 stimulations and the single ones, and of the PP10 stimulations and the single ones. The results are shown in the Table 2.



Short intracortical inhibition (SICI) is

reached when the peak-to-peak amplitude ratio PP2/S is minor of 1. With TMS, we reached a SICI in 15 subjects, and the mean ratio is (m) = 0.821±0.207. With the TST we reached a SICI in 16 subjects, the mean is (m) = 0.830±0.046. There is no significant difference between the two methods, p=0.131

Table 2 : short intracortical inhibition (SICI) and facilitation (ICF): individual data

Subject	TMS		TST	
	SICI %	ICF %	SICI %	ICF %
1	1,42	2,45	1,04	1,02
2	1,01	2,28	0,82	1,58
3	0,35	1,36	0,55	1,28
4	0,16	1,58	1,00	2,94
5	1,01	1,44	0,89	0,95
6	0,36	1,69	0,65	1,60
7	0,39	2,25	0,55	1,76
8	0,32	0,56	0,99	0,95
9	0,27	2,60	0,68	1,61
10	0,46	1,51	0,82	1,67
11	0,56	1,23	0,84	0,62
12	0,67	1,18	0,82	2,44
13	1,03	0,83	0,97	0,93
14	0,56	3,01	0,68	2,08
15	0,92	1,17	1,09	1,81
16	0,11	1,32	0,74	0,76
17	0,21	1,52	0,28	0,83
18	1,23	2,03	0,68	1,54
19	0,11	1,34	1,07	1,15
20	1,26	2,00	0,98	1,40
21	4,78	3,42	1,08	1,00
22	0,89	1,38	1,05	0,92

This table expose the mean SICI and ICF obtained for each subject with each condition. TMS = Transcranial magnetic stimulation; TST = Triple stimulation technique; SICI = short intracortical inhibition; ICF = Intracortica facilitation

Intracortical facilitation (ICF) is described by a peak-to-peak amplitude ratio PP10/S major of 1. Using the TMS we reached an ICF in 20 subjects, the mean ratio is (m) = 1.734±0.149. With the TST we reached an ICF in 15 subjects and the mean ratio is (m) = 1.403±0.123. As for the inhibition, there is no significant difference between the two methods, p=0.074.

The mean, median, variances, minimum and maximum values of short intracortical inhibition (SICI) and facilitation (ICF): are presented in the Table 3.

Table 3 : short intracortical inhibition (SICI) and facilitation (ICF):

	TMS		TST	
	SICI %	ICF %	SICI %	ICF %
Mean (±SD)	0.821 (±0.207)	1.734 (±0.149)	0.830 (±0.046)	1.403 (±0.123)
Median	0.559	1.515	0.830	1.340
Variance	0.945	0.491	0.046	0.333
Maximum	4.78	3.42	1.09	2.94
Minimum	0.11	0.56	0.28	0.62

This table expose the mean values oft he inhibition and facilitation obtained with both, TMS and TST methods. *SICI = Short intracortical inhibition; ICF = intracortical facilitation; TMS = Transcranial magnetic stimulation; TST = Triple stimulation technique*

Coefficients of variation

The coefficient of variation is the standard deviation divided by the mean (Kiers et al., 1993).

For single stimulations the mean coefficient of variation is (m) = 0.623±0.080 for TMS, (m) = 0.359±0.047 for TST. For PP2 paradigm the mean CV is (m) = 0.725±0.546 for TMS and (m) = 0.296±0.039. For single and PP2 paradigms there is a significant difference between the two methods, the p are respectively p=0.014 and p=0.000. For the PP10 paradigms, the mean CV is (m) =0.533±0.075 for the TMS and (m) =0.388±0.060 for the TST, this difference is not significant (p=0.200).

The results are presented in the table 4.

