RESEARCH CENTER OF NEUROLOGY
Neurorehabilitation department
TMS group

DIFFERENT TYPES OF NAVIGATED rTMS IN TREATMENT OF PHARMACORESISTANT SPASTICITY

Korzhova J., Poydasheva A., Synitsyn D., Chervyakov A., Suponeva N., Peresedova A., Zakharova M., Zavalishin I., Piradov M.

Berlin
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PLAN

1. The definition of spasticity, pathophysiology, models, problem;
2. A Literature Review and Meta-Analysis;
3. iTBS vs 10 Hz in spasticity treatment in Multiply sclerosis;
4. iTBS vs 20 Hz vs sham in spasticity treatment in Multiply sclerosis;
5. rTMS in post-stroke spasticity;
6. Why does it work?

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DEFINITION

- a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex as one component of upper motor neuron syndrome.

(Lance J. W., 1990)


THE

LANCET.

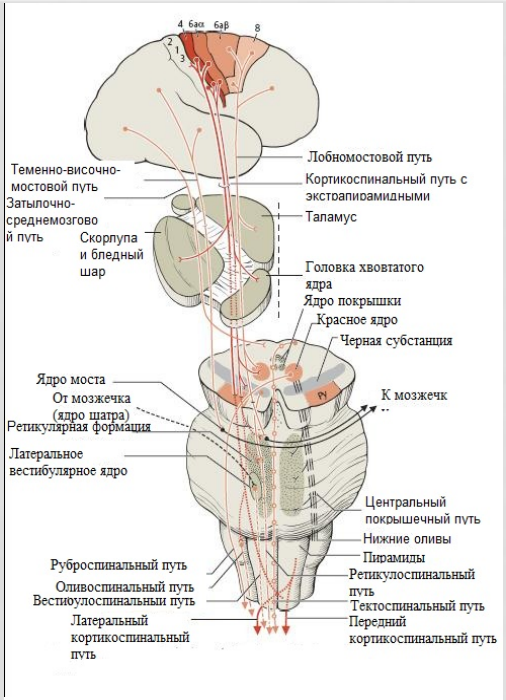
PREVALENCE

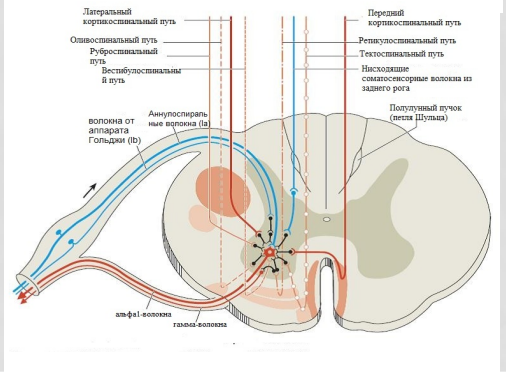
- 35,0% post-stroke patients *(Sommerfeld et al., 2004)*;
- 65,7% patients with MS, in 40% - severe spasticity*(Oreja-Guevara C. et al., 2013);*
- Cerebral palsy the most common cause of congenital spasticity.

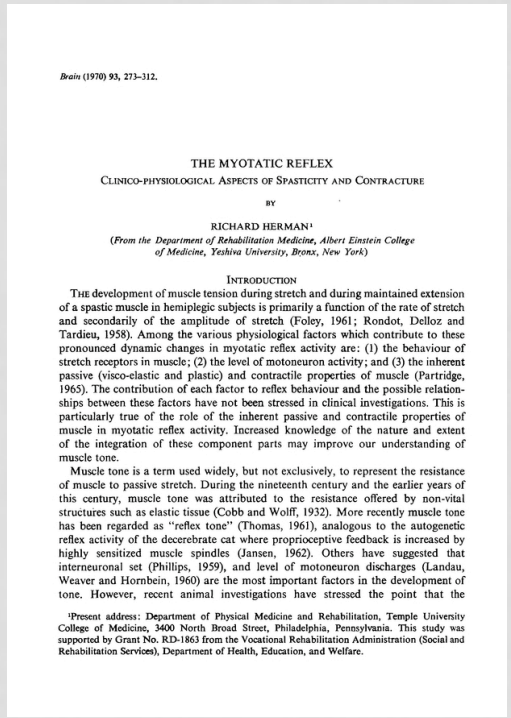
MODELS OF SPASTICITY

Cerebral spasticity

Spinal spasticity







Brain (1970) 93, 273–312.

THE MYOTATIC REFLEX

CLINICO-PHYSIOLOGICAL ASPECTS OF SPASTICITY AND CONTRACTURE

BY

RICHARD HERMAN[1]

(*From the Department of Rehabilitation Medicine, Albert Einstein College of Medicine, Yeshiva University, Bronx, New York*)

INTRODUCTION

THE development of muscle tension during stretch and during maintained extension of a spastic muscle in hemiplegic subjects is primarily a function of the rate of stretch and secondarily of the amplitude of stretch (Foley, 1961; Rondot, Delloz and Tardieu, 1958). Among the various physiological factors which contribute to these pronounced dynamic changes in myotatic reflex activity are: (1) the behaviour of stretch receptors in muscle; (2) the level of motoneuron activity; and (3) the inherent passive (visco-elastic and plastic) and contractile properties of muscle (Partridge, 1965). The contribution of each factor to reflex behaviour and the possible relationships between these factors have not been stressed in clinical investigations. This is particularly true of the role of the inherent passive and contractile properties of muscle in myotatic reflex activity. Increased knowledge of the nature and extent of the integration of these component parts may improve our understanding of muscle tone.

Muscle tone is a term used widely, but not exclusively, to represent the resistance of muscle to passive stretch. During the nineteenth century and the earlier years of this century, muscle tone was attributed to the resistance offered by non-vital structures such as elastic tissue (Cobb and Wolff, 1932). More recently muscle tone has been regarded as "reflex tone" (Thomas, 1961), analogous to the autogenetic reflex activity of the decerebrate cat where proprioceptive feedback is increased by highly sensitized muscle spindles (Jansen, 1962). Others have suggested that interneuronal set (Phillips, 1959), and level of motoneuron discharges (Landau, Weaver and Hornbein, 1960) are the most important factors in the development of tone. However, recent animal investigations have stressed the point that the

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Hermann R., 1970

PROBLEM

Medical treatment

Research	Group of patients	Drug	Spasticity decrease
Smith et al., 1994	MS	Tizanidine	No effect
UKTG, 1994	MS	Tizanidine	1 point on the MAS in 71% of patients;
Grazko et al. 1995	MS	Botulinum toxin	2 points on the MAS
Joder-Ohlenbusch 1984; Tell, 1981	MS	Vigabatrin	No effect
Killestein, 2002; Wade, 2003	MS	Cannabinoids	No effect
Vijayshree Yadav et al., 2014	MS	Cannabinoids	Significant decrease only on the VAS
Jody Corey-Bloom et al., 2012	MS	Cannabinoids for smoke	32%
Stamenova P. et al., 2005	Post-stroke	Tolperisone	34%
Mohammad Yazdchi et al., 2013	Post-stroke	Tizanidine	17%
Mohammad Yazdchi et al., 2013	Post-stroke	Botulinum toxin	50%

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REVIEW

Methods. Search for articles was conducted in databases PubMed, Willey, and Google. Keywords included “TMS”, “spasticity”, “TMS AND spasticity”, “non-invasive brain stimulation”, and “non-invasive spinal cord stimulation”.

