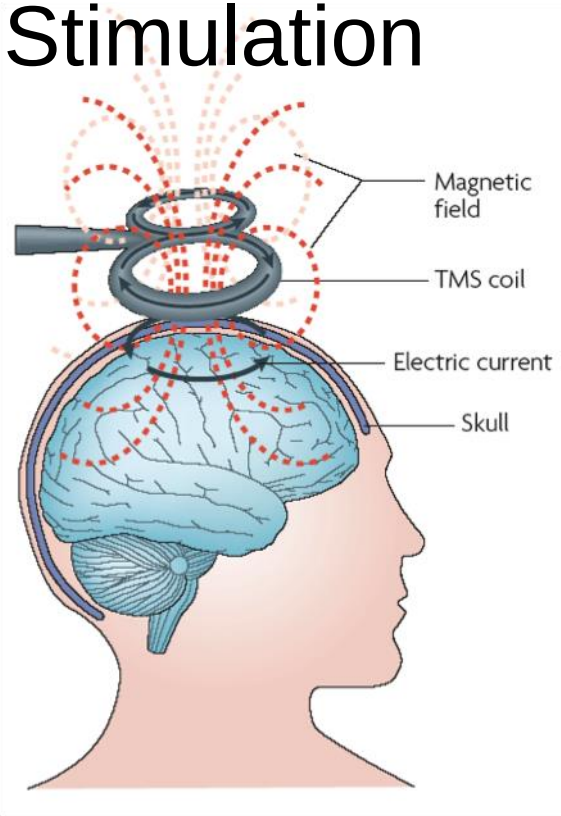
Cognitive effect of repetitive transcranial magnetic stimulation

재활의학과 김종문

repetitive Transcranial Magnetic Stimulation



◉ rTMS

- a coil connected to a magnetic stimulator placed on the human scalp

: Strong, brief electrical current

→ transient magnetic field

→ cross the scalp

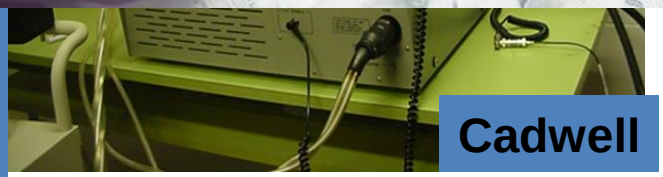
→ electric current in the cortex

→ depolarizing neurons in the targeted cortex

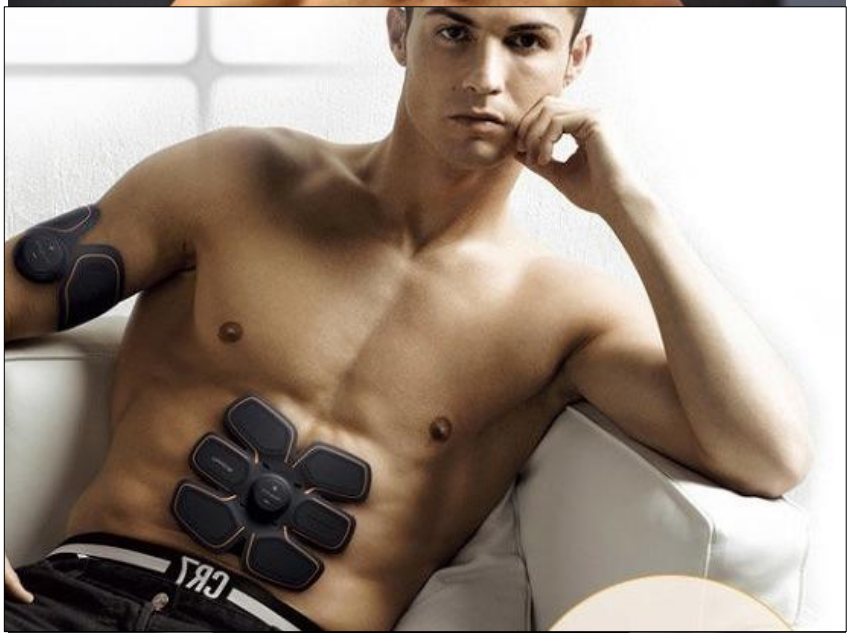
→ High(low) frequency to increase(suppress) cortical excitability

Barker, 1984

Stimulation of the Human Brain Cortex.



Cadwell


CR7

Strategy

- Top down
- Bottom up

Rehabilitation

- Neural plasticity
  - **Ability of the brain to change** (in response to changes in input)

- Principles
  - Use it or lose it
  - Use it and improve it
  - Experience specific
  - Repetition matters
  - Intensity matters
  - Time matters
  - Salience matters
  - Age matters
  - Transference
  - Interference

Rehabilitation

- Neural plasticity
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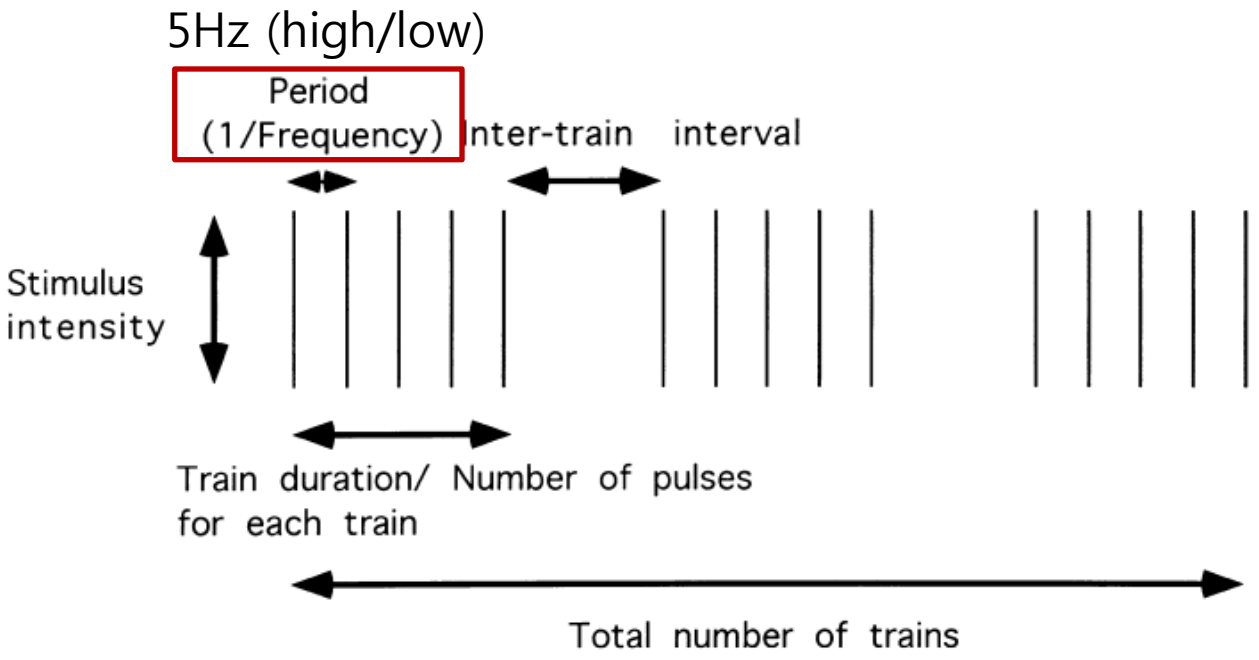
rTMS Protocol
- rTMS parameter



Safety

Maximum safe duration (expressed in seconds) of single trains of rTMS. Safety defined as absence of seizure, spread of excitation or afterdischarge of EMG activity. Numbers preceded by > are longest duration tested. Consensus has been reached for this table.

Frequency (Hz)	Intensity (% of MT)				
	90%	100%	110%	120%	130%
1	>1800[a]	>1800	>1800	>360	>50
5	>10	>10	>10	>10	>10
10	>5	>5	>5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

[a] In Japan, up to 5000 pulses have been applied without safety problems (communication of Y. Ugawa).

Clin Neurophysiol 2009

Indication

Table 15
Summary of recommendations on rTMS efficacy according to clinical indication.

Neuropathic pain	Definite analgesic effect of HF rTMS of M1 contralateral to pain side (Level A)
	LF rTMS of M1 contralateral to pain side is probably ineffective (Level B)
	No recommendation for cortical targets other than M1 contralateral to pain side
CRPS type I	Possible analgesic effect of HF rTMS of M1 contralateral to pain side (Level C)
Fibromyalgia	No recommendation for HF rTMS of the left M1 or DLPFC or for LF rTMS of the right DLPFC
Migraine	No recommendation for HF rTMS of the left M1 or DLPFC
Visceral pain	No recommendation for LF rTMS of the right S2 or for HF rTMS of the left DLPFC
Parkinson's disease	Possible antiparkinsonian effect of HF rTMS of bilateral (multiple) M1 regions (Level C)
	No recommendation for LF or HF rTMS of unilateral M1 representation of the hand
	No recommendation for rTMS of M1 and DLPFC using a non-focal coil or iTBS
	No recommendation for LF or HF rTMS of SMA or dPMC
	No recommendation for LF or HF rTMS of SMA, M1, or DLPFC or for cTBS of the cerebellum in levodopa-induced dyskinesia of PD patients
	Probable antidepressant effect of HF rTMS of the left DLPFC in PD patients (Level B)
Dystonia	No recommendation for LF rTMS of dPMC, M1, or S1
Alzheimer's disease	No recommendation for HF rTMS of DLPFC
	Possible effect of HF rTMS of the ipsilesional motor cortex in (post-)acute and chronic motor stroke (Level C)
	No recommendation for cTBS of the contralesional motor cortex or iTBS of the ipsilesional motor cortex
Broca's aphasia	No recommendation for LF rTMS of the (contralesional) right IFG
	No recommendation for HF rTMS or iTBS of the (ipsilesional) left IFG or DLPFC
Wernicke's aphasia	No recommendation for LF rTMS of the right superior temporal gyrus
Hemispatial neglect	Possible effect of cTBS of the (contralesional) left posterior parietal cortex (Level C)
	No recommendation for LF rTMS of the (contralesional) left posterior parietal cortex
	No recommendation for HF rTMS of the (ipsilesional) right posterior parietal cortex
Amyotrophic lateral sclerosis	No recommendation for cTBS or HF rTMS of M1
Multiple sclerosis	No recommendation for HF rTMS of M1
Epilepsy	Possible antiepileptic effect of focal LF rTMS of the epileptic focus (Level C)
	No recommendation for non-focal LF rTMS at the vertex
Disorders of consciousness	No recommendation for HF rTMS of DLPFC or M1
Alzheimer's disease	No recommendation for HF rTMS of DLPFC
Tinnitus	Possible effect of single sessions of "burst" or LF rTMS of the auditory cortex contralateral to tinnitus (Level C)
	Possible effect of repeated sessions of LF rTMS of the left (or contralateral to tinnitus) TPC (Level C)
	No recommendation for HF rTMS or cTBS of the auditory cortex
	No recommendation for HF rTMS of the left DLPFC combined with LF rTMS of both the right and left TPC