Table 4 : Coefficient of Variation						
	TMS (mV)			TST (mV)		
	S	SICI	ICF	S	SICI	ICF
Mean (±SD)	0.623 (±0.080)	0.725 (±0.055)	0.533 (±0.075)	0.359 (±0.047)	0.296 (±0.039)	0.388 (±0.060)
Median	0.492	0.729	0.422	0.364	0.241	0.315
Maximum	1.79	1.17	1.32	0.81	0.74	1.18
Minimum	0.14	0.25	0.16	0.05	0.09	0.06

This table expose the variation of the stimulation using both TMS and TST techniques. Coefficient of variation = Standard deviation divided by the mean ; TMS = Transcranial magnetic stimulation ; TST = triple stimulation technique

Discussion

In this study, we explored the cortical excitability, more specifically the short intra-cortical inhibition (SICI) and intra-cortical facilitation (ICF) with both the conventional TMS and the TST. Our results of SICI and ICF are in line with what was already demonstrated by Kujirai et al. (1993) with TMS, we were able to obtain a significantly inhibited MEP when the test stimulus is preceded by a conditioning stimulus with an ISI of 2 ms and a significantly enhanced MEP when the ISI is 10ms. The mean peak-to-peak amplitude of the MEP's with the SICI (PP2) paradigm was 82.1% of the single stimulation mean (=inihibition), when with the ICF (PP10) paradigm it is of 173.4% (=fazilitation).

In this study we demonstrated that the SICI and ICF phenomena are confirmed with the TST technique. As with the TMS when 2 magnetic stimulations are given over the hand motor cortex the resulting MEP is significantly ($p=0.004$) inhibited with an ISI of 2ms and significantly ($p=0.019$) enhanced with an ISI of 10ms. The mean peak-to-peak amplitude of the MEP's with the PP2 paradigm was 83.0% of the single stimulation mean, when with the PP10 paradigm it is of 140.3%. There is no significant difference ($p=0.074$) between the results fund with TST than TMS, this suggest there is no greater sensitivity of the TST to quantify inhibition or facilitation.

In order to measure the inter-individual variability, we calculated the coefficient of variation (CV) defined as the standard deviation divided by the mean. (Kiers et al., 1993). For the TMS, the CV is 0.62 ± 0.08 mV for single stimulations, CV = 0.73 ± 0.06 mV for SICI paradigm and CV = 0.53 ± 0.08 mV for ICF paradigm. The CV obtained with the TST were significantly lower for the single stimulations (CV = 0.36 ± 0.05 mV) and for the SICI paradigm (CV = 0.30 ± 0.04 mV) and not significantly for the ICF paradigm (CV = 0.39 ± 0.06 mV)

The precise mechanism of intracortical inhibition and facilitation remains undetermined. According to Chen et al. (2008) SICI is more likely to have an intra-cortical origin since inhibition (SICI) cannot be observed if the conditioning stimulus is given by Transcranial Electrical Stimulation (TES) which causes direct activation of the cortico-spinal axon and does not pass by intracortical neurons (Kujirai et al., 1993). Nakamura et al., 1997 and Di Lazzaro et al., 1998, could show in epidural (high cervical) spinal cord recording, that a test stimulus evokes 3-4 descending I-waves. In the paired-pulse SICI paradigm, there is an inhibition of the second and the subsequent descending waves, thus also suggesting a cortical origin to the inhibition.

The absence of significant difference of inhibition found in our study suggests also that the phase cancellation phenomena, corrected by the TST (Magistris et al., 2008), may not play an important role in the mechanism causing SICI. The significantly lower coefficient of variation of the TST for the SICI paradigm might suggest an utility of this technique to assess the individual amount of inhibition and its alterations. A recent Master Thesis of M. Bedulli, M. Stephan and D. Benninger (2013) show that TST also allow a more precise determination of the motor threshold that the conventional TMS, it would then be interesting to study if the TST, used to determine the MT and for the stimulation, allow a better detection of the alteration of SICI in certain pathologic condition (Parkinson, dystonia, …).

