TMS & MOVEMENT DISORDER

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MD neurology

INTRODUCTION

TMS developed in 1985 by Barker and colleagues

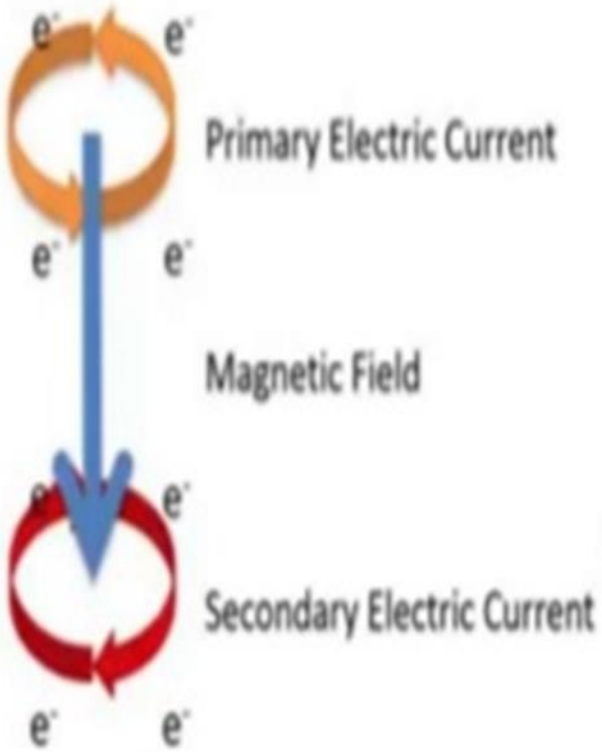
- it has been used to explore cortical function in healthy subjects and in patients with neurological and psychiatric disorders
- work performed on the human primary motor cortex (M1) and has given important pathophysiological and clinical insights in the field of movement disorders (MD).

- TMS is a safe & non-invasive tool for the electrical stimulation of neural tissue without pain.

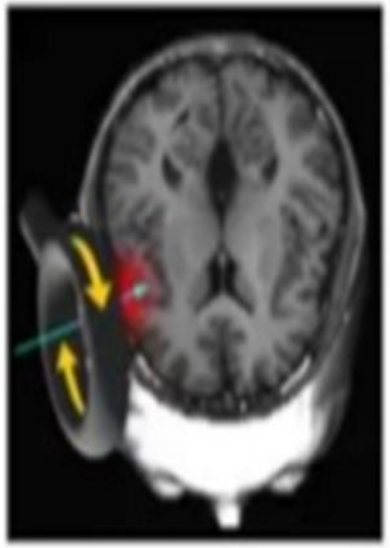
- Operates on Faraday’s principle of electromagnetic induction.

Transcranial Magnetic Stimulation

1831 Faraday's Electromagnetic Induction

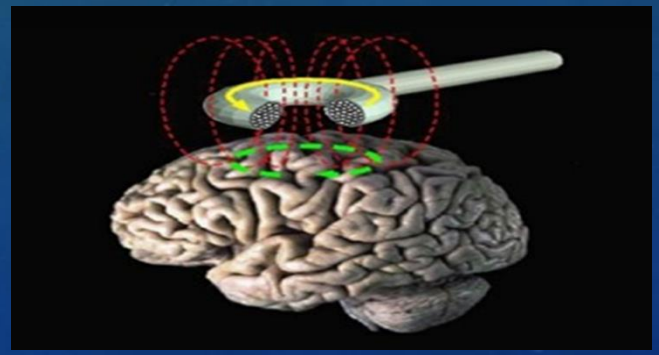


Anthony Barker 1984



MASSACHUSETTS GENERAL HOSPITAL

- This current produces a strong magnetic field, perpendicular to the coil, which can reach values of up to 3 Tesla; it easily passes through the scalp and skull inducing a secondary electric current in the brain.
- The intensity of the magnetic field declines quickly with distance from the coil so neural stimulation is limited to the cortex and superficial subcortical white matter.