Alzheimer's disease No recommendation for HF rTMS of DLPFC

Clin Neurophysiol 2014

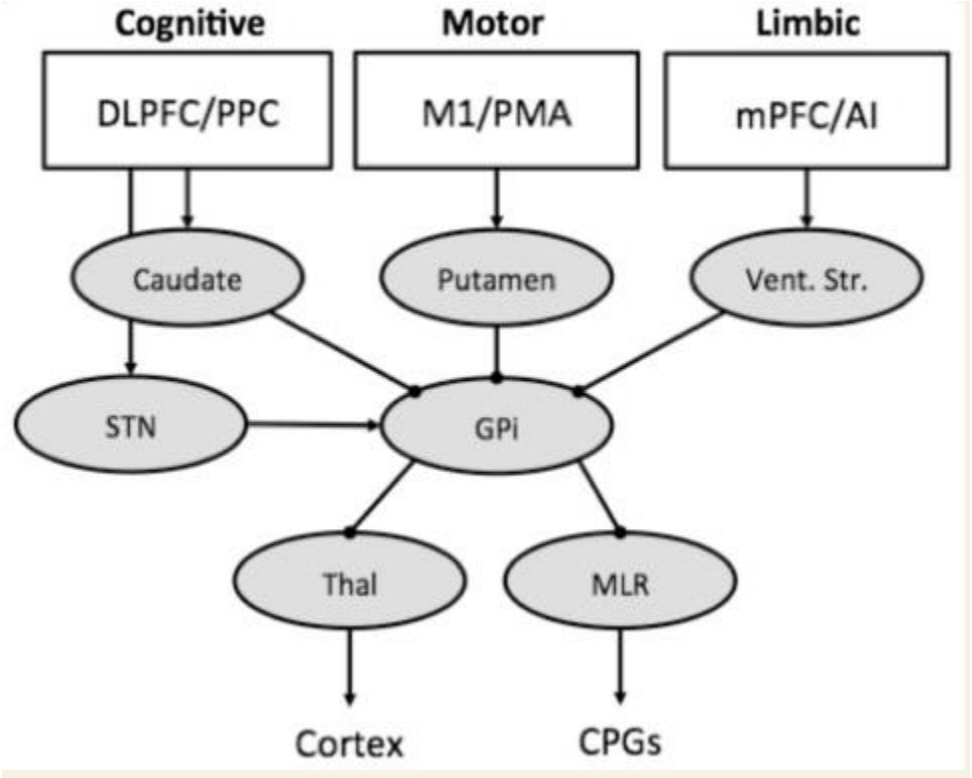
Indication

Depression	Definite antidepressant effect of HF rTMS of the left DLPFC (Level A)
	Probable antidepressant effect of LF rTMS of the right DLPFC (Level B) and probably no differential antidepressant effect between right LF rTMS and left HF rTMS (Level B)
	No recommendation for bilateral rTMS combining HF rTMS of the left DLPFC and LF rTMS of the right DLPFC
	Definite antidepressant effect of rTMS of DLPFC in unipolar depression (Level A), but no recommendation for bipolar depression
	Antidepressant effect of rTMS of DLPFC is probably additive to the efficacy of antidepressant drugs (Level B) and possibly potentiating (Level C)
	No recommendation for the overall respective antidepressant efficacy of rTMS of DLPFC compared to ECT
Anxiety disorders	Possible effect of HF rTMS of the right DLPFC in PTSD (Level C)
	No recommendation for LF rTMS of the right DLPFC in panic disorders
Obsessive compulsive disorder	No recommendation for HF or LF rTMS of the right or left DLPFC
	No recommendation for LF rTMS of SMA
Auditory hallucinations	Possible effect of LF rTMS of the left TPC (Level C)
	No recommendation for HF rTMS or cTBS of the left TPC
Negative symptom of schizophrenia	Probable effect of HF rTMS of the left DLPFC (Level B)
	No recommendation for bilateral HF rTMS of DLPFC and LF rTMS of the right DLPFC
Addiction and craving	Possible effect of HF rTMS of the left DLPFC on cigarette craving and consumption (Level C)
	No recommendation for HF rTMS of the right or left DLPFC for food or alcohol craving
Conversion	No recommendation for LF or HF rTMS of M1 or delivered at the vertex, using a focal or a non-focal coil

"No recommendation" means the absence of sufficient evidence to date, but not the evidence for an absence of effect

Clin Neurophysiol 2014

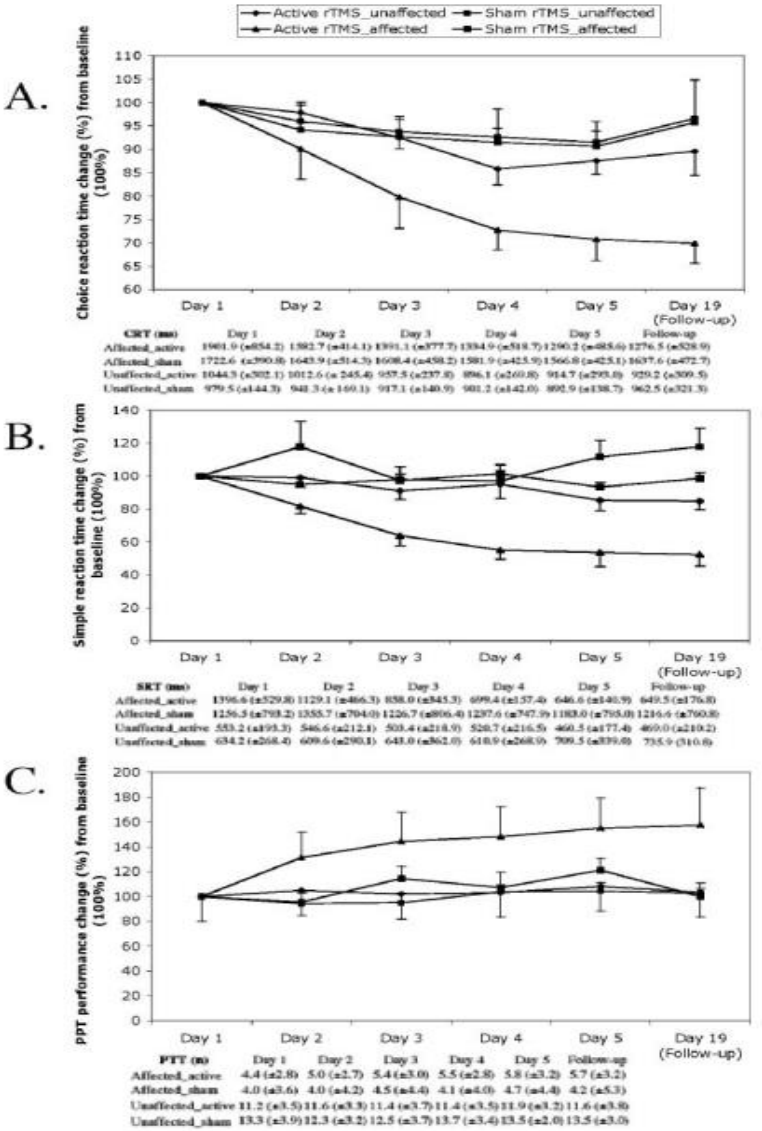
Target



Shine et al. Brain 2013

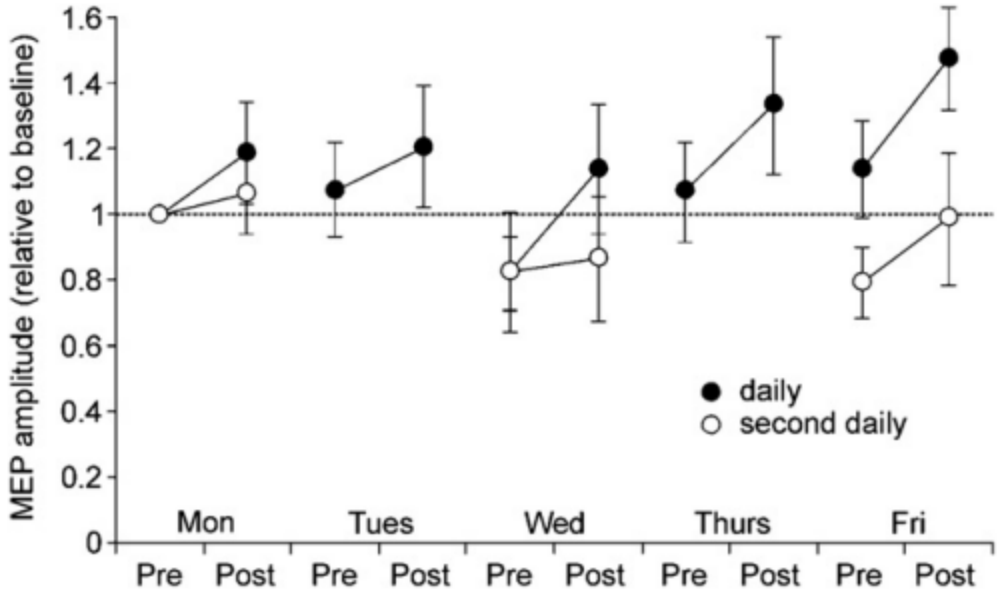
Long lasting effect

- 15 patients with chronic stroke
- rTMS
  - 5 sessions of rTMS to the affected & unaffected hemisphere over M1
  - Intensity of 100% rMT
  - Frequency of 1 Hz
  - 1,200 stimuli
  - For 20 min