Totally, 26 publications were found :

- 5 - review articles *(Mori F.et al., 2009; Amatya B., 2013; Awad B. et al., 2013; Toshiki Tazoe et al., 2014, Aysegul Gunduz et al., 2014)* – not included.
- 2 articles *(Kakuda W. et al., 2011a; Kakuda W. et al., 2012)* were not considered because they used not only rTMS but also levodopa drugs and botulinum toxin injections.
- **Thus, the systematic review included 19 publications.**

- The mean reduction in the spasticity level (MAS) amounted to **35.8%**, on average, after a TMS course and **3.6%** after placebo .
- A reduction in spasticity in the case of the cerebral lesion level was observed in 5 of 9 studies and amounted to **31.4%**.
- A reduction in spinal spasticity was observed in all 9 studies and was **38%**.

META-ANALYSIS

The meta-analysis inclusion criteria:

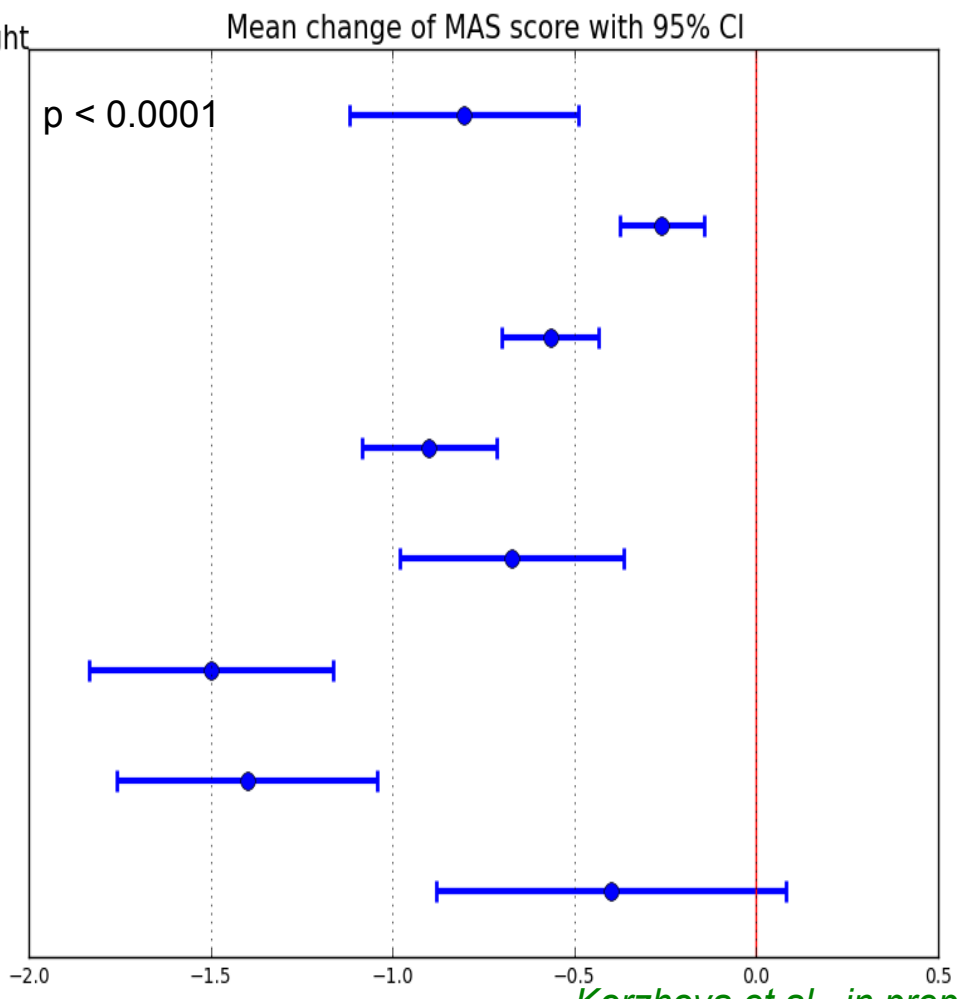
1. Presence of MAS in a publication as a grading scale of the spasticity syndrome;
2. Stimulation zones include motor representation of the arm or leg or the vertex;
3. The causes of spasticity were cerebrovascular diseases, multiple sclerosis, and spinal cord injuries;
4. A clear description of the study design and outcomes, the availability of standard deviation parameters and mean MAS values.

Only 6 of 19 publications with a total of 149 patients who were subjected to real stimulation (n=104) and sham simulation (n=45) were selected for further statistical processing and meta-analysis.

META-ANALYSIS

Real stimulation (n=104)

Study	Mean change of MAS score with 95% CI and relative weight
Total mean n = 104	-0.80 (-1.12; -0.49)
Kakuda W. et al., 2011 n = 39	-0.26 (-0.38; -0.14) w = 15.89%
Mori F. et al., 2011 n = 10	-0.57 (-0.70; -0.43) w = 15.78%
Barros Galvao et al., 2013 n = 10	-0.90 (-1.09; -0.71) w = 15.37%
Centonze D. et al., 2007 n = 12	-0.67 (-0.98; -0.37) w = 14.05%
Kumru H. et al., 2010, right knee n = 14	-1.50 (-1.84; -1.16) w = 13.71%
Kumru H. et al., 2010, left knee n = 14	-1.40 (-1.76; -1.04) w = 13.41%
Shin-Ichi Izumi et al., 2008 n = 5	-0.40 (-0.88; 0.08) w = 11.78%



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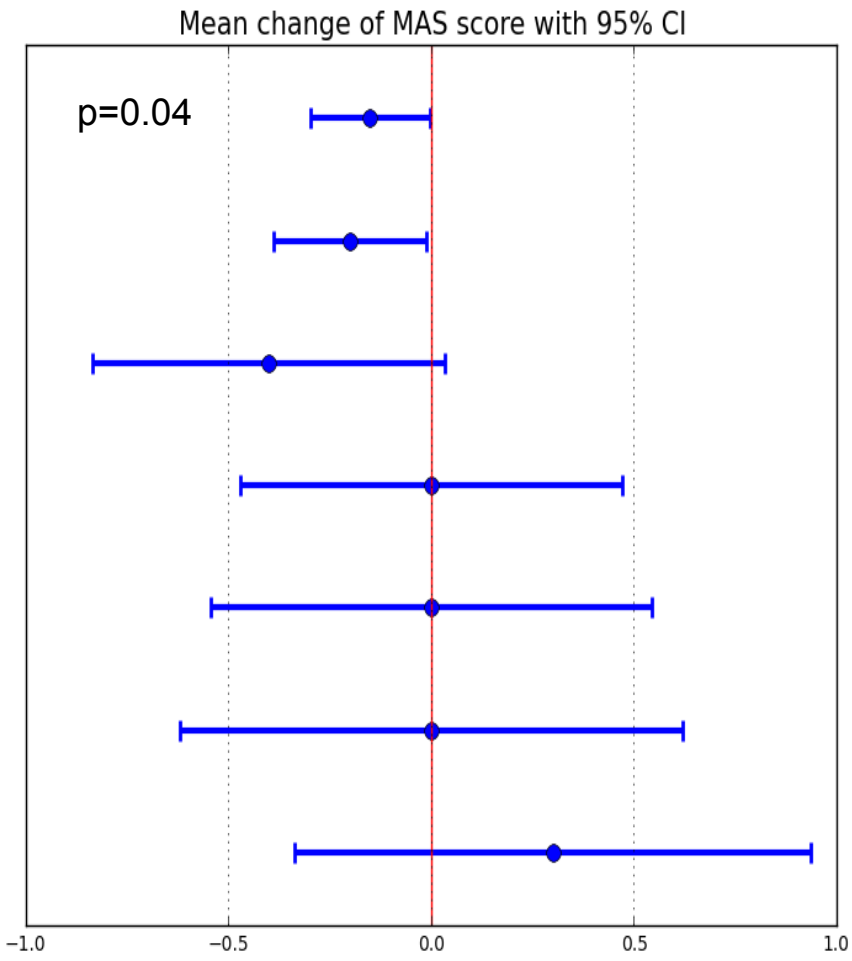
META-ANALYSIS