TYPES OF TMS

- Single pulse TMS
- Paired pulse TMS
- Repetitive TMS
  - Conventional
  - Patterned

TYPES OF RTMS

Conventional

- Low frequency rTMS (Stimulus rates of 1 Hz or less) inhibitory
- High frequency rTMS (Stimulus rates > 1 Hz)

  facilitatory (5Hz, 10Hz, 20 Hz)

Patterned rTMS

- Theta burst stimulation 3 pulses are given at 50 Hz every 200ms (10 bursts every 2 seconds) Train each train comprises of 10 bursts cTBS no off phase Inhibitory
- (iTBS) 2s on and 8s off phase facilitatory

Longer effect on neuroplasticity compared to conventional rTMS

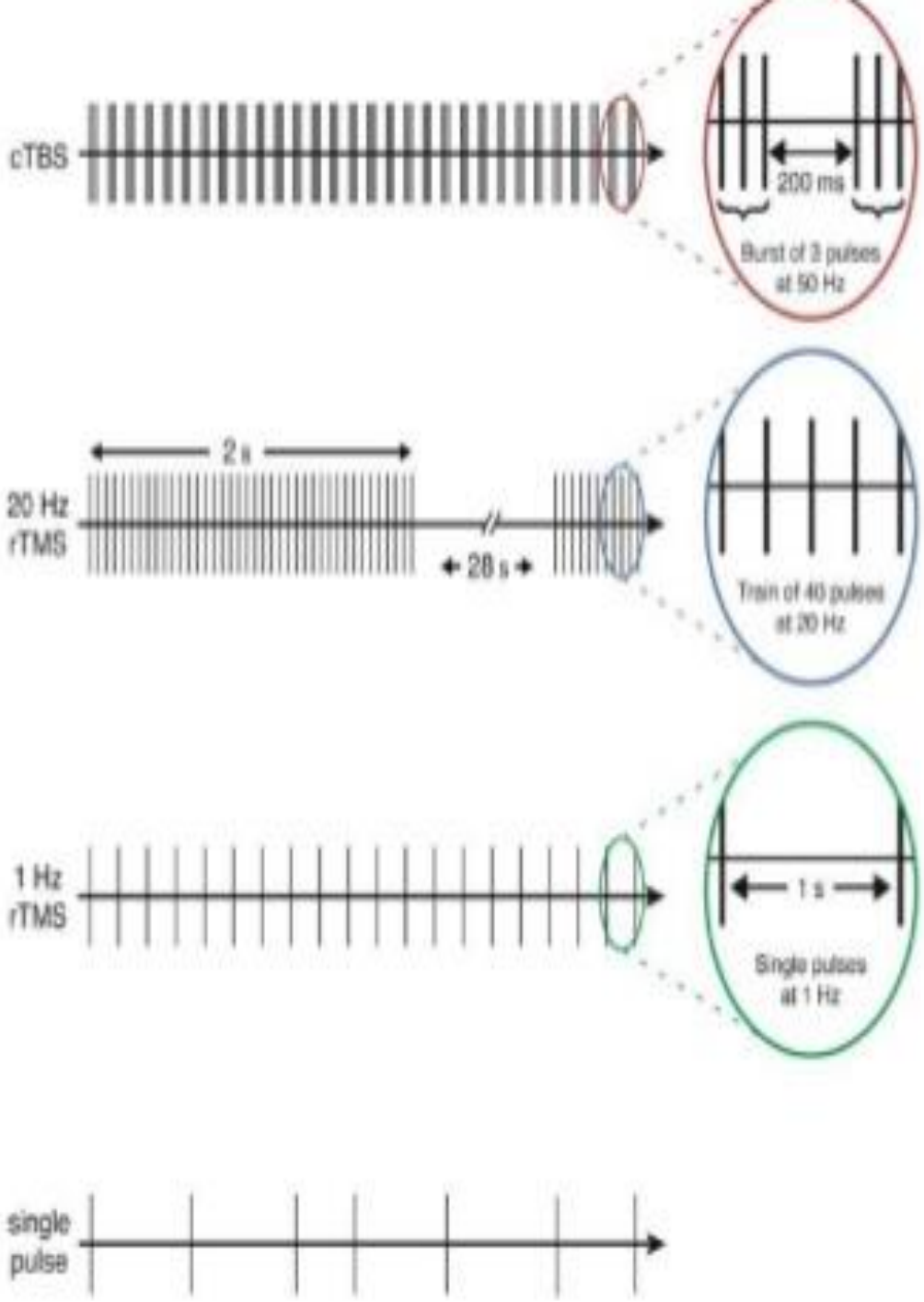
COMMONLY USED RTMS TECHNIQUES

rTMS: consecutive TMS stimuli at a specific frequency, with variable interstimulus intervals.

Short train of regular 5 Hz rTMS: MEP facilitation

Long train of regular ≤1 Hz rTMS: MEP inhibition

Long train of regular ≥5 Hz rTMS: MEP facilitation


cTBS
200 ms
Burst of 3 pulses
at 50 Hz
2 s
20 Hz
rTMS
28 s
Train of 40 pulses
at 20 Hz
1 Hz
rTMS
1 s
Single pulses
at 1 Hz
single
pulse

DIAGNOSTIC & PROGNOSTIC APPLICATION

TMS provides information about :

- Excitability of the motor cortex
- Functional integrity of intracortical neuronal structures
- Conduction along CS, corticonuclear, and callosal fibre
- Function of nerve roots and PNS to the muscles.