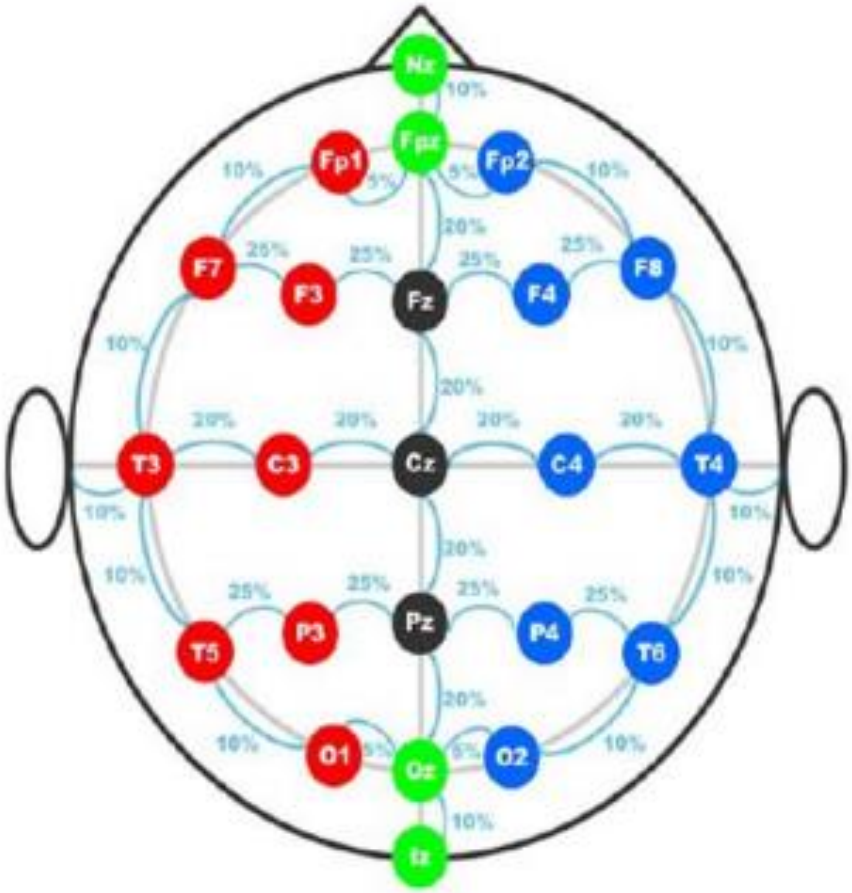
Fregni et al. Stroke 2006

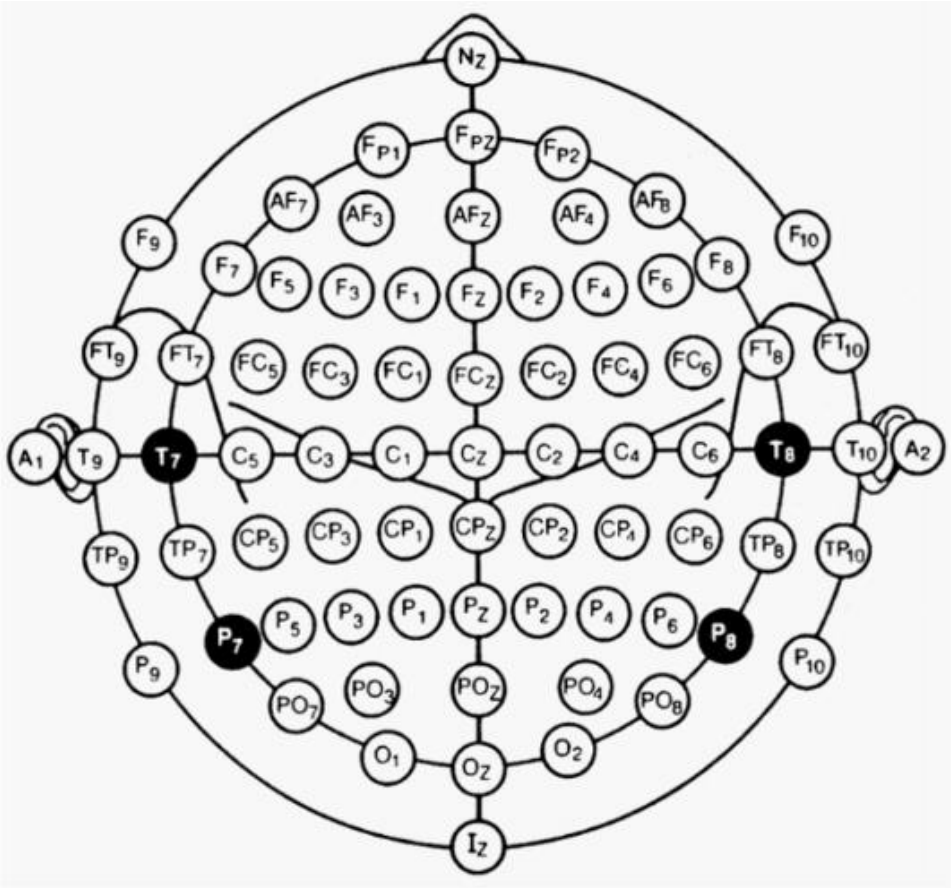
Long lasting effect



Alonzo et al. Brain Stimulation 2012

10-20 system


Nz
Fp1
Fpz
Fp2
F7
F3
Fz
F4
F8
T3
C3
Cz
C4
T4
T5
P3
Pz
P4
T6
O1
Oz
O2
Iz
10%
20%
25%
5%


Nz
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FC1
FCZ
FC2
FC4
FC6
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FT10
A1
T9
T7
C5
C3
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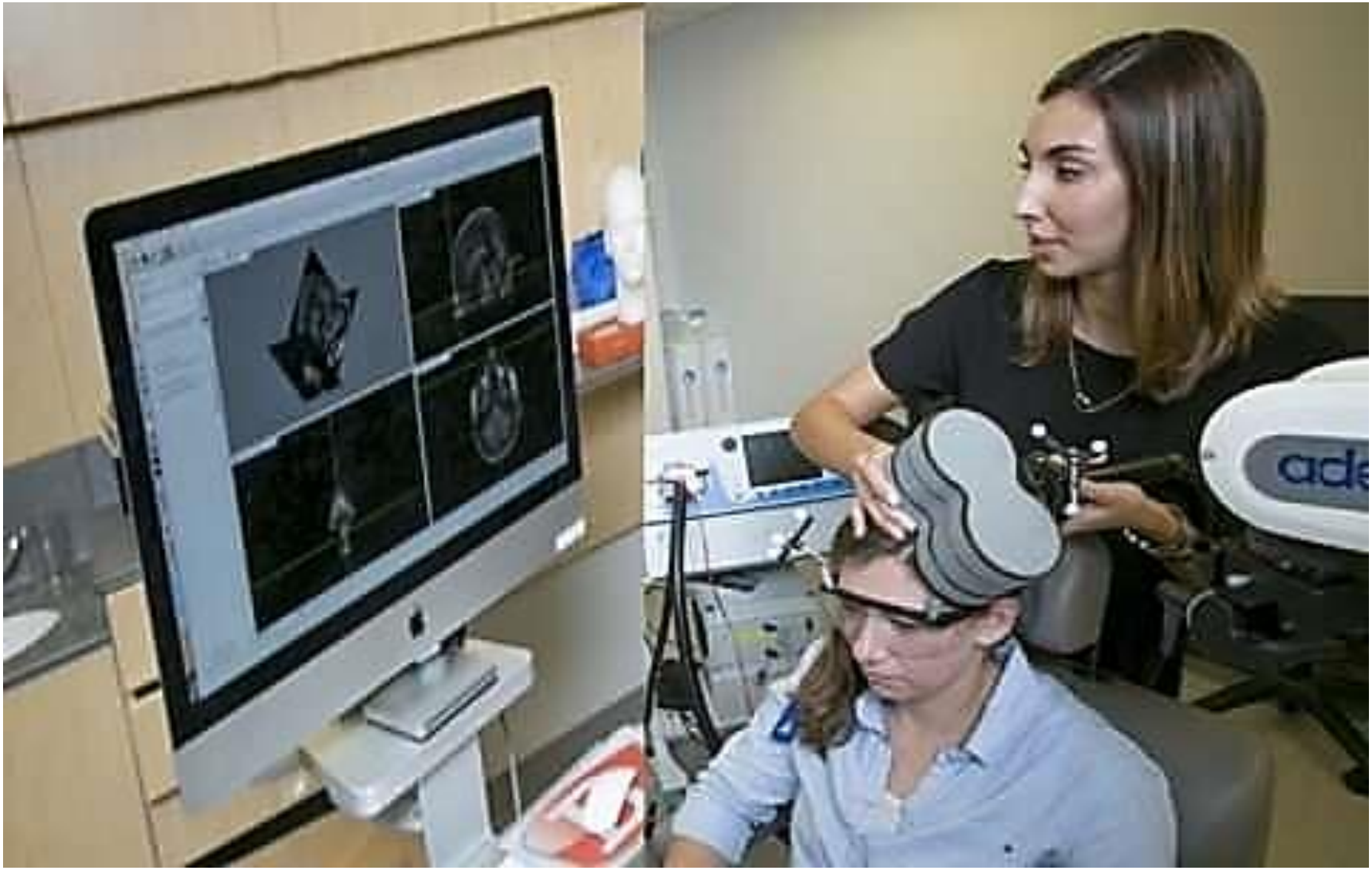


Clinical indication & Effect

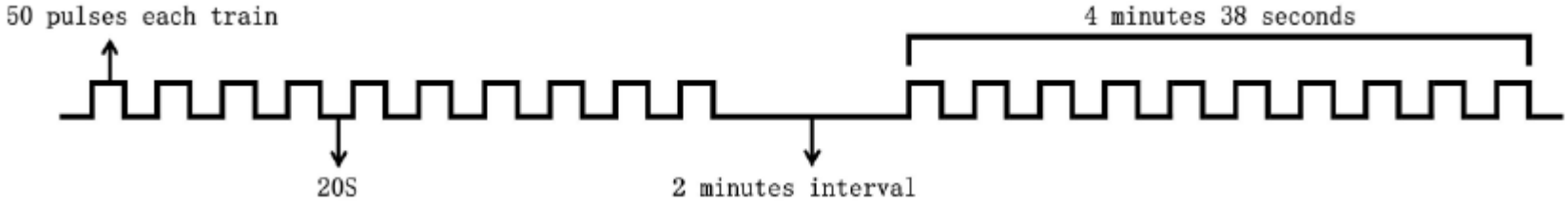
- Patients (category, severity)
  - Alzheimer dementia
  - Vascular dementia
  - MCI, memory impairment
- Procedure
  - Combined Tx
  - rTMS protocol : Frequency (Hz), intensity, mode, location,…
- Outcome
  - MMSE, visual recognition, verbal/non-verbal,…

Cellular Physiology and Biochemistry Cell Physiol Biochem 2017;41:137-144

The Role of Hippocampal Structural Synaptic Plasticity in Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Function in Male SAMP8 Mice

Jiang Ma[a] Jinhua Wang[b] Chaonan Lv[b] Jingjuan Pang[c] Bing Han[b] Yuan Gen[d] Mingwei Wang[b, d]

- Senesense-accelerated-prone mouse 8 (SAMP8)
- 5Hz, 30% of maximum output rTMS



- Western blot: anti-SYN, PSD95, anti-beta Actin
- qPCR: SYN, PSD95
- Water maze test

Cellular Physiology and Biochemistry Cell Physiol Biochem 2017;41:137-144

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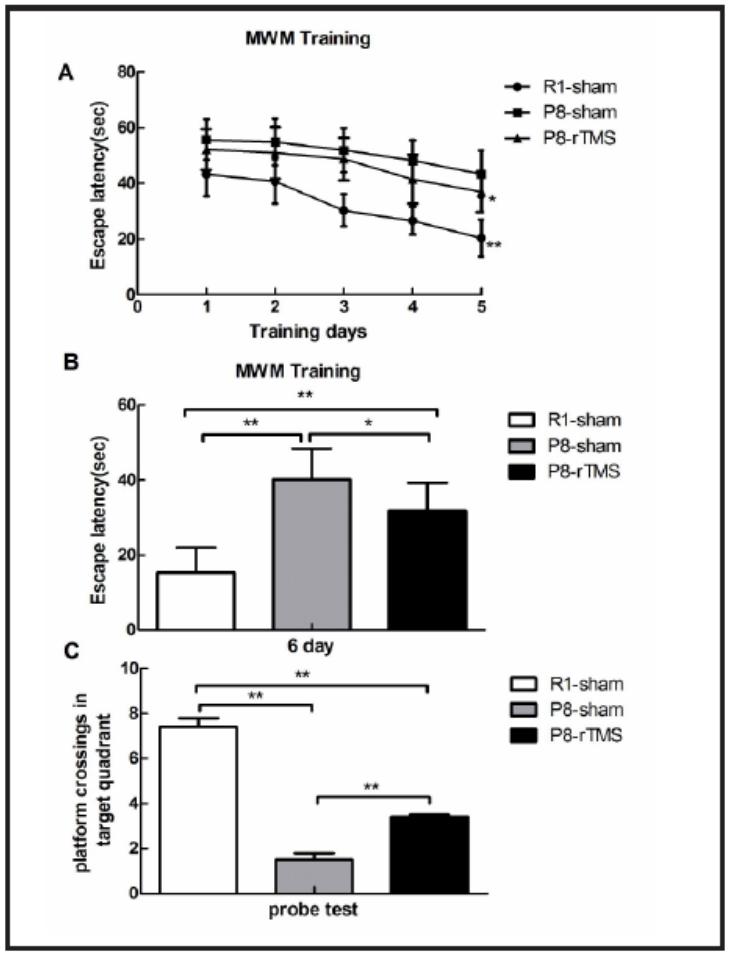