Sham (n=45)

Study	Mean change of MAS score with 95% CI and relative weight
Total mean n = 45	-0.15 (-0.30; -0.00)
F. Mori et al., 2011 n = 10	-0.20 (-0.39; -0.01) w = 60.44%
Barros Galvao et al., 2013 n = 10	-0.40 (-0.83; 0.03) w = 11.51%
Kumru H. et al., 2010, right knee n = 7	0.00 (-0.47; 0.47) w = 9.75%
D. Centonze et al., 2007 n = 7	0.00 (-0.54; 0.54) w = 7.31%
Shin-Ichi Izumi et al., 2008 n = 4	0.00 (-0.62; 0.62) w = 5.64%
Kumru H. et al., 2010, left knee n = 7	0.30 (-0.34; 0.94) w = 5.34%



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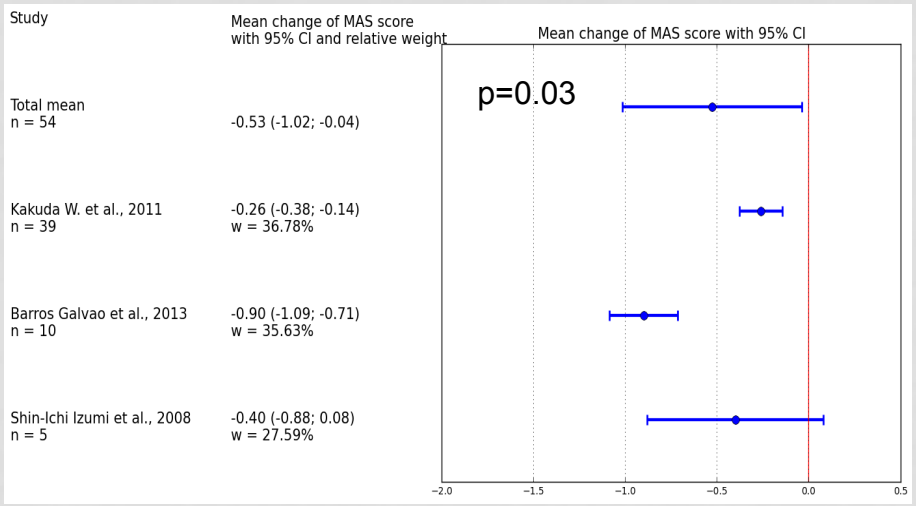
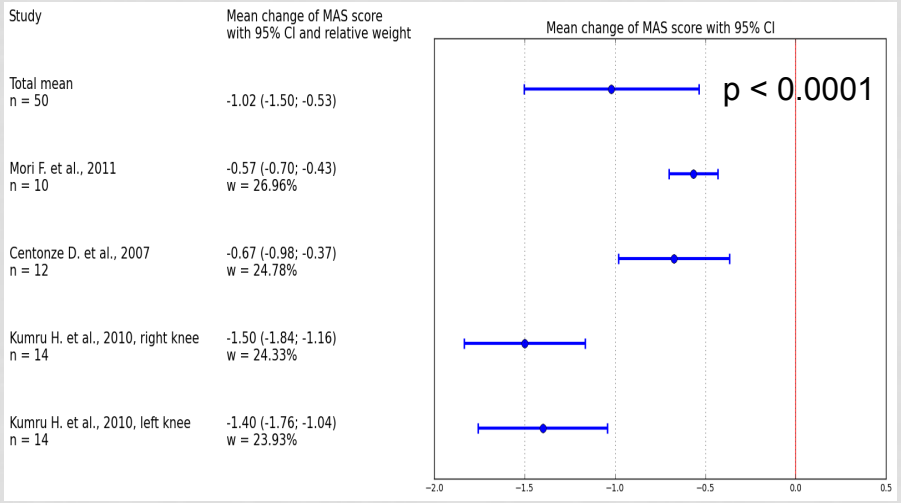
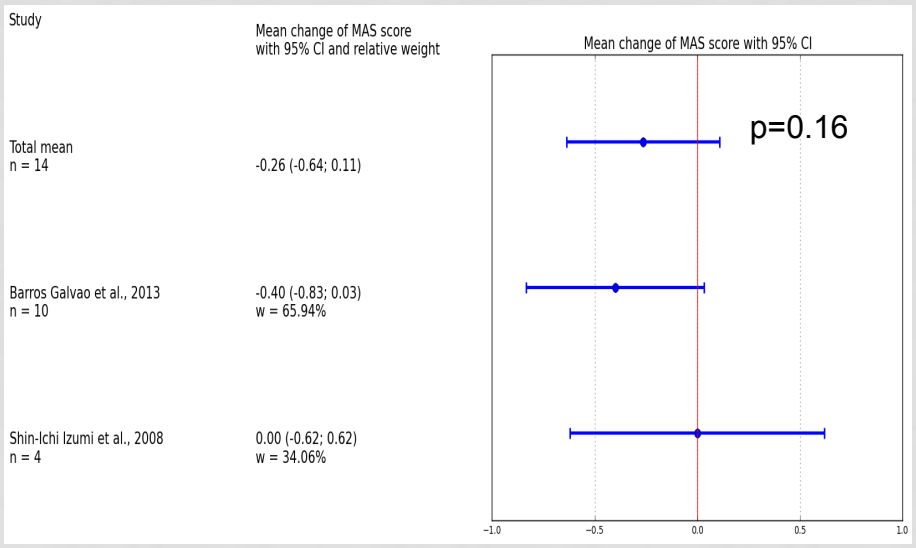
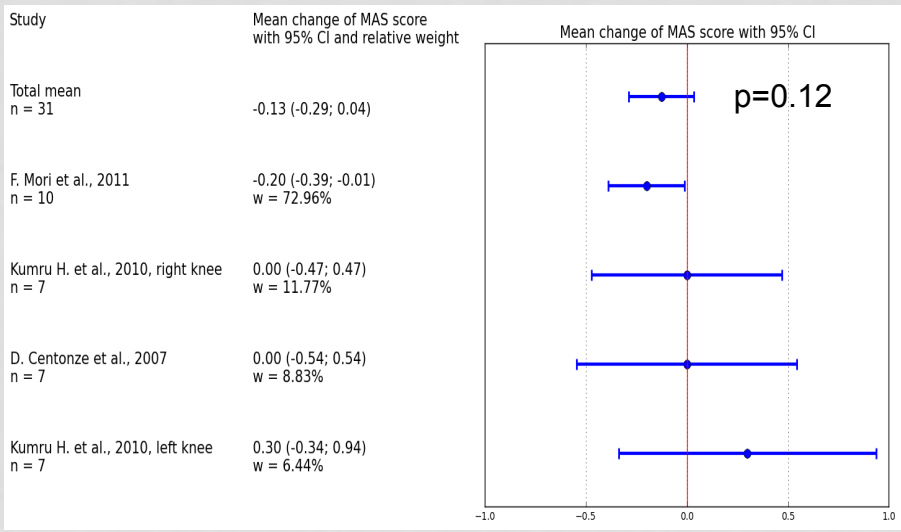
META-ANALYSIS

Cerebral vs Spinal spastisity









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SUMMARY (1)

- High-frequency or iTBS stimulation of the M1 zone of the spastic leg could have possible efficacy on spasticity in the cases of a lesion at the spinal cord level; average spasticity decrease - 38%;
- Low-frequency (1 Hz) stimulation of the unaffected hemisphere does not effective in treatment post-stroke spasticity;
- It's necessary to conduct additional larger placebo-controlled trials to assess the efficacy of various rTMS protocols in spasticity.