WHY rTMS MIGHT BE USED AS A THERAPEUTIC TOOL

- rTMS is safe, non-invasive, painless brain stimulation provide additional benefit to conventional treatment especially for refractory symptoms

- changes in synaptic plasticity produced by periods of rTMs.

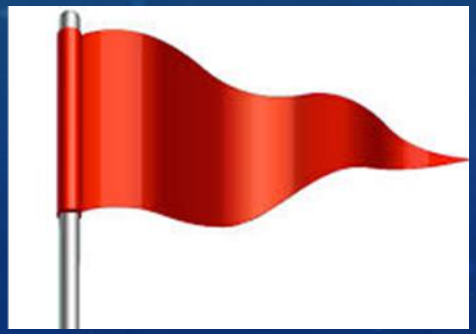
TMS AND SYNAPTIC PLASTICITY

- Change in synaptic efficacy, leading to Long term potentiation or long term depression
- Alteration in neurotropic factor
- Modulation of cortical excitability
- Modulation of functional connectivity

Repeated induction of plasticity is thought to reinforce the change from transitory early to more permanent late LTP/LTD

greater rTMS effect associated with

- a higher number of pulses across sessions
- total number of pulses across sessions adjusted by intensity (ie, total number of pulses across sessions times intensity).



TMS & MOVEMENT DISORDER

The core anatomical and functional impairment in MD in the basal ganglia

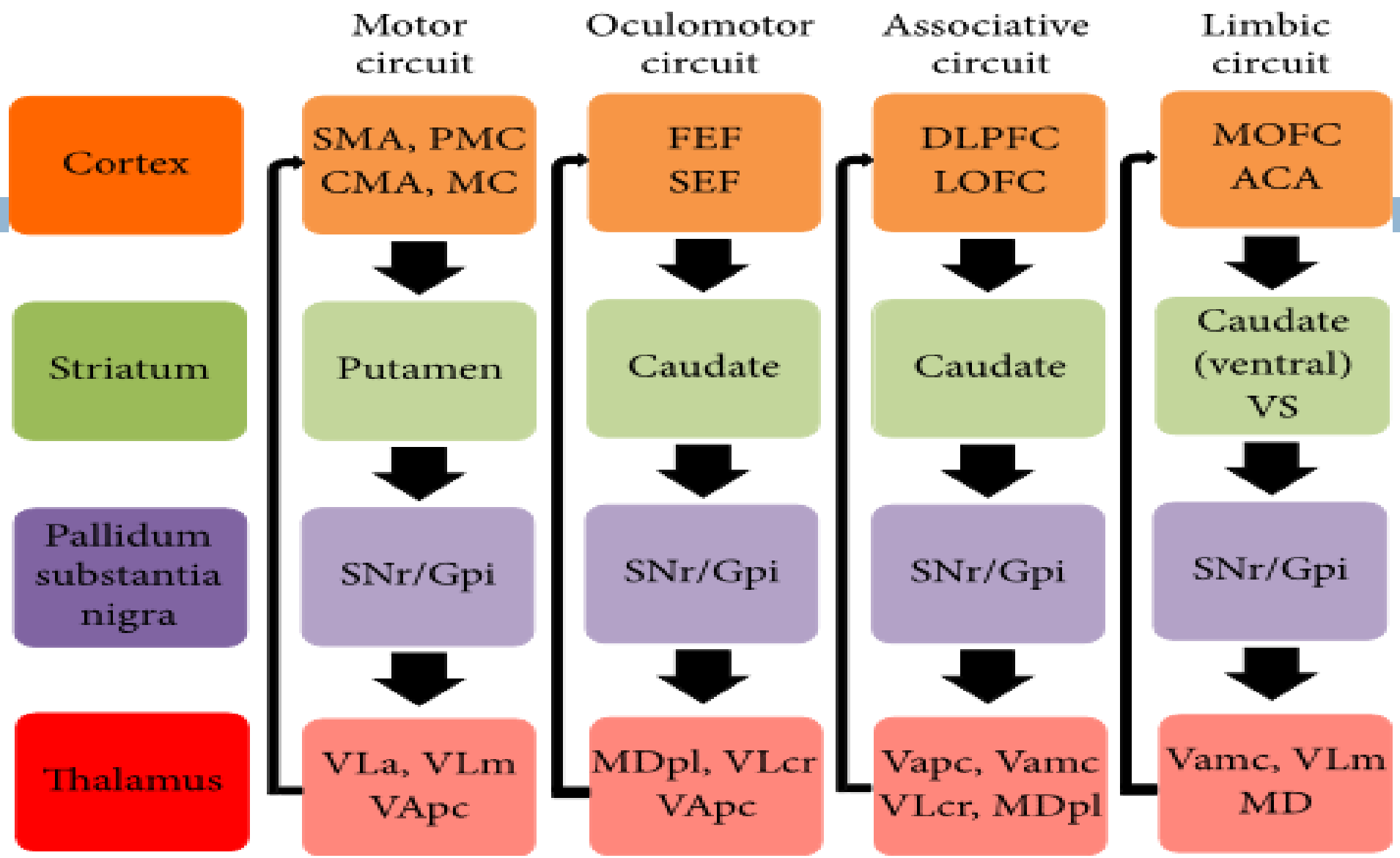
too deep to be readily stimulated with conventional TMS coils??

