Transcranial Magnetic Stimulation for Mild Cognitive Impairment and Alzheimer's Disease

Ying-hui Chou
Associate Professor of Psychology
Arizona Center on Aging, Evelyn F. McKnight Brain Institute
University of Arizona

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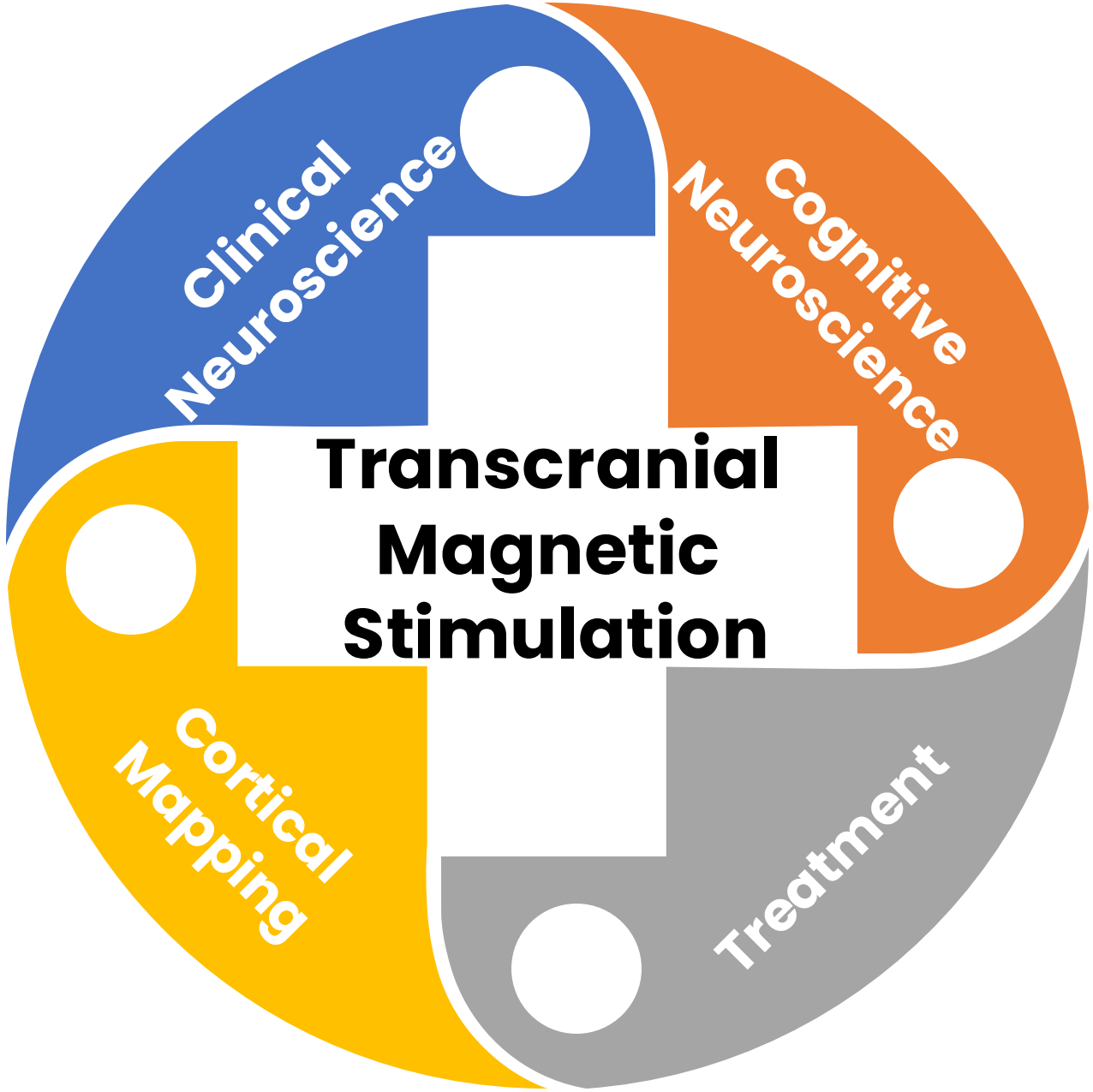
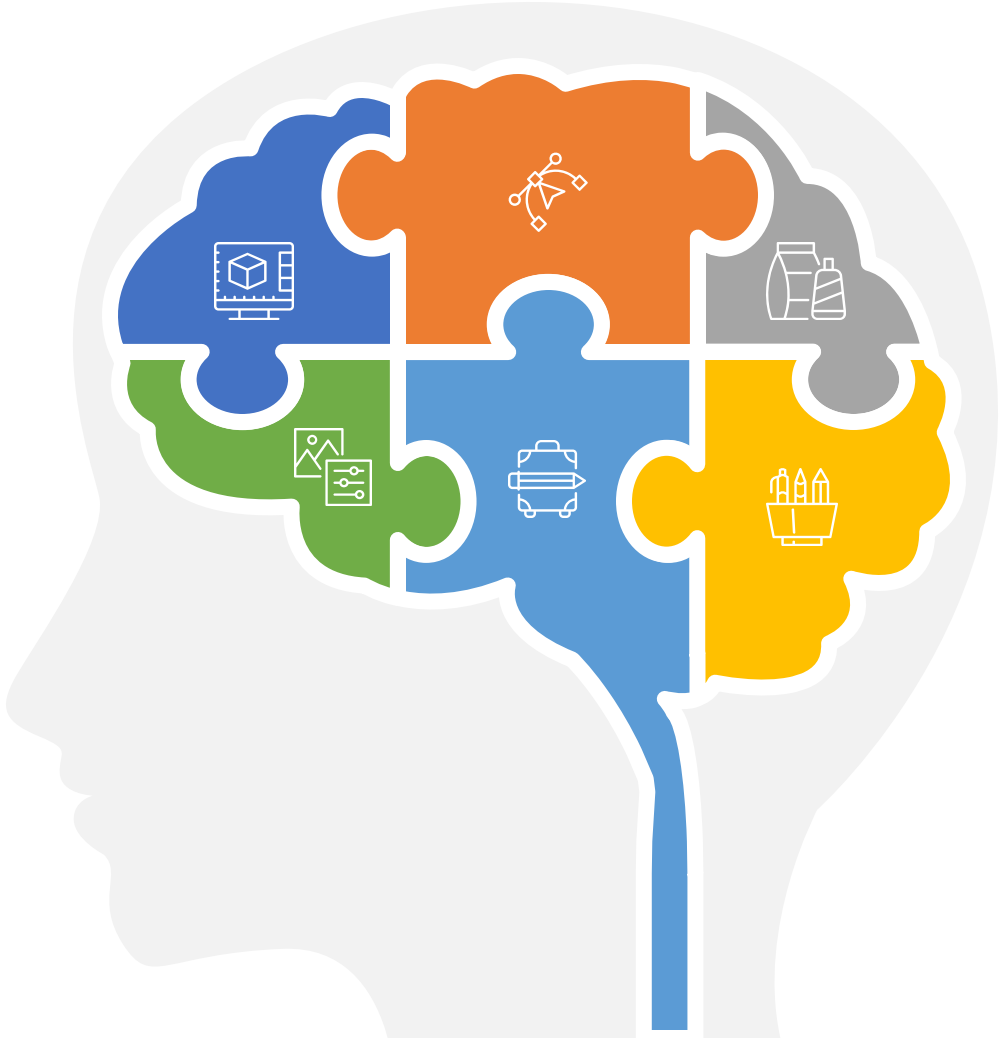