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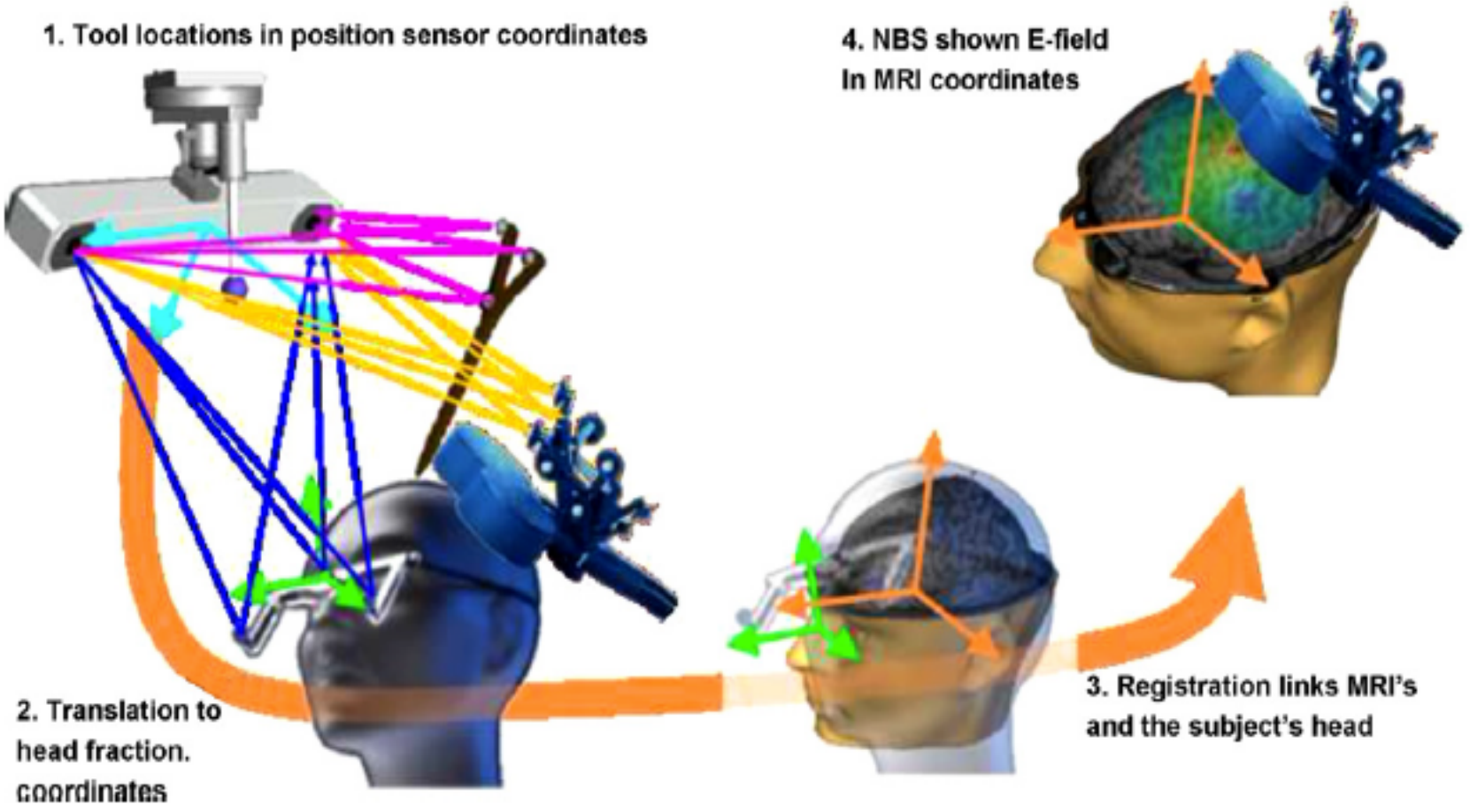
iTBS VS 10 HZ

Groups **n=22 patients with secondary progredient MS ; mean age: 44,32 ± 8,89 years, 59% males**	
N=12	N=10
iTBS 80% Motor threshold (MT), 10 min, (M1, TA) - 10 sessions	**High-frequency rTMS** 10 Hz, 80% Motor threshold (MT), 10 min, 200 stimulus (M1, TA) – 10 sessions
Mean age 44,89 ± 9,33; 83% males	Mean age 45,23 ± 8,19; 30% males

NBS eXimia Nexstim - and Magstim Rapid2.

NAVIGATION FOR TRANSCRANIAL MAGNETIC STIMULATION



Ruohonena, Karhua, 2010

STUDY DESIGN

Screening	• Neurological and physical examination; • EDSS; • EEG (to exclude epileptiform activity).
Visit 1 (before stimulation)	• Neurological and physical examination; • MRI (T1 MPR); • Mapping motor representation of the tibialis anterior muscles using the navigation TMS; • Completion of clinical scales and questionnaires.
Pseudo randomization	
iTBS • Standard neurorehabilitation therapy; • iTBS with Magstim Rapid2 (10 sessions).	**rTMS** • Standard neurorehabilitation activities; • rTMS with Magstim Rapid2 (10 sessions).
Visit 2 (after stimulation)	• Neurological and physical examination; • Mapping motor representation of the tibialis anterior muscles using the navigation TMS; • Filling the clinical scales and questionnaires.

STUDY DESIGN

Visit 4 - phone call (2 weeks after stimulation)	• Completion of clinical scales and questionnaires
Visit 5 – phone call (12 weeks after stimulation)	• Completion of clinical scales and questionnaires

METHODS

Methods of clinical assessment of spasticity:

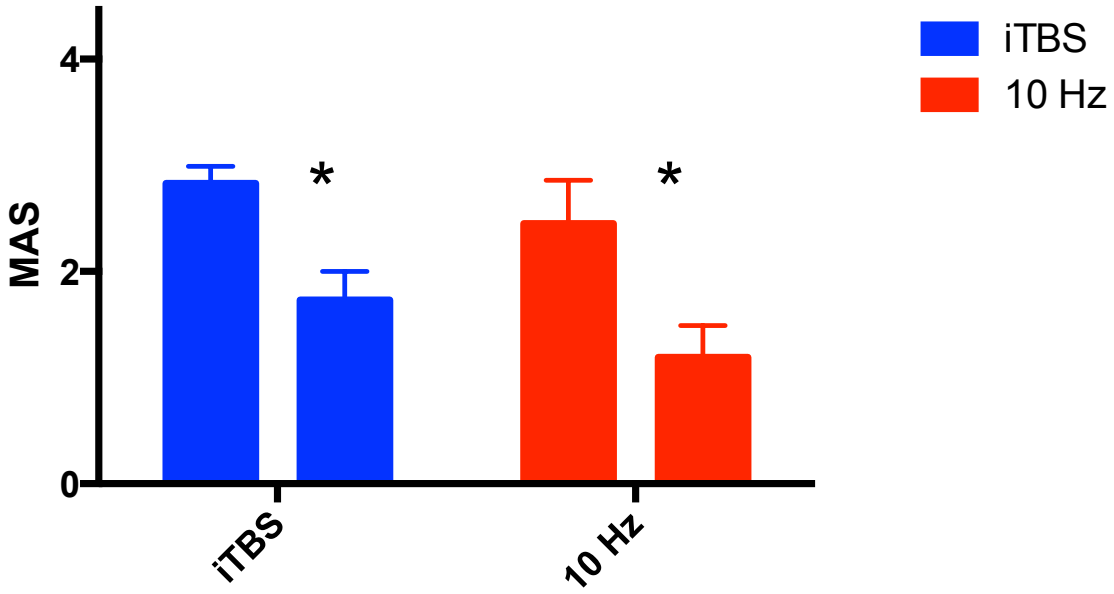
- The Modified Ashworth scale (MAS);
- Subjective evaluation spasticity scale (SESS);
- Visual analog scale (VAS)