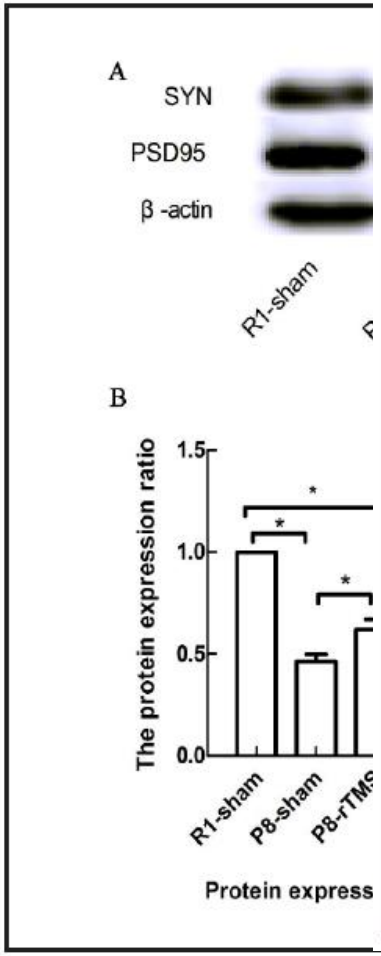

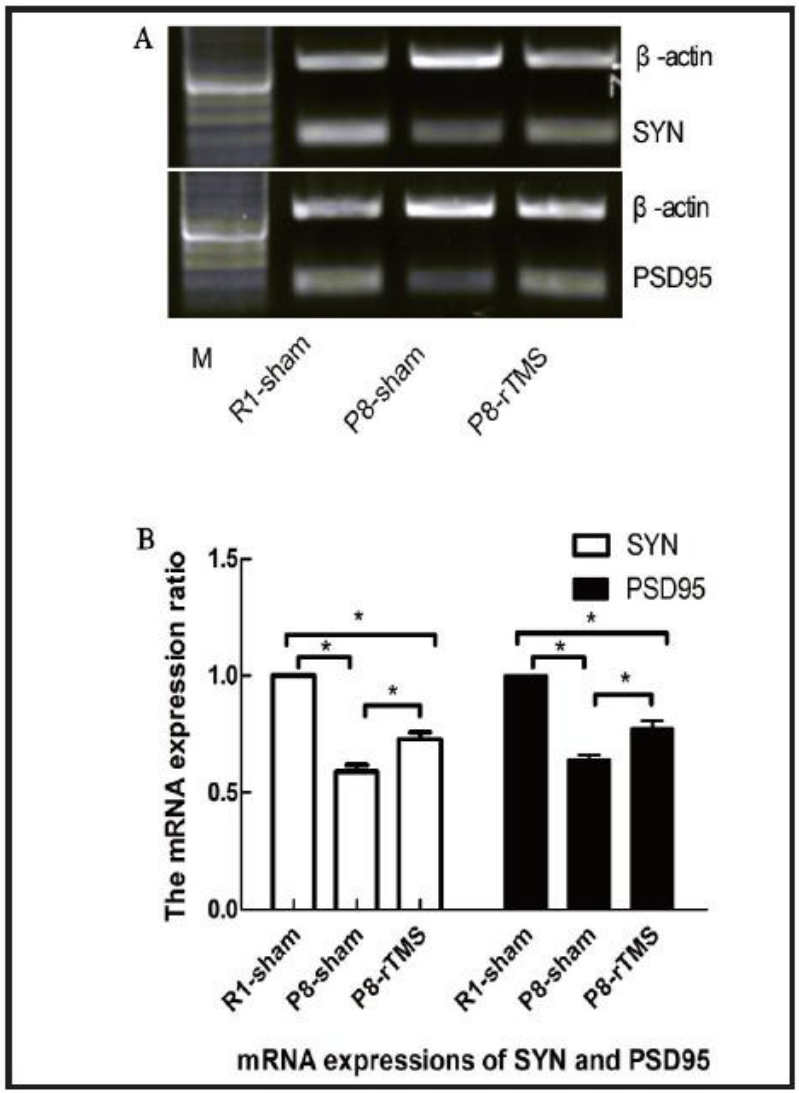

J Neural Transm (2011) 118:463–471

Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study

Jonathan Bentwich · Evgenia Dobronevsky · Sergio Aichenbaum · Ran Shorer · Ruth Peretz · Michael Khaigrekht · Revital Gandelman Marton · Jose M. Rabey

Combined Tx

- Patients (n = 7)

early or moderate AD, according to the DSM-IV criteria

MMSE score of 18–24

CDR score of 1

- Procedure

rTMS + Cog task, 5/week for 6 weeks > 2/week for 3 additional month

  - rTMS

    Broca, R&L DLPFC/Wernicke, R-pSAC and L-pSAC

    1,200 pulse, 20 trains, 2s of 10Hz, 90% of RMT

  - Cog task

    computer touch screen (Elo-Touch, USA) which is part of the Neuronix System

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- Outcomes
  - **Alzheimer Disease Assessment Scale-Cognitive**
  - Alzheimer Disease Assessment Scale-Activities of Daily Living
  - **Clinical Global Impression of Change scale**
  - MMSE
  - HAMILTON
  - Neuropsychiatric Inventory test

J Neurol (2012) 259:83–92

Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia

Mohamed A. Ahmed · Esam S. Darwish · Eman M. Khedr · Yasser M. El serogy · Anwer M. Ali

Frequency

- Patients (n = 45, each group = 15)

Group 1 : 20 Hz rTMS

Group 2 : 1Hz rTMS

Group 3 : Sham

National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)

- Procedure

5 days

  - rTMS

    Rt. DLPFC > Lt.DLPFC

    Group 1 : 2,000 pulse, 20 trains, 5s of 20Hz, 90% of RMT

    Group 2 : 2,000 pulse, continuous 1Hz, 100% of RMT

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Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia

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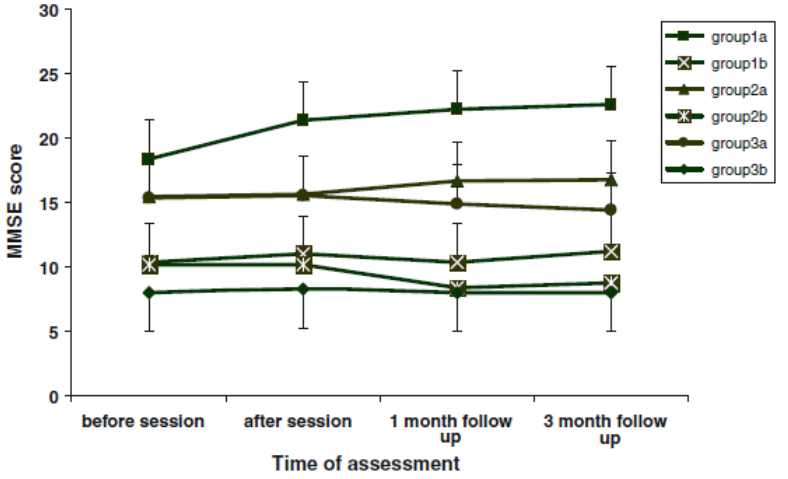
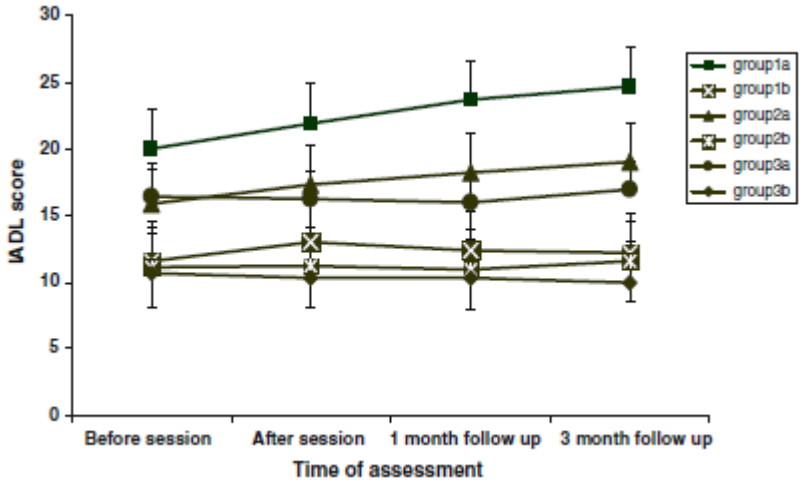
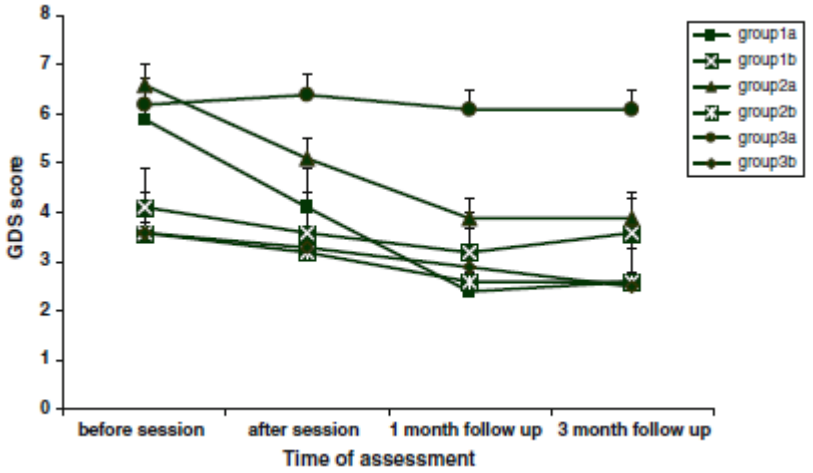
- Outcomes (1, 3 month f/u)
  - MMSE
  - iADL
  - GDS
- High Frequency, mild~moderate







Neuropharmacology 97 (2015) 210–219

Improvement of spatial learning by facilitating large-conductance calcium-activated potassium channel with transcranial magnetic stimulation in Alzheimer's disease model mice

Furong Wang [a, b], Yu Zhang [a, c], Li Wang [a, d], Peng Sun [a, b], Xianwen Luo [a, b], Yasuhito Ishigaki [e], Tokio Sugai [a], Ryo Yamamoto [a], Nobuo Kato [a, *]

[a] Department of Physiology, Kanazawa Medical University, Ishikawa 920-0293, Japan
[b] Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[c] Medical College, Qinghai University, Xinin 810016, China
[d] China-Japan Friendship Hospital, Beijing 100029, China
[e] Medical Research Institute, Kanazawa Medical University, Ishikawa 920-0293, Japan

Frequency

- Alzheimer's disease model mice (3xTg)
- 1, 10 or 15 Hz daily for 4 weeks
- the pulse uprise time, 60 ms, duration 250 ms, 80% of the maximum output (1.26T)

- Water maze test
- Activity of the large conductance calcium-activated potassium channels