BUT

basal ganglia are part of a group of parallel closed circuits (the basal ganglia-thalamo-cortico-basal ganglia loop) that originate in the cerebral cortex, traverse the thalamus, and return to their individual sites of origin in the frontal lobe.

SO changing the function of cortical regions directly with rTMS have secondary effects on connected structures in the basal ganglia–cortex loop

- functional MRI after TMS of the left dorsal premotor cortex and pre supplementary motor area showed increase the BOLD signal in the striatum and thalamus
- PET imaging reveals that TMS can produce a transient release of dopamine in the striatum.


Motor circuit
Oculomotor circuit
Associative circuit
Limbic circuit
Cortex
Striatum
Pallidum substantia nigra
Thalamus
SMA, PMC CMA, MC
FEF SEF
DLPFC LOFC
MOFC ACA
Putamen
Caudate
Caudate
Caudate (ventral) VS
SNr/Gpi
SNr/Gpi
SNr/Gpi
SNr/Gpi
VLa, VLm VApc
MDpl, VLcr VApc
Vapc, Vamc VLcr, MDpl
Vamc, VLm MD

functional deficits of BG circuits either produce exacerbated or reduced brain signal manifested as

hyperkinetic movement disorder	hypokinetic movement disorder
↓	↓
essential tremor (ET) dystonia	bradykinesia or freezing of gait in PD

Although in hyperkinetic motor disorders the rationale of rTMS protocol is to reduce abnormal cortical hyperexcitability

this is not true in all the circumstances as it depends on several methodological and clinical factors

cortical baseline activity

hyperexcitable

hypoexcitable

THE MOTOR INHIBITION SYSTEM

Composed by STN, basal ganglia, SMA, and IFC control/modulate the primary motor output pathway.

PATHOPHYSIOLOGY OF HYPERKINETIC MOTOR DISORDERS

- striato-thalamo-cortical pathways
- the cerebello-thalamic circuitry
- intra-cortical connections between the premotor cortex and the inferior frontal cortex (IFC) would seem to play a key role

altered pathophysiology in hyperkinetic movement disorders establishes motor, premotor or cerebellar structures as candidate regions to reset cortico-subcortical pathways back to normal.