Clinical scales:

- EDSS
- Fatigue scale (MFIS2);
- Questionnaire of urinary disorders;
- Questionnaire of defecation disorders;
- Questionnaire of pain associated with spasticity

THE MODIFIED ASHWORTH SCALE (MAS)

	iTBS		10 Hz	
	Before	After	Before	After
Left	3,0 [3,0; 3,0]	2,0 [1,0; 2,0]*	3,0 [2,0; 3,0]	1,5 [0,5; 2,0]*
Right	3,0 [3,0; 3,0]	2,0 [1,0; 2,0]*	2,5 [2,0; 3,0]	0,5 [0; 2,0]*



* - Sign test, p<0,05

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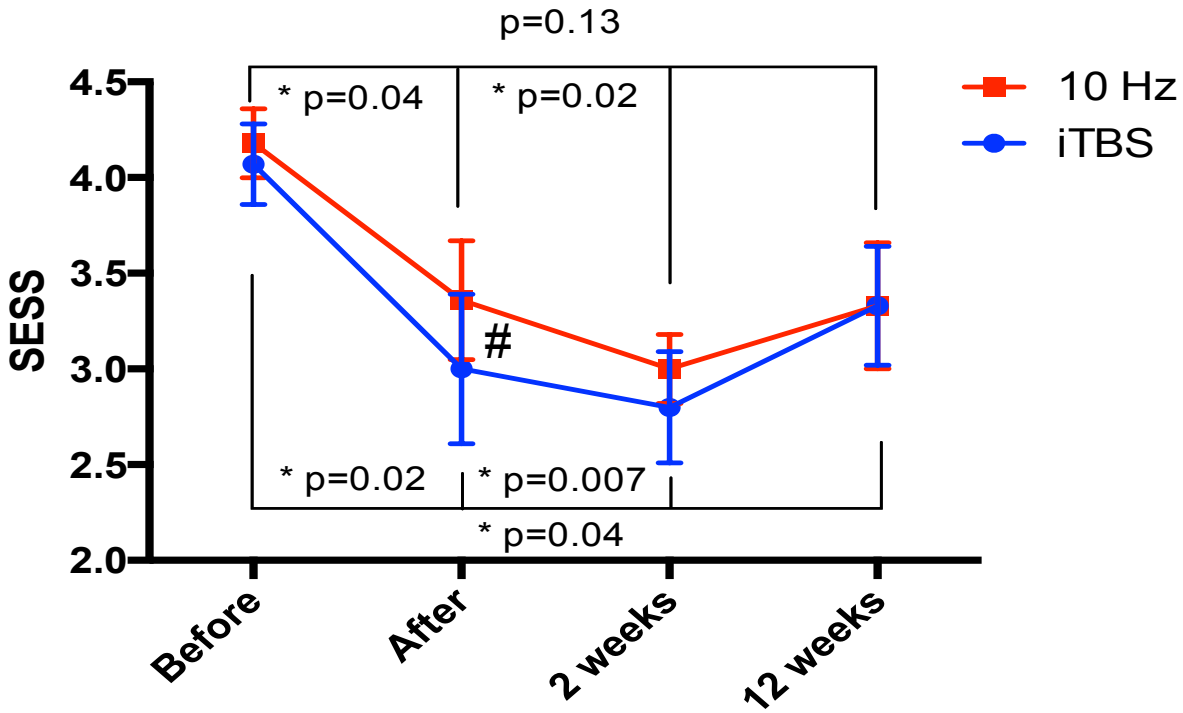
SUBJECTIVE EVALUATION SPASTICITY SCALE (SESS)

iTBS				10 Hz			
Before	After	2 weeks	12 weeks	Before	After	2 weeks	12 weeks
4,0 [3,5;5,0]	3,0* [1,0;4,0]	3,0* [2,0;3,0]	3,0 [3,0;4,0]	4,0 [4,0;4,0]	3,5* [3,0;4,0]	3,0* [3,0;3,0]	4,0 [3,0;4,0]