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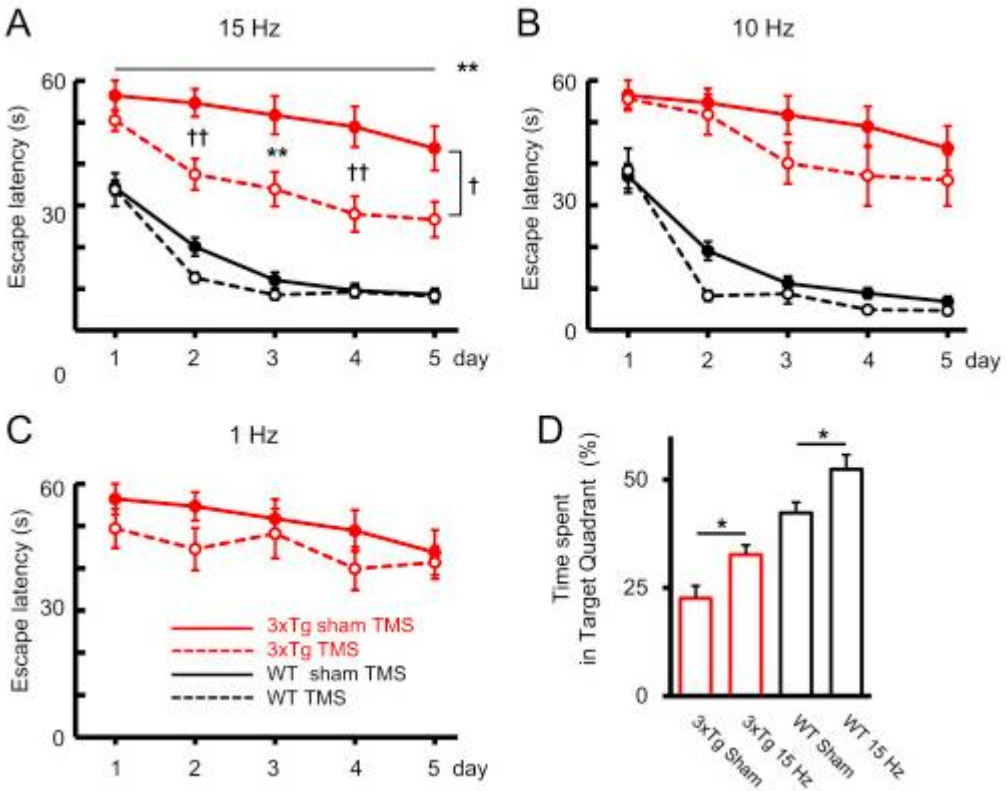

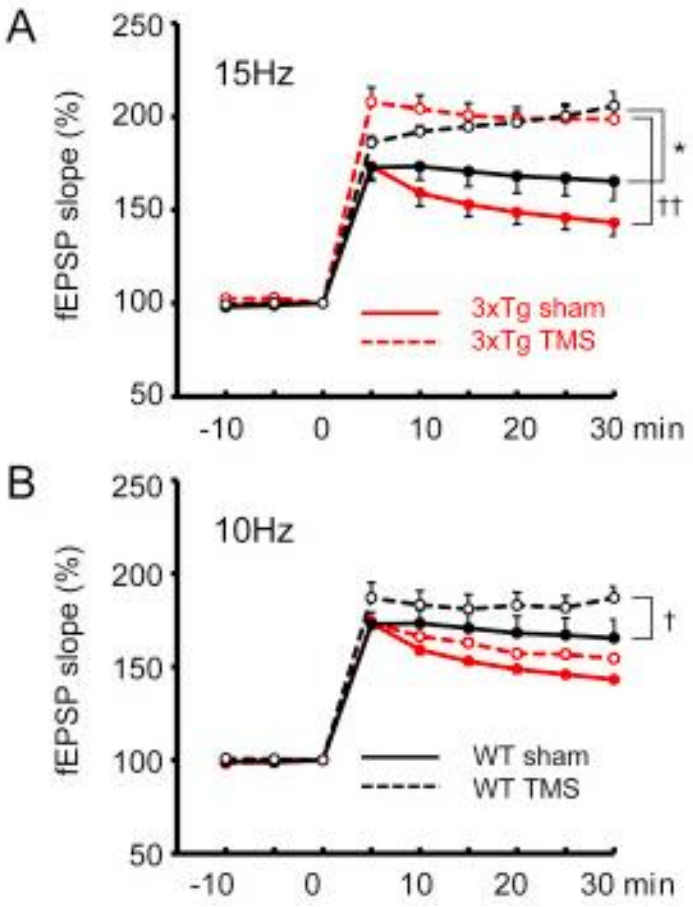

frontiers in
HUMAN NEUROSCIENCE
April 2012 | Volume 6 | Article 62

Enhancing memory performance with rTMS in healthy subjects and individuals with Mild Cognitive Impairment: the role of the right dorsolateral prefrontal cortex

Patrizia Turriziani[1], Daniela Smirni[1], Giuseppe Zappalà[4], Giuseppa R. Mangano[1], Massimiliano Oliveri[1,3] and Lisa Cipolotti[1,2]*

Mode, Location

- Patients

Health subject (n = 100)

MCI (n = 8)

(1) subjective memory impairment(over1–2 years)

(2) objective poor memory performance asassessed by the California Verbal Learning test and the Rey Complex figure

(3) normal general cognitive functioning asassessed by the Raven's Colored Progressive Matrices and tests of short term memory,naming,and frontal"executive"functions

(4) Clinical Dementia Rating score below 0.5

(5) no or minimal impairment inactivities of daily living (ADL) asassessed by the Instrumental Activities of Daily Living scale (IADL) and by the ADLscale

(6) absence of dementia [score > 24 on MMSE

- Procedure
  - Verbal (word), non-verbal task (face, building recognition)
  - rTMS

    experiment 1,2,4: 600 pulse, continuous 1Hz, 90% of RMT

    experiment 3 : 600 pulse,50Hz 3 pulse, every 200ms for 2s, once every 10s for 20 repetition, 80% of RMT

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Patrizia Turriziani[1], Daniela Smirni[1], Giuseppe Zappalà[4], Giuseppa R. Mangano[1], Massimiliano Oliveri[1,3] and Lisa Cipolotti[1,2]*

- Procedure (Sham과 rTMS group으로 나누고, 6hr 후 바꾸어서 동일한 실험을 진행)
  - Experiment 1: 1 HZ rTMS of the DLPFC. Non-Verbal Recognition Memory Lt.DLPFC (n = 20), Rt.DLPFC (n = 20)
  - Experiment 2: 1 HZ rTMS of the DLPFC. Verbal Recognition Memory Lt.DLPFC (n = 20), Rt.DLPFC (n = 20)
  - Experiment 3: iTBS of the DLPFC. Non-Verbal Recognition Memory Lt.DLPFC (n = 10), Rt.DLPFC (n = 10)
  - Experiment 4: 1 HZ rTMS of the DLPFC. Non-Verbal Recognition Memory in MCI Patients

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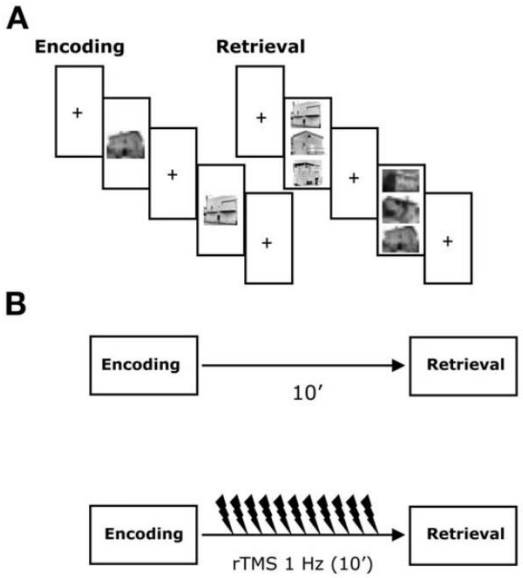
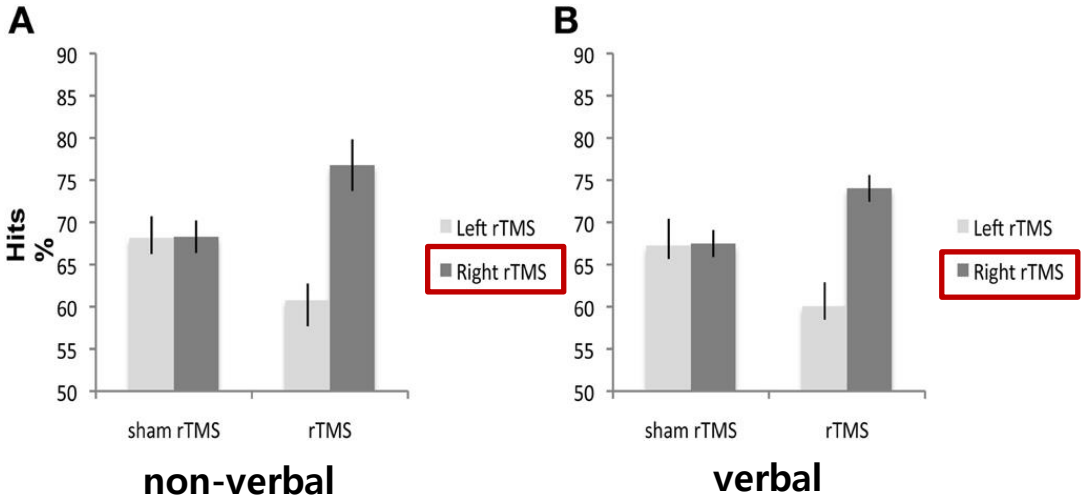
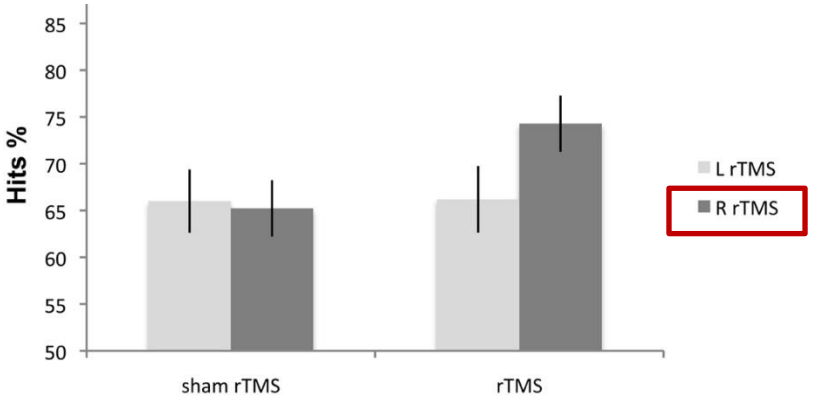


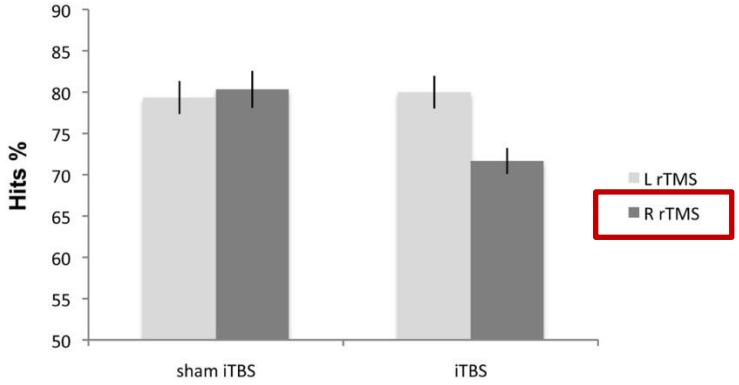


non-verbal

verbal



non-verbal+MCI



non-verbal+iTBS

Experimental Gerontology xxx (2014) xxx–xxx

Repetitive transcranial magnetic stimulation (rTMS) influences spatial cognition and modulates hippocampal structural synaptic plasticity in aging mice