The origin of ICF is also suggested to be cortical, but supposedly mediated by a neural population distinct from those mediating SICI (Chen et al. 2008). But, epidural spinal cord recording of the descending volley generated with an ICF paradigm do not differ suggesting no cortical origin (Di Lazzaro et al., 2006). Therefore "ICF may be due to a so far undetected effect on spinal cord excitability, alteration of the composition (but not the amplitude) of the descending volleys set up by the test stimulus, or there may be additional descending activity that is more dispersed than the epidural volleys and was not evident in the recording of descending corticospinal activity" (Chen et al., 2008). As with SICI, the absence of difference between the TMS results and the TST ones suggest that the phase cancellation phenomena may not contribute to ICF

Interestingly we have found that, with the ICF (PP10) paradigm, the coefficient of variation (CV) found with TST was not significantly ($p=0.200$) lower than the one obtained with TMS, as it was instead for single stimulation and SICI (PP2) paradigms. The significance of these results remains unknown. A possible explanation could be a contributing factor to ICF, which is either absent or less important in the SICI (PP2) paradigm.

In 2005 Z'Graggen et al. showed that facilitatory muscle contraction correlated with repeated discharges of the spinal motor neuron (MN). With the TST this repetitive discharges of spinal MN (repMNDs) are seen but not taken in consideration to calculate the area or amplitude of the response, so if they introduce variability in the size of enhanced MEPs, this variability wouldn't be corrected with TST. ICF could be due to repMNDs.

Moreover, a recent Master Thesis of Bedulli et al., 2013 raises questions regarding the significance of the motor threshold (MT) definition used to perform the paired-pulses paradigms. The maximum likelihood threshold hunting procedure described by Awiszus (Awiszus, 2003) give an operational definition of the MT motor threshold but the

"physiological basis" remains undetermined. The work of Bedulli et al. 2013 show that the stimulation of the brain at 80% of the MT, used for the conditioning stimulus (CS) is sufficient to cause MN discharges and could modify the excitability of the cortico-spinal tract or the spinal MN, possibly facilitating repMNDs.

Zgraggen et al (2005) described the quadruple (QuadS) and the quintuple (QuintS) stimulation technique (this technique are based on the TST but with additional wrist stimulations) as being able to asses the repMNDs and their effect on the size of the MEPs. It would thus be interesting to use the QuadS and QuintS to explore the role of the repMNDs in the ICF.

In conclusion, TST confirms the presence of SICI and ICF, which is comparable to findings with conventional TMS. This suggests that phase cancellation does not contribute to inhibition and facilitation as measured in the paired-pulse paradigm. The advantage of TST compared to the TMS is that it allows a better measure of the individual amount of SICI, but does not apply to ICF. Further studies on SICI and ICF, particularly using TST to determine the MT and TST associated with additional peripheral stimulation (quadruple stimulation technique, quintuple stimulation technique, Z'Graggen et al., 2005) are needed to explore these phenomena.

Abbreviations

ADM	Abductor Digiti Minimi
Area	Area under the curb
CS	Conditioning Stimulus
CV	Coeficient of Variation
ICF	Intra-Cortical Facilitation
ISI	Inter Stimuli Interval
(m)	Mean
Max	Maximum
MaxMin	Peak-to-Peak Amplitude
MEP	Motor Evoked Potential
Min	Minimum
MN	Motor Neuron
PP2	Paired Pulse 2 (2 stimulations with ISI = 2)
PP10	Paired Pulse 10 (2 stimulations with ISI = 10)
QuadS	Quadruple Stimulation Technique
QuintS	Quintuple Stimulation Technique
RMS	Root Mean Square
rMT	Resting Motor Threshold
SICI	Short Intra-Cortical Inhibition
TMS	Transcranial Magnetic Stimulation
TS	Test Stimulus
TST	Triple Stimulation Technique

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