* p<0,05, Sign test
# p<0,05, RM-ANOVA

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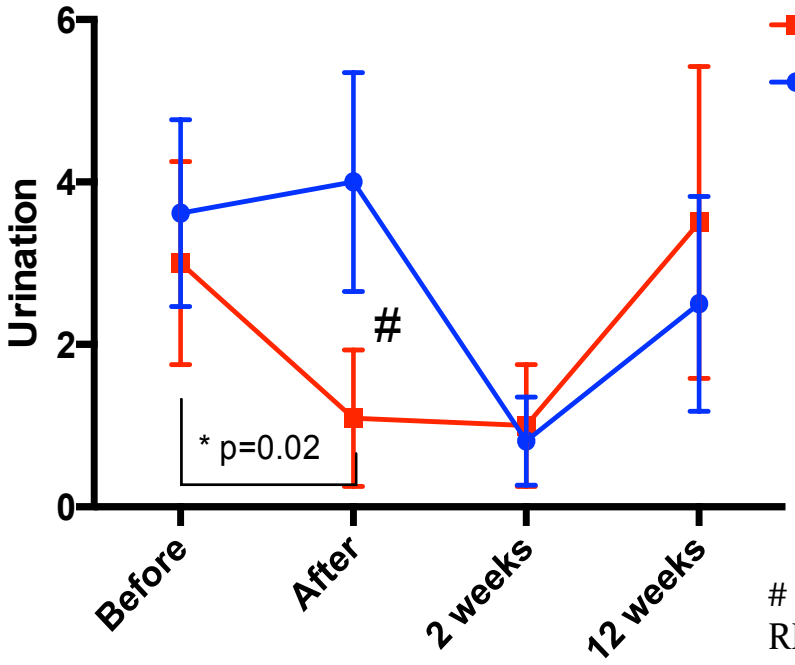
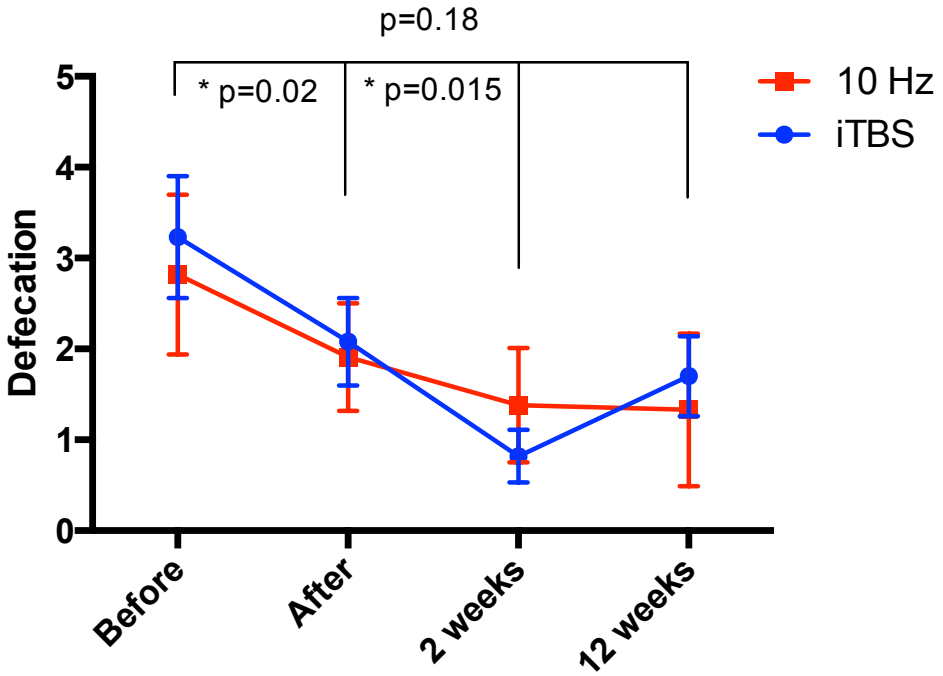
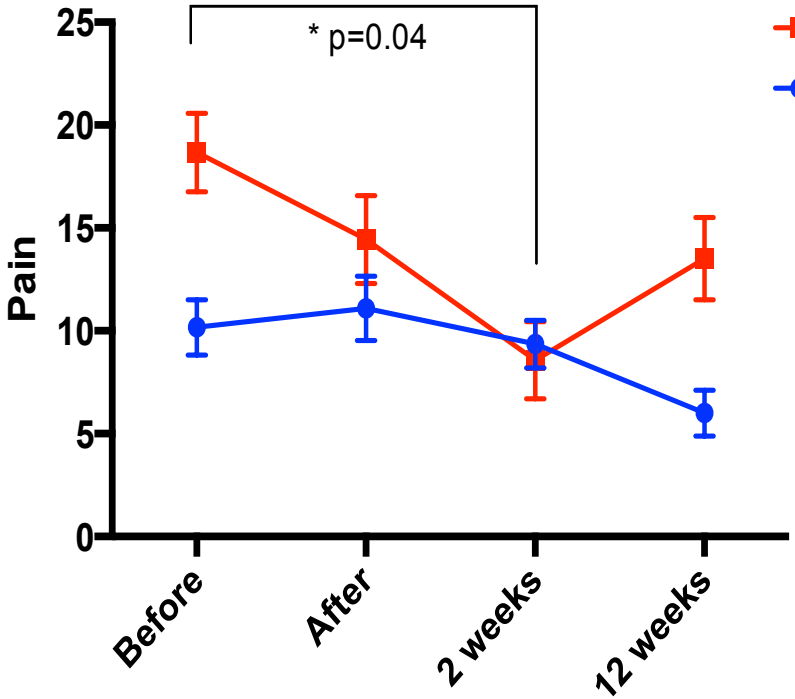
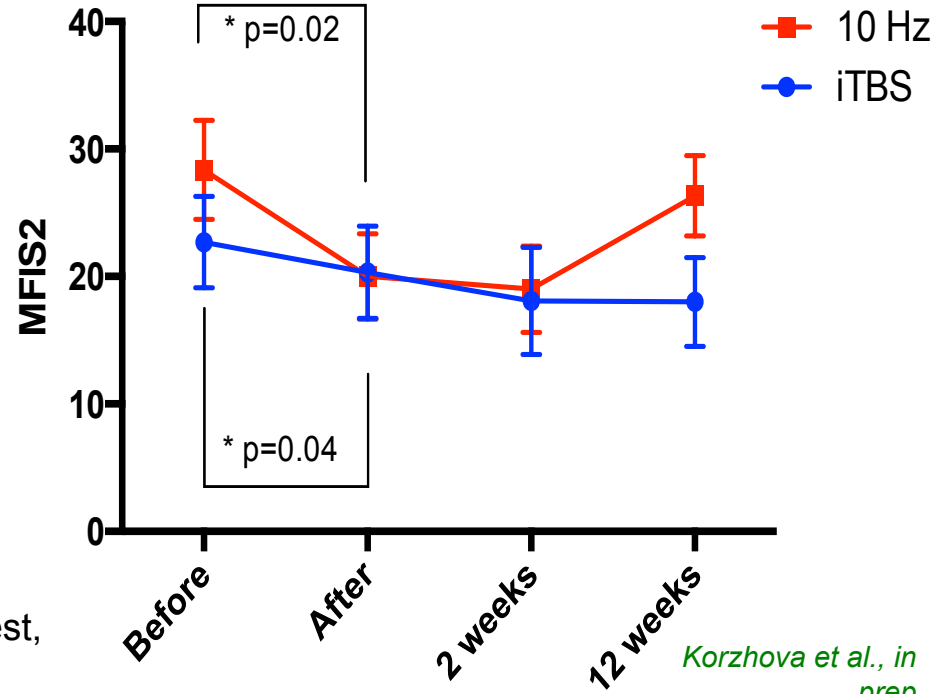


- p<0,05, RM-ANOV





* - Sign test, p<0,05



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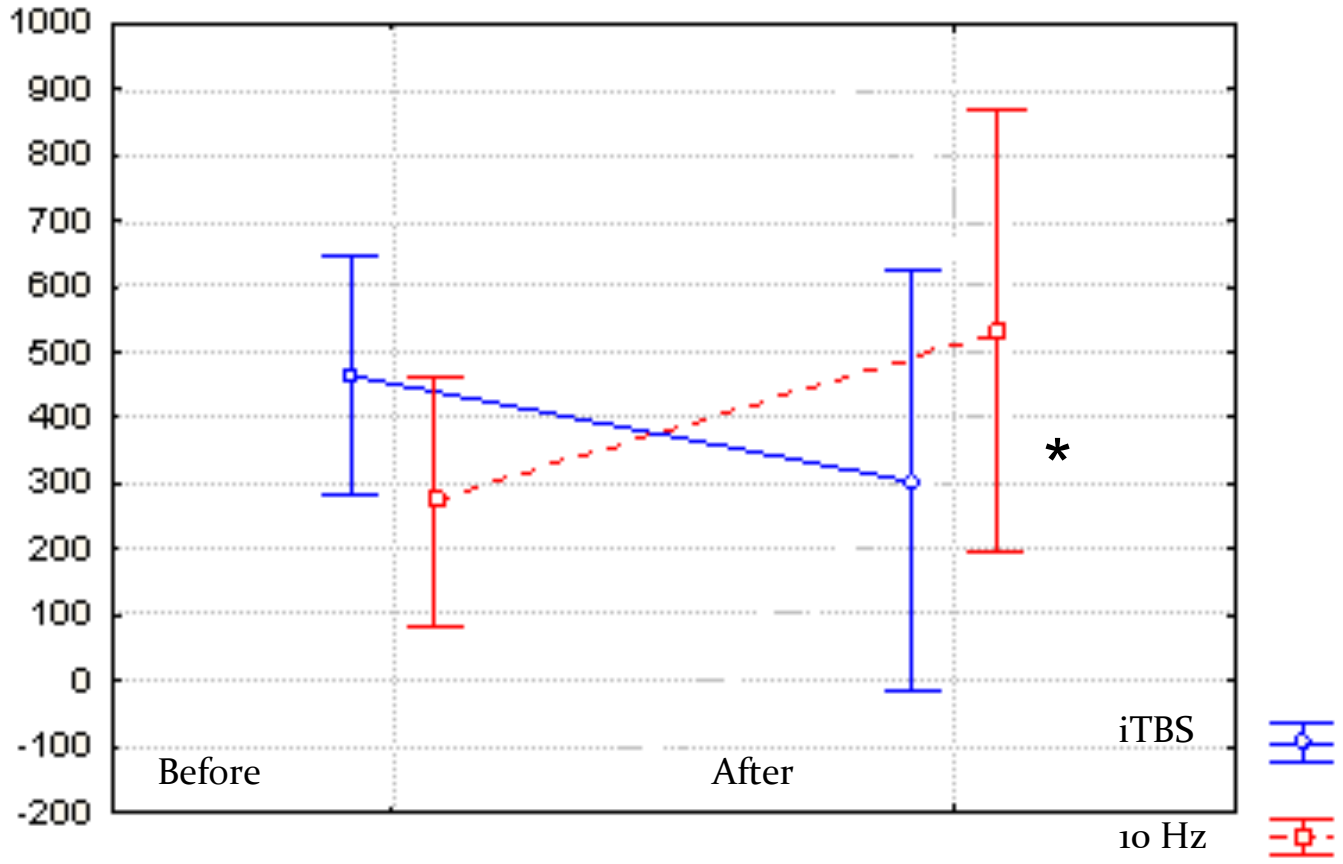
SIDE EFFECTS