Jun Ma [a,b,1], Zhanchi Zhang [a,1], Lin Kang [a], Dandan Geng [a], Yanyong Wang [b,c], Mingwei Wang [b,c], Huixi

[a] Department of Human Anatomy, Hebei Medical University, Shijiazhuang 050017, Hebei, PR China
[b] Hebei Key Laboratory for Brain Aging and Cognitive Neuroscience, Shijiazhuang 050031, Hebei, PR China
[c] First Hospital of Hebei Medical University, Shijiazhuang 050031, Hebei, PR China

Intensity

- **low-frequency rTMS (≤ 1 Hz)** affects synaptic plasticity in rats with vascular dementia (VaD)
- spatial memory behavior, neuron and synapse morphology in the hippocampus, and synaptic protein markers and brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB)
- **rTMS with low intensity (110% average resting motor threshold intensity, 1 Hz, LIMS)**

  > activation of **BDNF and TrkB,**

  upregulated the level of synaptic protein markers

  increased synapse density and thickened **PSD** (post-synaptic density protein)

Experimental Gerontology xxx (2014) xxx–xxx

Repetitive transcranial magnetic stimulation (rTMS) influences spatial cognition and modulates hippocampal structural synaptic plasticity in aging mice

Jun Ma [a,b,1], Zhanchi Zhang [a,1], Lin Kang [a], Dandan Geng [a], Yanyong Wang [b,c], Mingwei Wang [b,c], Huixian Cui [a,b,*]

[a] Department of Human Anatomy, Hebei Medical University, Shijiazhuang 050017, Hebei, PR China
[b] Hebei Key Laboratory for Brain Aging and Cognitive Neuroscience, Shijiazhuang 050031, Hebei, PR China
[c] First Hospital of Hebei Medical University, Shijiazhuang 050031, Hebei, PR China

- **high-intensity magnetic stimulation (150% average resting motor threshold intensity, 1 Hz, HIMS)**

  > inducing thinning of PSDs

  disordered synaptic structure

  large number of lipofuscin accumulations

  number of synapses and downregulating BDNF–TrkB and synaptic proteins

Experimental Gerontology xxx (2014) xxx–xxx

Repetitive transcranial magnetic stimulation (rTMS) influences spatial cognition and modulates hippocampal structural synaptic plasticity in aging mice

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- **Protocol**
  - Normal aging (15-month-old) and adult (6-month-old) male Swiss mice (28–32 g)
  - aging-control, aging-sham, aging-LIMS and aging-HIMS groups (n = 24 mice/group)
  - Low-frequency (1 Hz) rTMS for **14 consecutive days**
  - Morris Water Maze
  - Immunohistochemical Staining for **SYN, GAP43 and PSD95**
  - Western Blotting Analyses for **SYN, GAP43, PSD95, BDNF and TrkB**
  - RT-PCR Analyses for **SYN, GAP43, PSD95, BDNF and TrkB**

Journal of the Neurological Sciences 346 (2014) 318–322

Non-invasive brain stimulation of the right inferior frontal gyrus may improve attention in early Alzheimer's disease: A pilot study

Ilona Eliasova, Lubomira Anderkova, Radek Marecek, Irena Rektorova *

Location

- Patients (n = 10)

7 AD, 3 MCI

- Procedure

2 session

  - rTMS

    Rt. inferior frontal gyrus, Rt. superior temporal gyrus, vertex

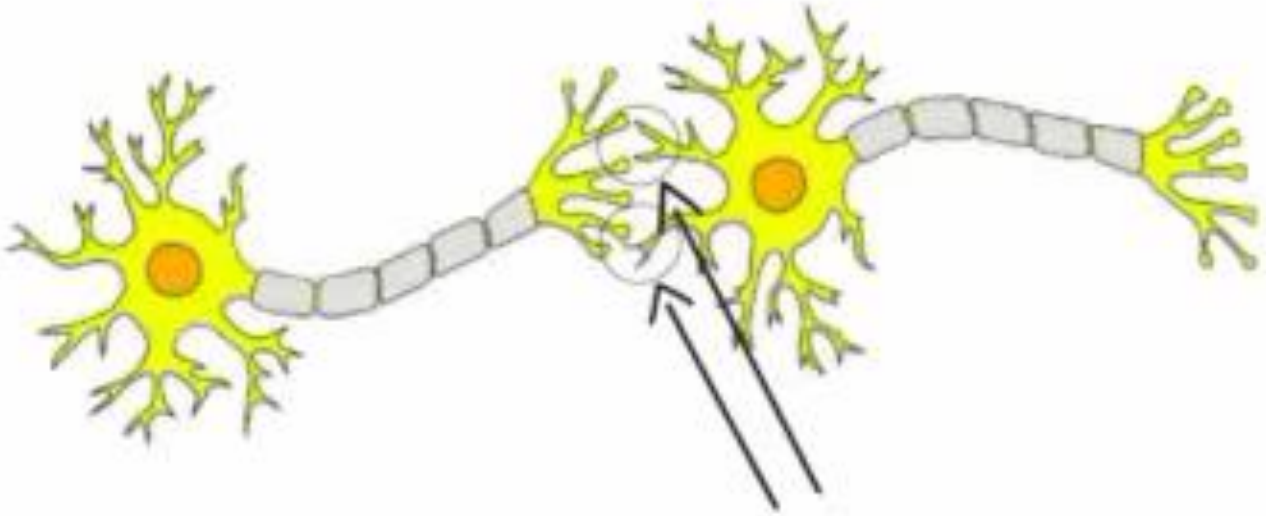
    2,250 pulse, 45 trains, 4.9s of 10Hz, 90% of RMT

- Outcome

Trail Making Test, Stroop test, complex visual scene encoding task

	Patients					rTMS protocol						
	Dz	Age	Level of Dementia	MMSE	n	stim site	frequency (Hz)	Train number	Train duration	Intertrain interval	Pulses per session	intensity
Ahmed et al	alzheimer	65.9 ± 5.9	Mild~severe	14.7 ± 3.7	10, 5	R-L DLPFC	20	20	5	25	2000	90% of RMT
	alzheimer	68.6 ± 6.7	Mild~severe	12.7 ± 3.9	11, 4	R-L DLPFC	1	2	1000	30	2000	100%
	alzheimer	68.3 ± 4.9	Mild~severe	13.9 ± 3.9	11, 4	sham	Sham	5	5	25	2000	
Bentwich et al	alzheimer	75.4±4.4	mild~moderate		7	Broca, R&L DLPFC	10	20/20/20	2		1200	90%
Eliasova et al.	alzheimer	75 ± 7.5	Mild		10	IFG, STG, Vertex	10	45	4.9	25	2250	90%
Rabey et al.	alzheimer	72.6 ± 8.9	mild~moderate		7	R-L DLPFC, Broca, Vernicke, R-L PSAC	10	25/25/25	2		1500	90% 110%
	alzheimer	75.4 ± 9.07	mild~moderate		8	R-L DLPFC, Broca, Vernicke, R-L PSAC	Sham	25/25/25	2		1500	90% 110%
Cotelli et al.	alzheimer	71.2 ± 6.1	Moderate	16.2 ± 2.7	5	L DLPFC	20	50	2	28	2000	100%
	alzheimer	74.4 ± 3.8	moderate	16.0 ± 2.0	5	L DLPFC	placebo	50	2	28	2000	100%
Turriziani et al.	alzheimer	66.4 ± 5.7	mild		8	L DLPFC	1	10	60		600	90%
						R DLPFC	1	10	60		600	90%
						sham	Sham	10	60		600	90%
Cotelli et al.	alzheimer	75 ± 6.2	mild	19.7 ± 1.6	12	L DLPFC	20					90%
						R DLPFC						90%
						sham						90%
Turriziani et al.	MCI	66.4±5.7	mild	26.9 ± 2.0	8	L DLPFC	1	600				90%
						R DLPFC	1	600				90%
Jorge et al.	Poststorke	63.1 ± 8.1		26.5 ± 1.7	20	L PFC	10	20	5	60	1000	100%
Rektorova et al.	executive dysfunction	72.9 ± 3.4			7	L DLPFC or L MC	10	45	1	10	450	100%
Sole´-Padulle´s et al	memory complaint	66.95 ± 9.43		26.5 ± 2.06	20	L PFC	5	10	10	20	500	80%
Du D et al.	stroke	57.6 ± 10.8			60	bilateral frontal lobe	0.5					60%
Fregni et al.	stroke	56 ± 11.5			15	M1	1				1200	100%

LONG-TERM POTENTIATION (LTP)



Effect of Ipsi-lesional Dorsolateral Prefrontal rTMS on Cognitive Function in Subacute Phase Stroke Patients

- Retrospective review to patients with acute stroke (onset < 3 months) visiting between March, 2014 and September, 2016

- Exclusion criteria
  1) Previous stroke
  2) Degenerative disease such as Parkinson's disease
  3) Severe cognitive impairment (MCS, Vegetative state)
  4) mild cognitive impairment(MMSE > 26)

- rTMS intervention group (n=38)
  - Received rTMS sessions ≥ 5 (3days per week for 4weeks)
- Control group (n=67)
  - Did not received any rTMS session

Effect of Ipsi-lesional Dorsolateral Prefrontal rTMS on Cognitive Function in Subacute Phase Stroke Patients

- All patients received
  - 1hr-occupational therapy per day, 5days/week for 4weeks

- rTMS protocol
  - ipsi-lesional dorsolateral prefrontal cortex (BA 46)
  - Intensity: 80% motor threshold
  - 10Hz / 5-second train duration / 55-second intertrain interval
  - for 20 minutes (1,000 pulses per session)

- Primary outcome
  - MMSE total and sub-scores
  - IQ (WAIS-IV)
  - Digit span (forward and backward)

Baseline characteristics

Characteristic	rTMS group (n = 38)	Control group (n = 67)	P value
Sex			
Male / Female, n	23/15	40/27	0.53
Age			
Mean ± SD (range), years	60.6±14.7	61.7±13.4	0.69
Laterality of the lesion			
Right / Left / Both, n	18/17/3	32/28/6	
Type of stroke			
Cerebral infarction, n	15	26	0.43
Intracerebral hemorrhage, n	17	35	0.47
Subarachnoid hemorrhage, n	6	6	0.26
Number of rTMS	9.3 (Rt.: 9.9 / Lt. 8.7)		

Initial evaluation

Characteristic	rTMS group (n = 38)	Control group (n = 67)	P value
Mini-Mental Status Exam			
MMSE total	13.31	14.29	0.55
Orientation	4.26	4.66	0.50
Calculation	1.03	1.00	0.93
Registration	2.13	2.34	0.40
Recall	1.11	1.22	0.63
Language	4.53	4.92	0.49
Drawing	0.23	0.24	0.98
Balance			
Berg Balance Scale	14.3	18.9	0.11
Trunk Impairment Score	7.5	8.9	0.31
Geriatric Depression Scale	14.5	15.0	0.82

Changes in evaluations (Total)

	Baseline evaluation			Changes after 4weeks		
	Control	rTMS	p value	Control (n=67)	rTMS (n=38)	p value
Mean age (Yr)	61.7	60.6	0.80			
MMSE – total	14.3	13.3	0.55	5.3 (n=67)	8.4 (n=38)	**0.02***
MMSE - attention	1.00	1.03	0.90	0.79	1.50	**0.03***
IQ	63.2	61.0	0.52	9.1 (n=43)	13.5 (n=17)	0.14
언어이해	80.7	81.3	0.81	9.0	8.0	0.80
지각추론	65.2	60.8	0.22	9.5	15.6	0.13
작업기억	73.3	73.4	0.93	7.9	8.8	0.77
처리속도	60.5	56.8	0.24	6.2	12.8	0.14
Digit span – forward	4.50	3.56	0.11	0.52 (n=44)	1.75 (n=32)	**0.01***
Digit span - backward	2.36	1.68	0.10	0.52	0.90	0.09