TMS PROTOCOLS IN MD

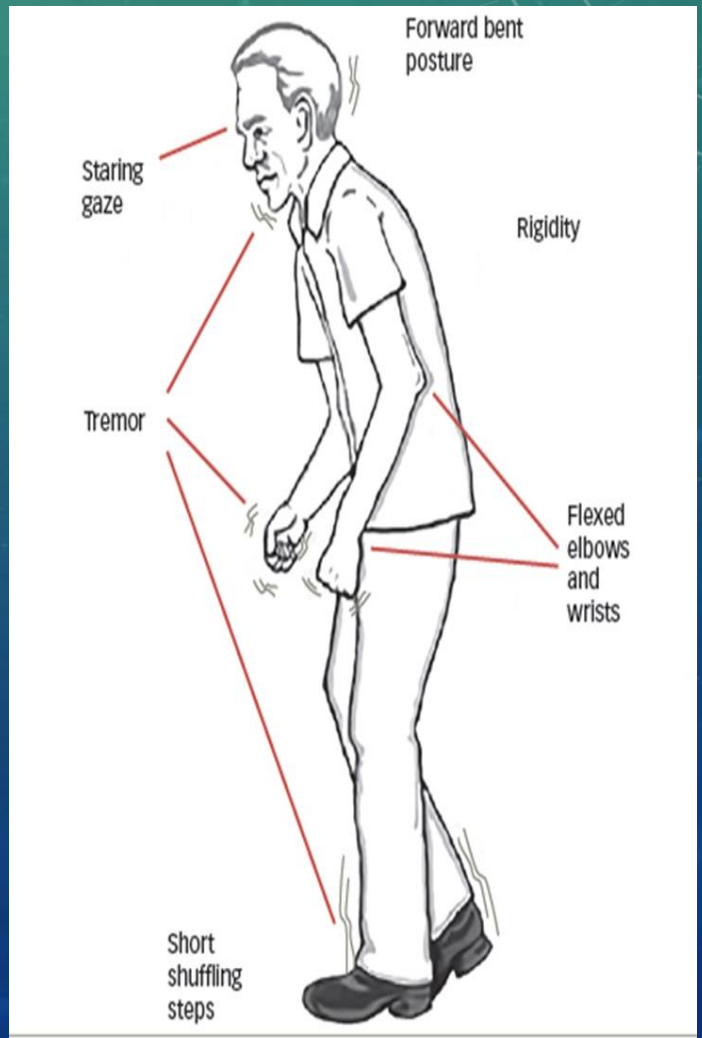
PARKINSON DISEASE

Idiopathic PD

➢primarily a disorder of response initiation characterized by

an excessive motor inhibition

(i.e., akinesia, bradykinesia),



pted from information presented in Rodriguez-Oroz et al., 2009.[4]

RTMS IN PARKINSON'S DISEASE

- HF rTMS over the M1 or DLPFC with 6–12 sessions
- LF (1 Hz) rTMS of the SMA with a weekly schedule for 8 weeks

- 1 Hz rTMS over SMA improves UPDRS motor scores more effective on posture and gait

- whereas 5 Hz rTMS over M1improves UPDRS motor scores more effective on bradykinesia

SO

rTMS is a promising add-on therapy for motor symptoms of PD

rTMS & NON MOTOR SYMPTOMS OF PD

improvement in mood, depression.

high-frequency rTMS of the left DLPFC has a level B recommendation in the treatment of depression associated with PD

LEVODOPA INDUCED DYSKINESIA(LID)

LIDs are clearly a clinical expression of disinhibition of movement

- PD patients with LIDs characterized by dysfunctional coupling between the prefrontal cortex, including the right IFC and the SMA and basal ganglia measured at rest.

rTMS &LID

prolonged session (2 weeks) applied on the bilateral cerebellar cortex using high frequency (50 Hz) cTBS

- showed persistent clinical beneficial effects in LIDs patients for up to 4 weeks
- cerebellum has greater plastic mechanisms involved in motor learning

DYSTONIA

- pathophysiology of dystonia:

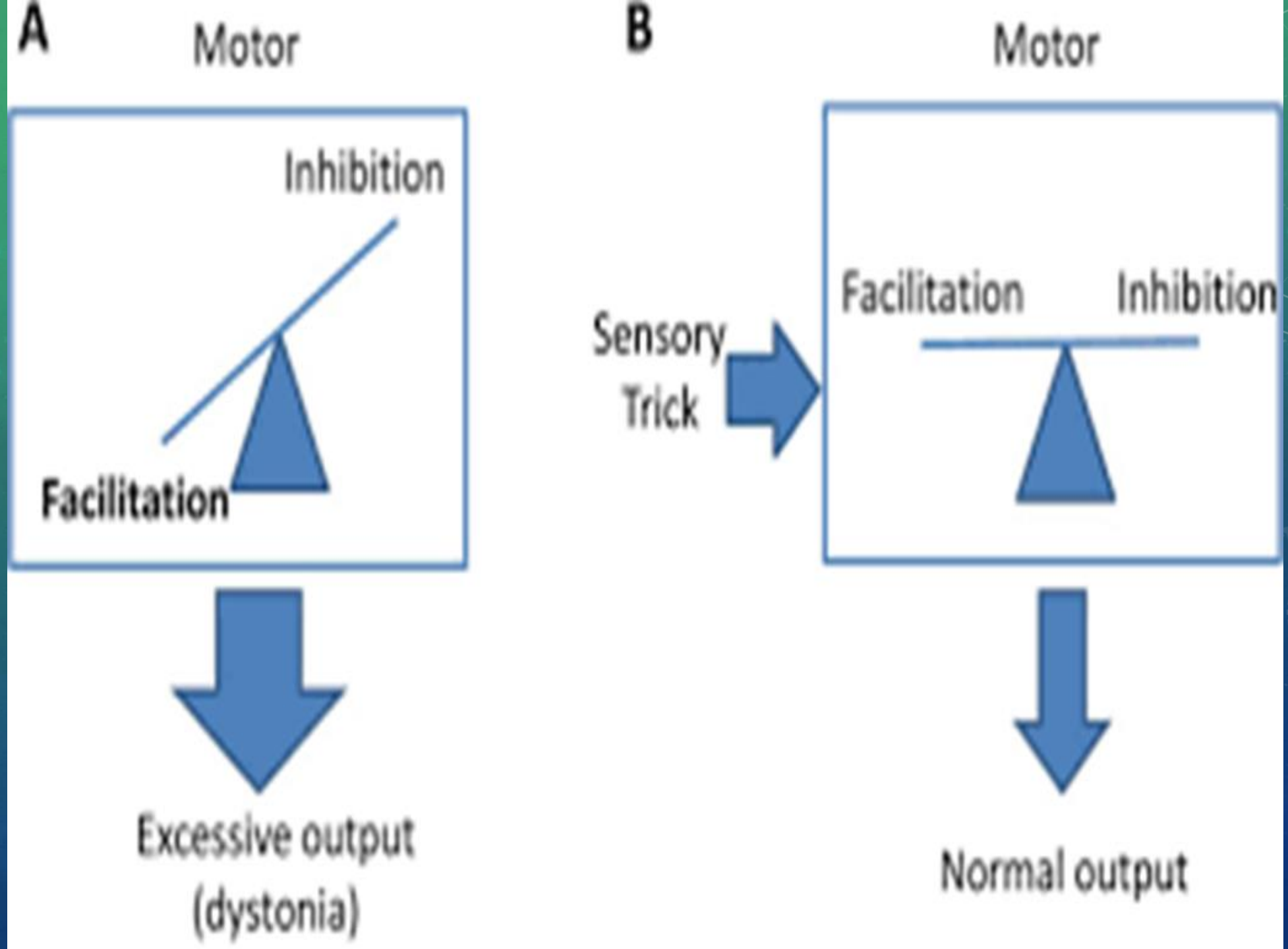
loss of inhibition at different levels

of the central nervous system

abnormal sensorimotor integration

and excessive plasticity

- rTMS as a therapeutic tool for dystonia act on the inhibitory circuits and reducing the excessive cortical plasticity.


A
Motor
Inhibition
Facilitation
Excessive output
(dystonia)
B
Motor
Sensory
Trick
Facilitation
Inhibition
Normal output

Dystonia not only considered to be dependent upon the basal ganglia-thalamo-cortical pathway

but Also on the cerebellar cortex and its direct connections with the motor cortex

- the cerebellum in dystonic patients involved in compensatory modulation

or

abnormal activity detected in the motor cortex

BG dysfunction state

- However, the gold-standard in dystonia seems to be targeting motor regions that produce functional changes over basal ganglia

RTMS & DYSTONIA

- inhibition of the premotor–motor interactions through a cTBS protocol might be the promising strategy for dystonia treatment characterized by functional and compensatory changes in the subcortical regions.

- low-frequency rTMS and cTBS. applied on M1 and the PMC, SMA, primary somatosensory cortex, and cerebellum with different protocols has some favorable outcomes

TOURETTE SYNDROME AND OTHER CHRONIC TIC DISORDERS

The SMA is involved in the preparation and organization of self-initiated movements and have an important role in the pathophysiology of tics

- normalizing its excitability might be a potential treatment for tics.
- Low-frequency rTMS of SMA, but not of M1 or the PMC, has been shown to reduce tic severity as well as comorbid obsessive-compulsive disorder

HUNTINGTON'S DISEASE AND OTHER CHOREAS

- In HD, SMA is thought to play a central role in maintaining the executive aspects of motor control that increases with approaching disease onset
- effect of rTMS in HD evaluated on non-motor symptoms, such as depression, showing sustained improvement in mood after 1 Hz rTMS on M1

The SMA might be a promising target for rTMS treatment

- however, the results need to be confirmed in a large cohort of patients with HD. rTMS needs to be tested in other forms of chorea to prove its efficacy

- cTBS has been tested for therapeutic purpose in 1 patient with hemichorea because of hemorrhage of the STN with satisfactory results