- There were no serious side effects, such as seizures;
- In 4 patients in the iTBS group (40%) muscle hypotonia developed before the end of 10 sessions (increase paresis);

MEP AMPLITUDE



* - p<0,05, ANOVA

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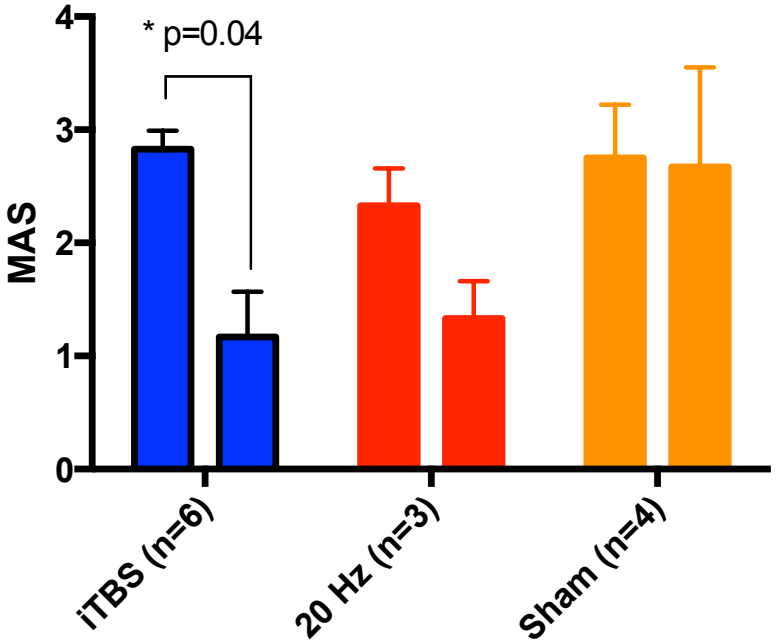
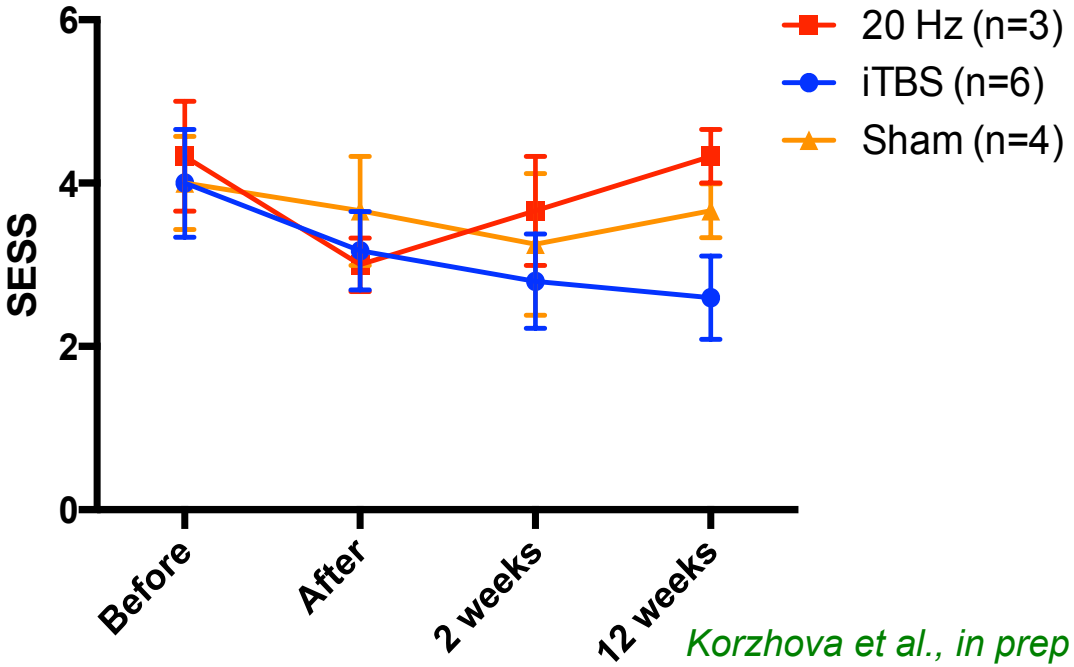
PRELIMINARY RESULTS
Randomized blind sham-controlled study





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Patient G., 30 years old; before treatment; MAS 3

Patient G., 30 years old; after treatment (20 Hz); MAS 1

SUMMARY (2)

• High-frequency rTMS (10 Гц и iTBS) primary motor cortex leg area significant decrease spasticity in patients with secondary progredient MS;

• iTBS reduce spasticity more quickly and at more long time (up to 12 weeks), but associated with "excessive spasticity reduction" (increase paresis);

• rTMS decrease spasticity-associated symptoms (dysfunction of the pelvic organs, pain, fatigue);

• rTMS is a safe method, subject to the rules for the selection of patients.

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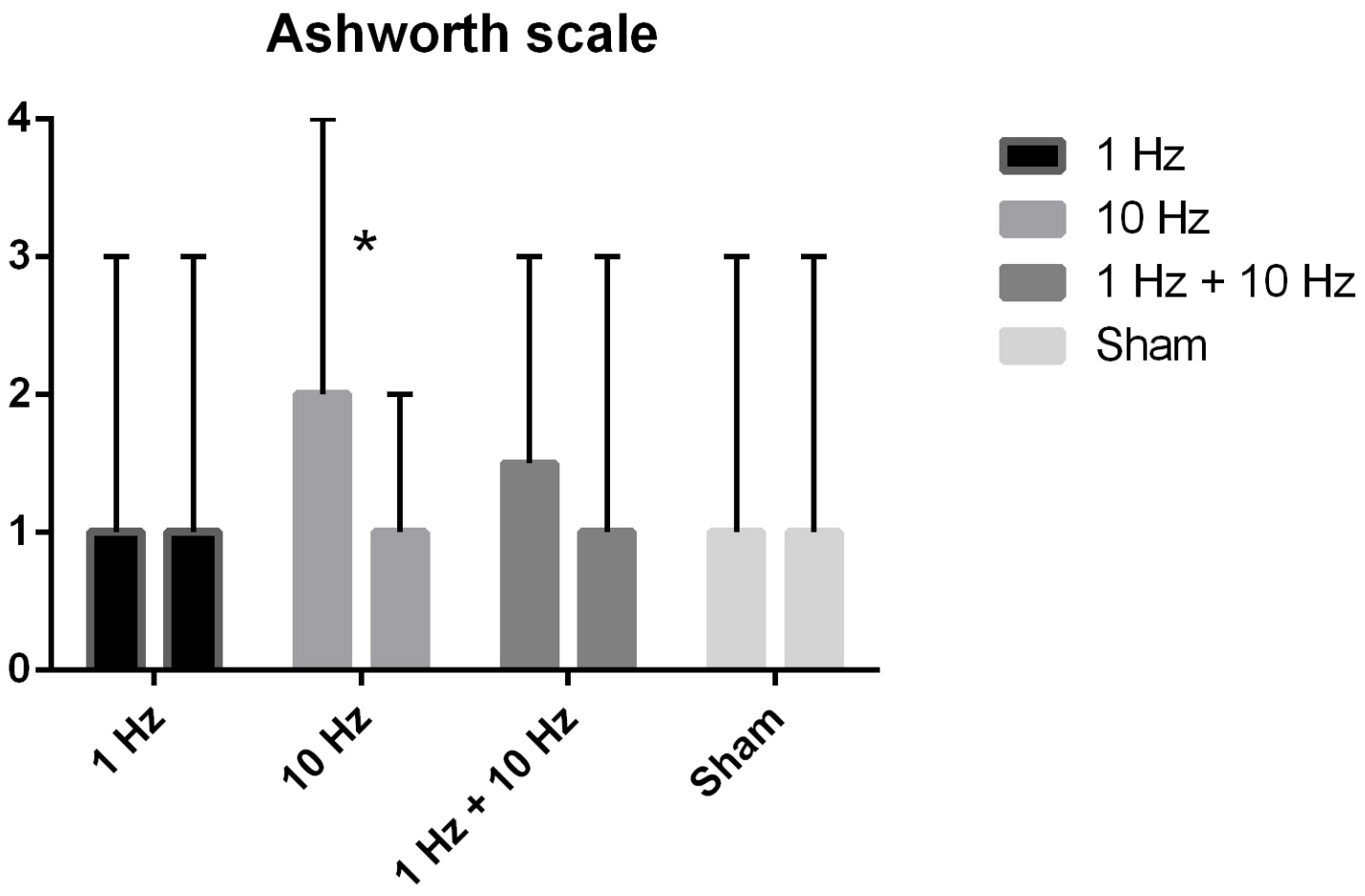
RTMS IN POST-STROKE SPASTICITY (N=68)