Changes in evaluations (Rt.Brain)

	Baseline evaluation			Changes after 4weeks		
	Control	rTMS	p value	Control (n=67)	rTMS (n=38)	p value
Mean age (Yr)	62.4	60.9	0.67			
MMSE – total	16.8	14.9	0.42	4.8 (n=32)	8.4 (n=18)	**0.04***
MMSE - attention	1.11	1.35	0.27	0.80	1.70	**0.04***
IQ	65.2	67.9	0.55	5.7 (n=27)	13.1 (n=11)	**0.04***
언어이해	87.1	87.3	0.88	6.1	7.3	0.70
지각추론	62.2	63.3	0.67	7.1	15.8	**0.03***
작업기억	75.5	78.7	0.46	4.8	7.0	0.37
처리속도	60.3	59.9	0.81	4.8	12.6	**0.03***
Digit span – forward	4.59	3.78	0.23	0.34 (n=26)	1.68 (n=16)	**0.01***
Digit span - backward	2.35	1.89	0.31	0.31	1.15	**0.01***

Changes in evaluations (Lt.Brain)

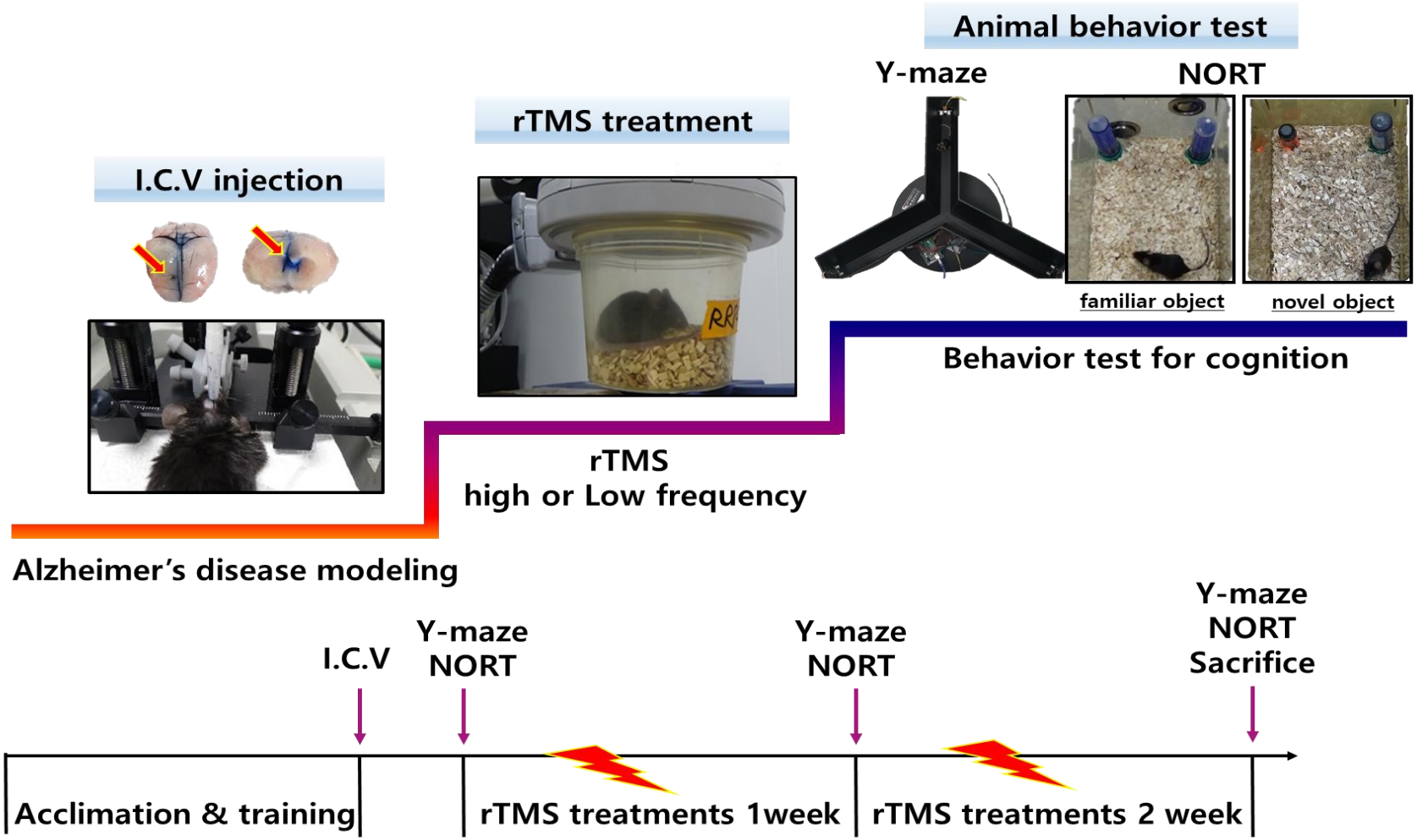
	Baseline evaluation		p value	Changes after 4weeks		p value
	Control	rTMS		Control (n=28)	rTMS (n=17)	
Mean age (Yr)	61.1	60.3	0.78			
MMSE – total	11.7	11.5	0.87	5.9 (n=28)	7.6 (n=17)	0.37
MMSE - attention	0.90	0.67	0.69	0.80	1.32	0.25
IQ	56.3	55.8	0.75	12.7 (n=16)	14.3 (n=6)	0.72
언어이해	70.2	64.7	0.88	11.9	9.3	0.85
지각추론	63.4	53.7	0.53	11.7	15.2	0.61
작업기억	66.4	67.8	0.82	11.3	12.0	0.93
처리속도	60.3	46.5	0.81	7.3	13.3	0.82
Digit span – forward	4.58	3.78	0.13	0.80 (n=17)	1.76 (n=13)	0.09
Digit span - backward	2.45	1.59	0.21	0.80	0.54	0.44
AQ (K-WAB)	52.1	45.0	0.56	19.7 (n=15)	30.6 (n=9)	0.15

Conclusion

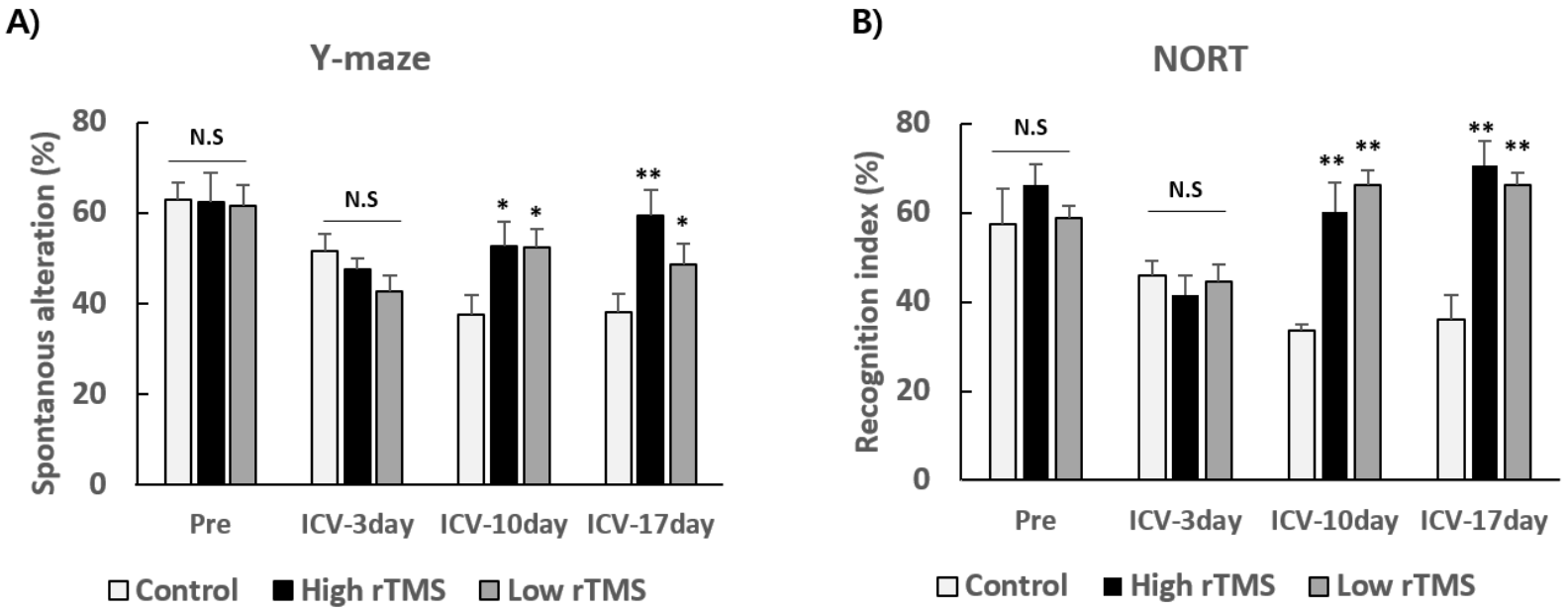
- It is helpful to perform high-frequency rTMS on the ipsi-lesional DLPFC can be helpful for improving cognition (especially attention).
- The efficacy could be verified by 5 rTMS sessions per month.

- Large-scale, controlled trials with long-term follow-up will be necessary.
- Specifying the optimal time after stroke for starting rTMS treatment and the optimal parameters of stimulation will be necessary.