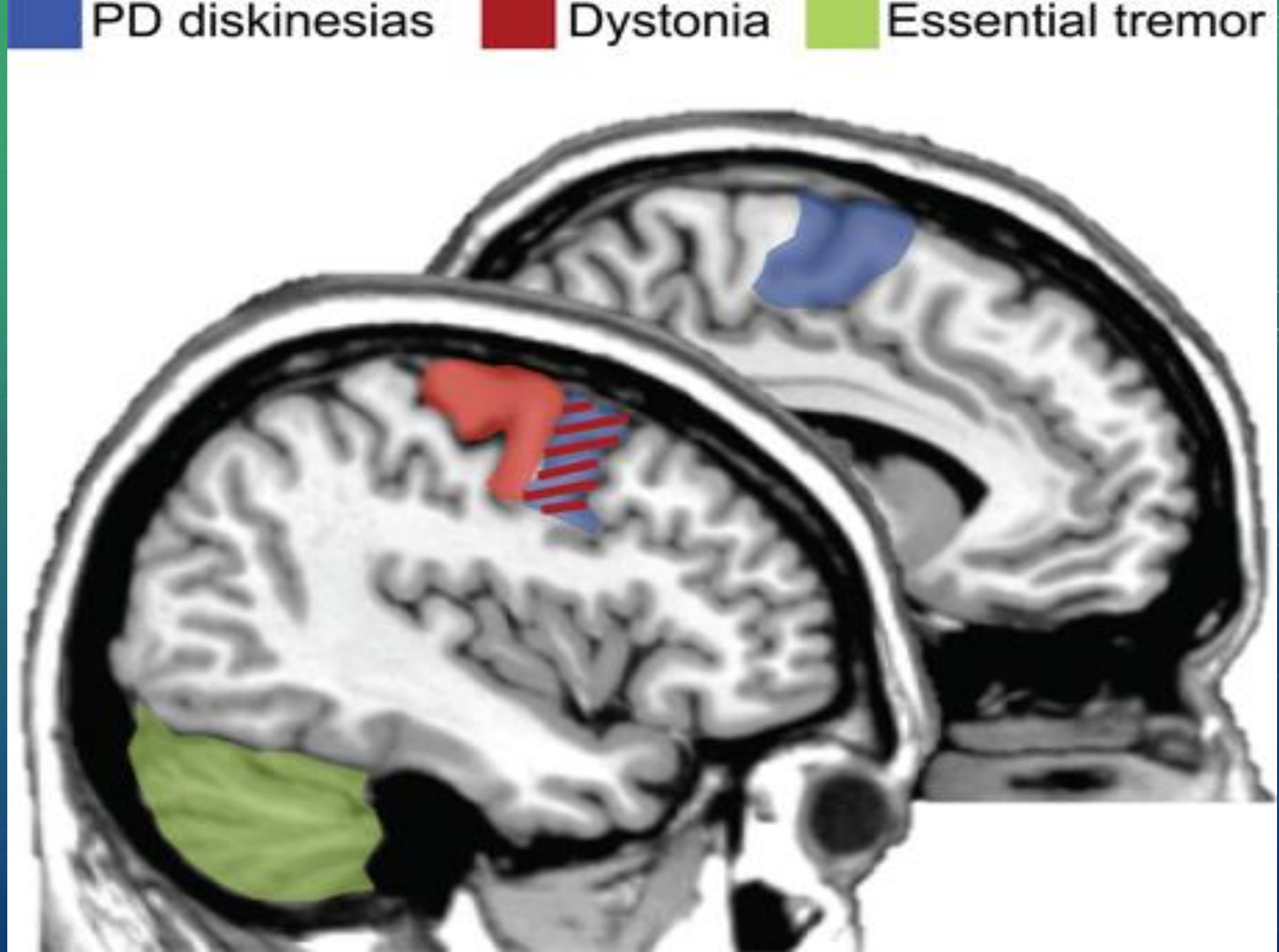
ESSENTIAL TREMOR

- tremor is generated by a dysfunction in the cerebello-thalamo-cortical network
- pharmacological treatment in ET remains poor and unsatisfactory
- prolonged sessions of low frequency rTMS on cerebullum, for a time-period of 3 weeks in ET patients refractory to medical treatment give good response

.

OPTIMAL BRAIN TARGETS OF STIMULATION FOR THERAPEUTIC PURPOSES IN MD

- The premotor cortex and SMA for dyskinesias in PD
- The motor and premotor cortices for dystonic patients
- The cerebellum for patients with ET.