Chervyakov et al., in prep

SUMMARY (3)

- High-frequency stimulation of the affected hemisphere reduces spasticity on 33%;
- More research is needed to confirm this statement.

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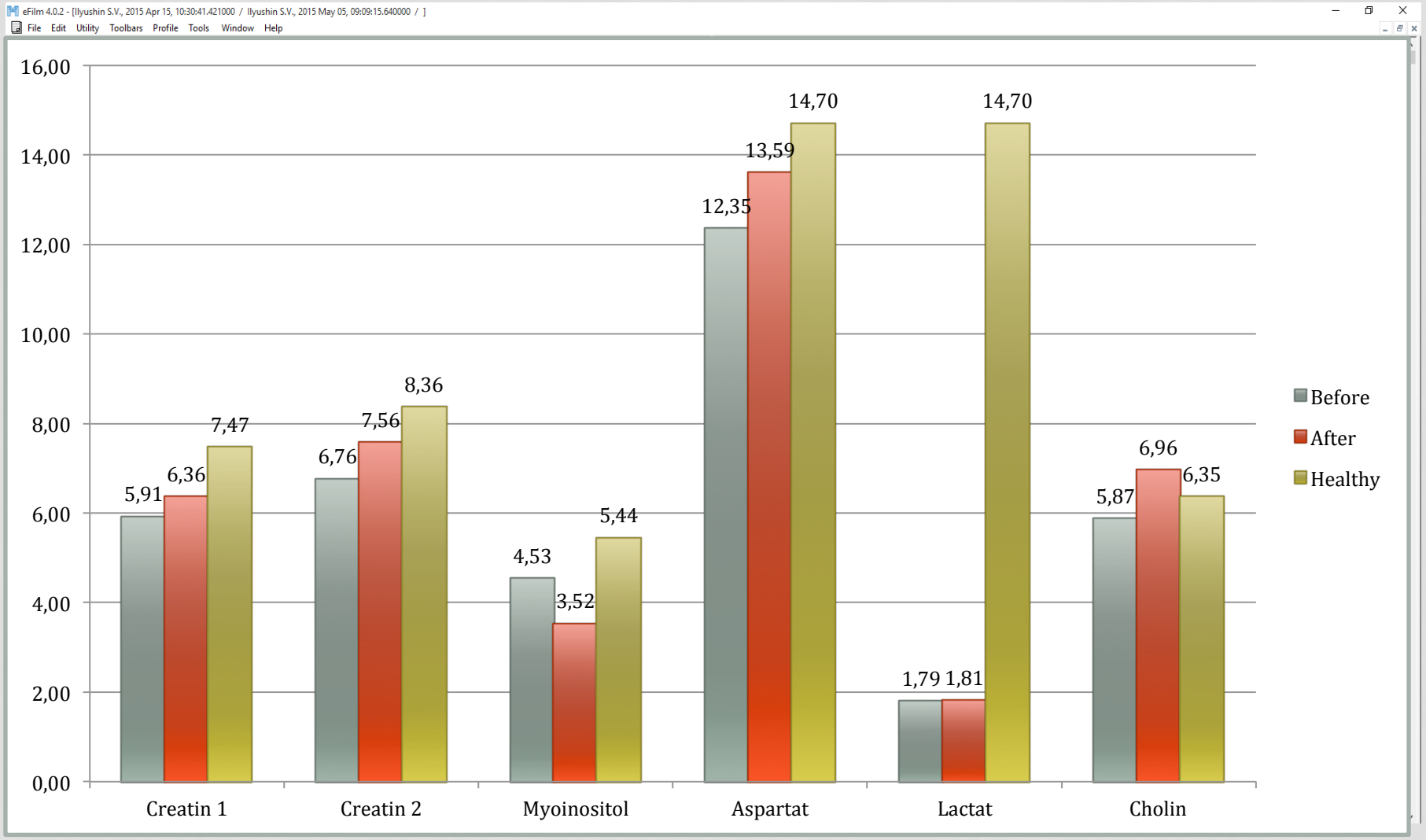
WHY DOES IT WORK?



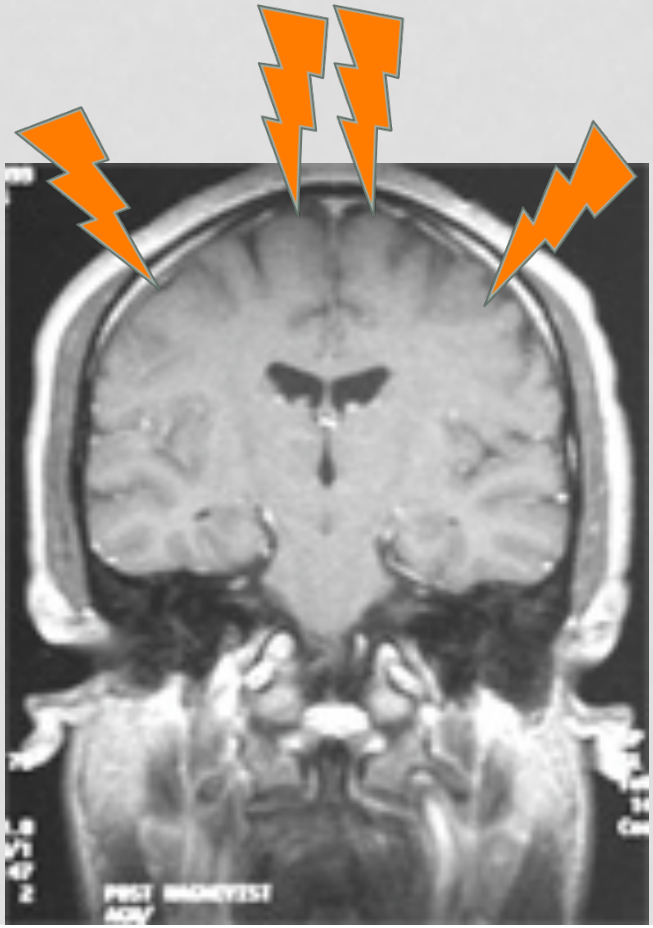
CONCLUSION

Cerebral spasticity

Spinal spasticity

Spinal spastisity - High frequency rTMS and iTBS on M1 foot area

Cerebral spastisity - High frequency rTMS on affected M1 hand area?



Cerebral spastisity - Low frequency rTMS on un affected M1 hand area – **Not effective!**

RESEARCH CENTER OF NEUROLOGY

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