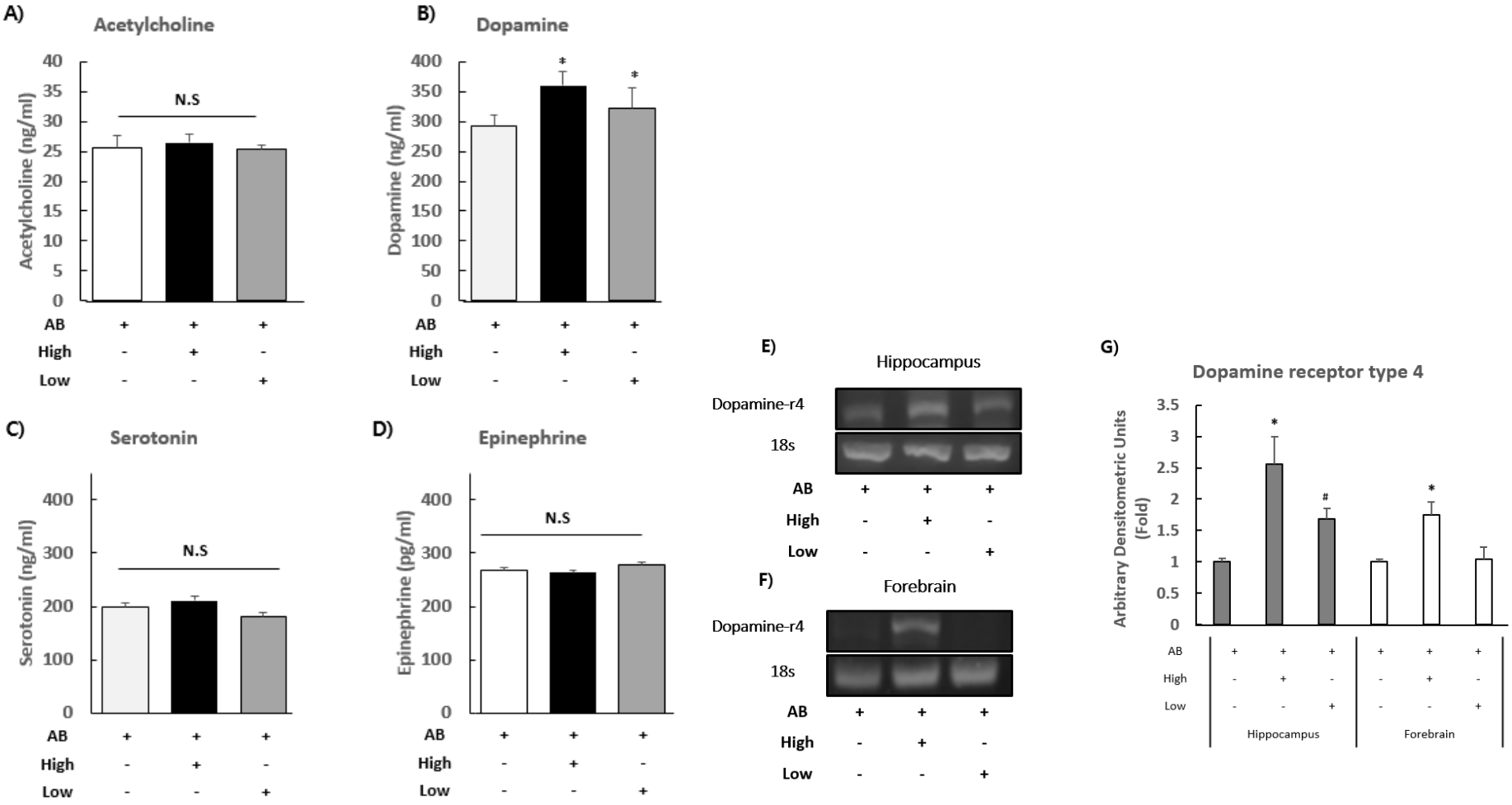
Therapeutic efficacy of repetitive transcranial magnetic stimulation in an animal model of Alzheimer's disease



Experimental schematic and amyloid beta induced animal behavior test

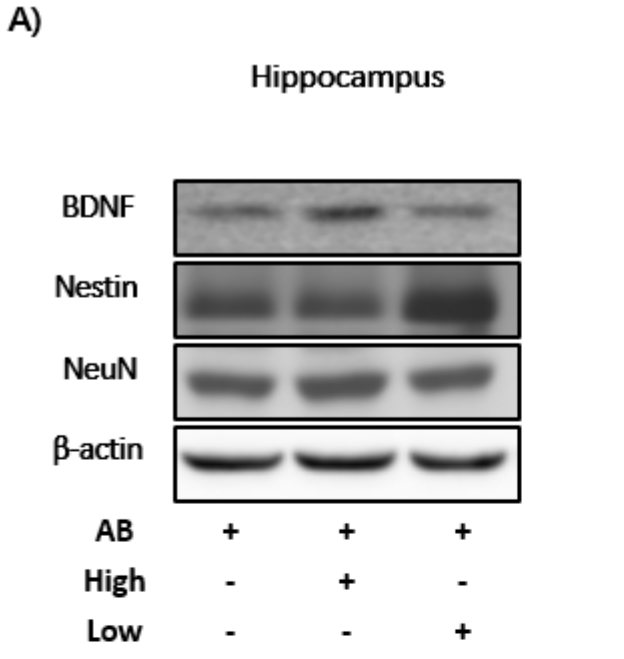


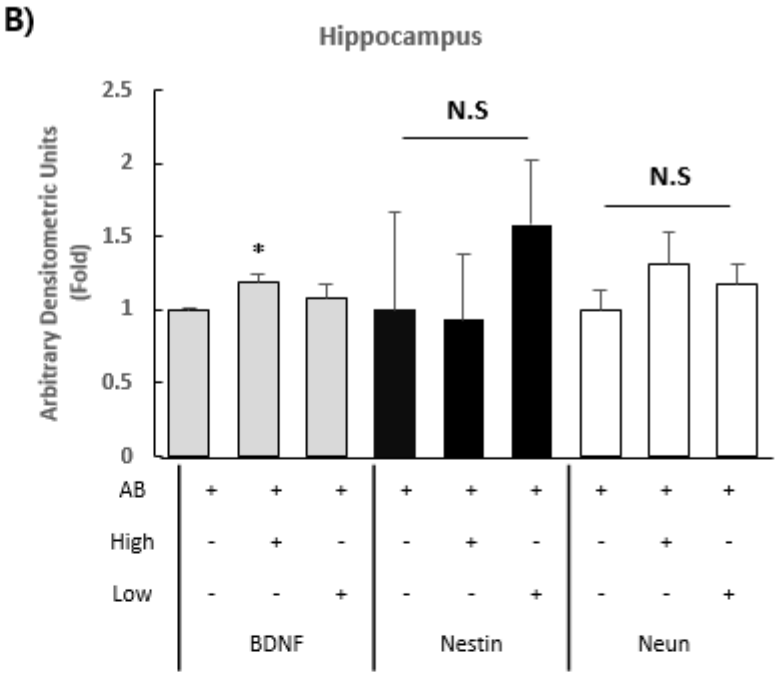
Amyloid beta induced animal behavior test

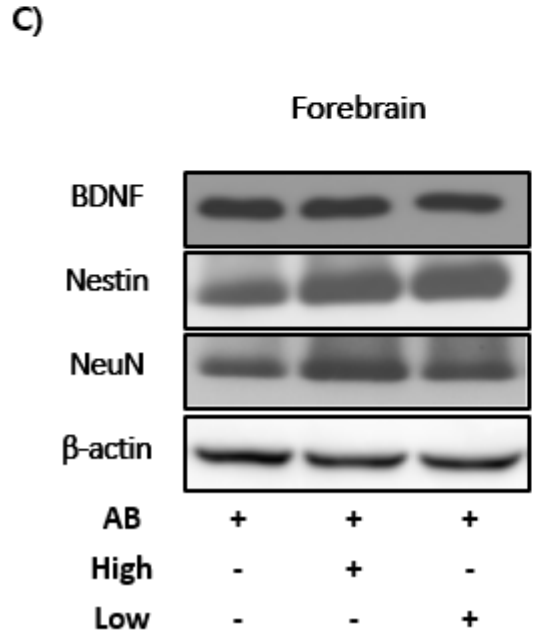


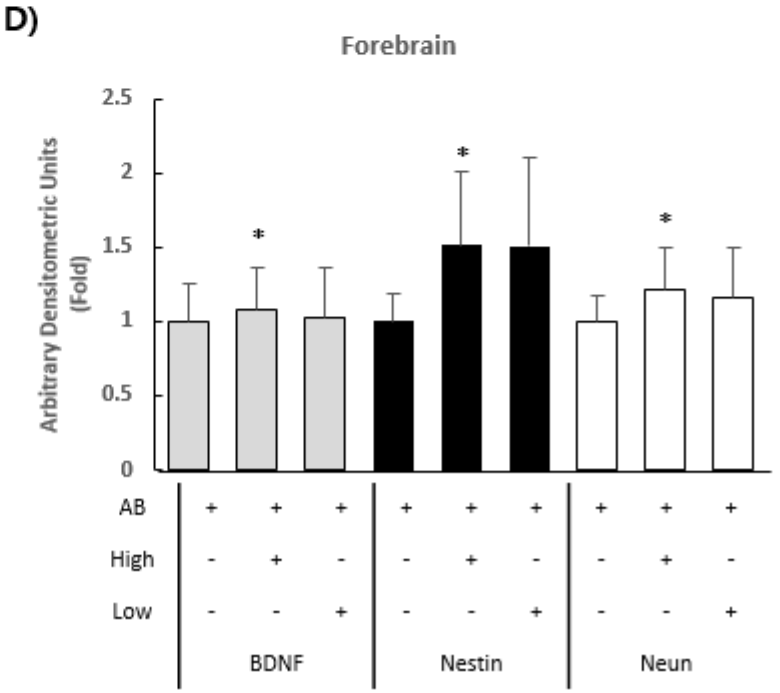
rTMS regulate neurotransmitter in amyloid beta induced mice hippocampus through dopamine receptor type 4.

rTMS increased neuro-signaling markers in amyloid beta induced mice

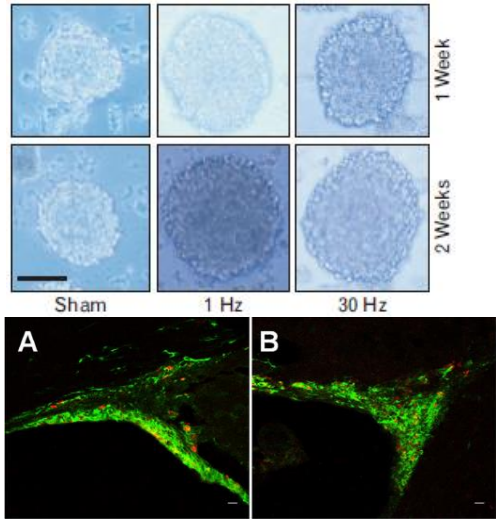








뇌졸중 동물모델에서 rTMS와 Hepatocyte growth factor를 이용한 융합치료법의 개발



In vitro 연구

신경줄기세포- OGD

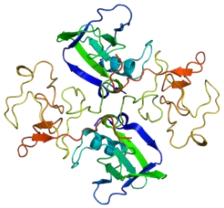
rTMS, HGF를 투여하여

Western blot, qPCR 확인

MCAO

∞

rTMS



HGF

In vivo 연구

MCAO SD rat

rTMS, HGF를 투여하여

Western blot, qPCR 확인

행동분석

임 상 시 험 계 획 서 Ver 4.0

뇌졸중 후 혈관성 인지 장애자에서 반복적 경두개 자기자극술이 우울증 및 인지기능에 미치는 효과를 평가하기 위한 임상시험

Clinical Trial for Evaluation of Effect after rTMS on Cognition and Depressive Mood in Post-Stroke Patient with Vascular Cognitive Impairment

임상시험계획서 번호	:
버전(작성일)	: 4.0
이전 버전(작성일)	: NA
임상시험단계	: 의료기기 임상시험

Primary endpoint

1) K-MMSE (Korean-Mini Mental Status Examination) 변화
2) 우울증 여부 (GDS, Geriatric Depression Scale) 변화

Secondary endpoint

1) MoCA (Montreal Cognitive Assessment) 변화
2) K-WAIS-IV (Korean Wechsler adult intelligence scale-IV) 변화
3) Rey-Kim 검사상 MQ(Memory Quotient)의 변화
4) GDS (Global Deterioration Scale) 변화
5) CDR (Clinical Dementia Rating, 임상치매척도) 변화
6) S-IADL (Seoul Instrumental Activities of Daily Living
7) MRC (Medical research council) scale변화
8) MFT (Manual Function Test) 변화
9) FMA (Fugl-Meyer Assessment) 변화
10) MBI (Modified Barthel index) 변화
11) BBS (Berg Balance Scale) 변화
12) TIS (Trunk Imbalance Scale) 변화
13) SSQoL (Stroke Specific Quality of Life Scale) 변화
14) 초기검사 대비 Imaging의 변화 (Brain fMRI)


Thank you for listening