PD diskinesias
Dystonia
Essential tremor

RTMS protocol

PD (motor symptoms)	PD (depression)	Dystonia	TS	HD	ET
High-frequency on M1 or low-frequency rTMS applied over other frontal regions	High-frequency rTMS on left DLPFC	Low-frequency rTMS on dorsal PMC	Low-frequency rTMS on SMA	Controversial data	Low-frequency rTMS on cerebellum

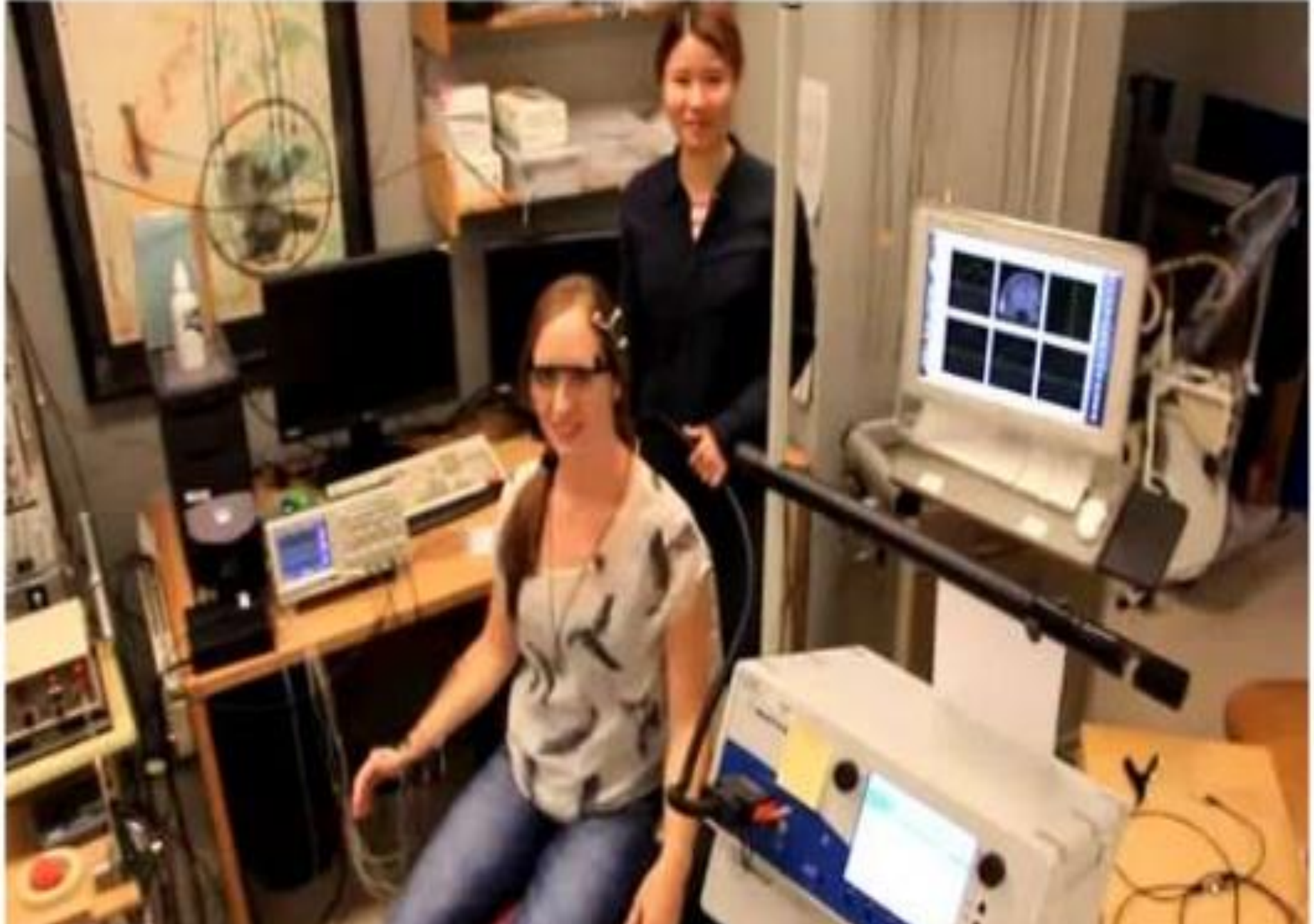
Although rTMS has the potential to become a powerful tool for ameliorating the clinical outcome of movement disorder

NO a clear consensus on optimal protocols for these motor disorders.

WHY DIDN'T RTMS INDUCE CLEAR THERAPEUTIC BENEFITS IN MD SO FAR????

- lack of a clear rationale to stimulate one cortical area compared with another.

- technical reasons, the presence of large parameter space in terms of stimulation frequency and intensity, duration of trains, intertrain interval, number of sessions, and time between them
- It is effect is transient .



THANK YOU