Photo credit: Yu-Chin Chen, Lisbeth Haahein and Lisbeth's Dad

TMS

MRI

EEG



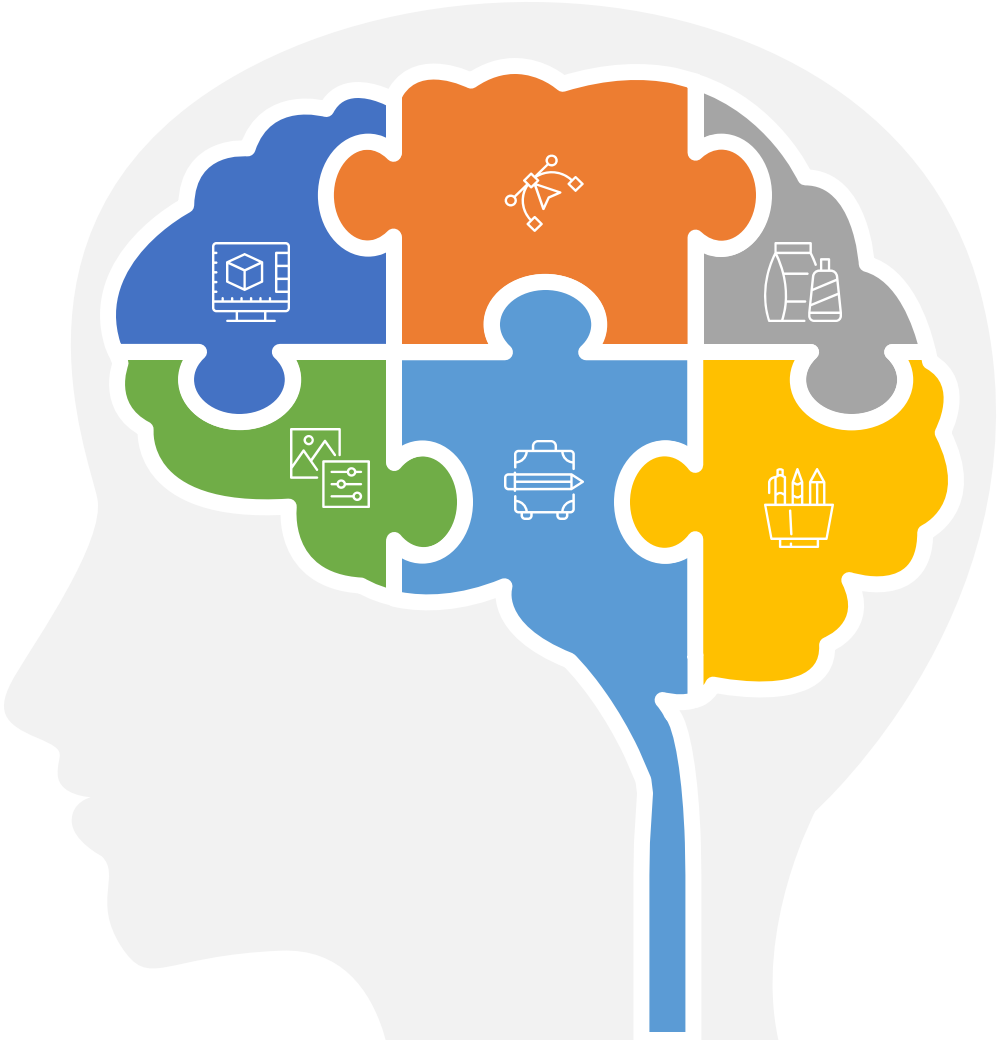
EMG

Behavioral Measures

Plasma AD Biomarkers

- **Identify MRI- and TMS-based markers to enable early identification of AD and predict therapeutic outcomes**

- **Develop therapeutic TMS protocols for memory enhancement in mild cognitive impairment (MCI)**



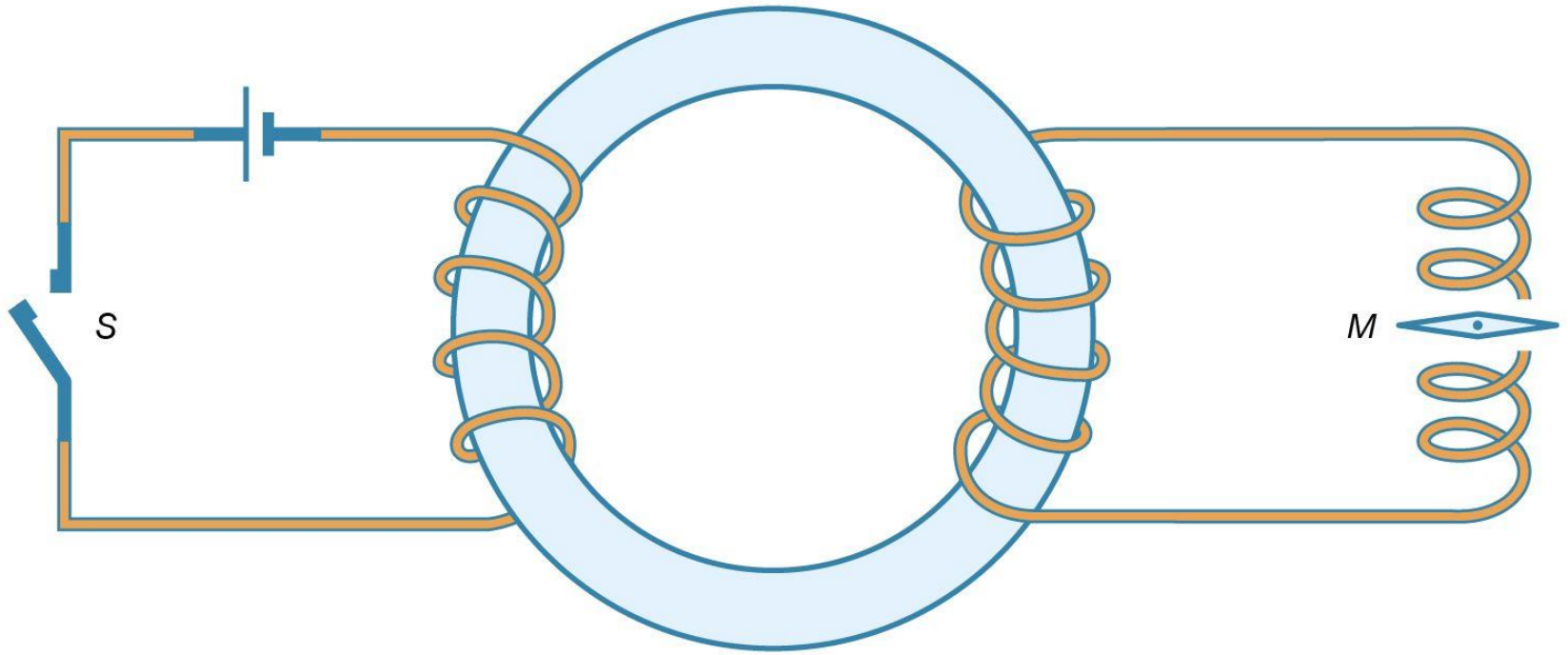
Introducing TMS

TMS-based Assessment

Therapeutic TMS

INTRODUCING TMS

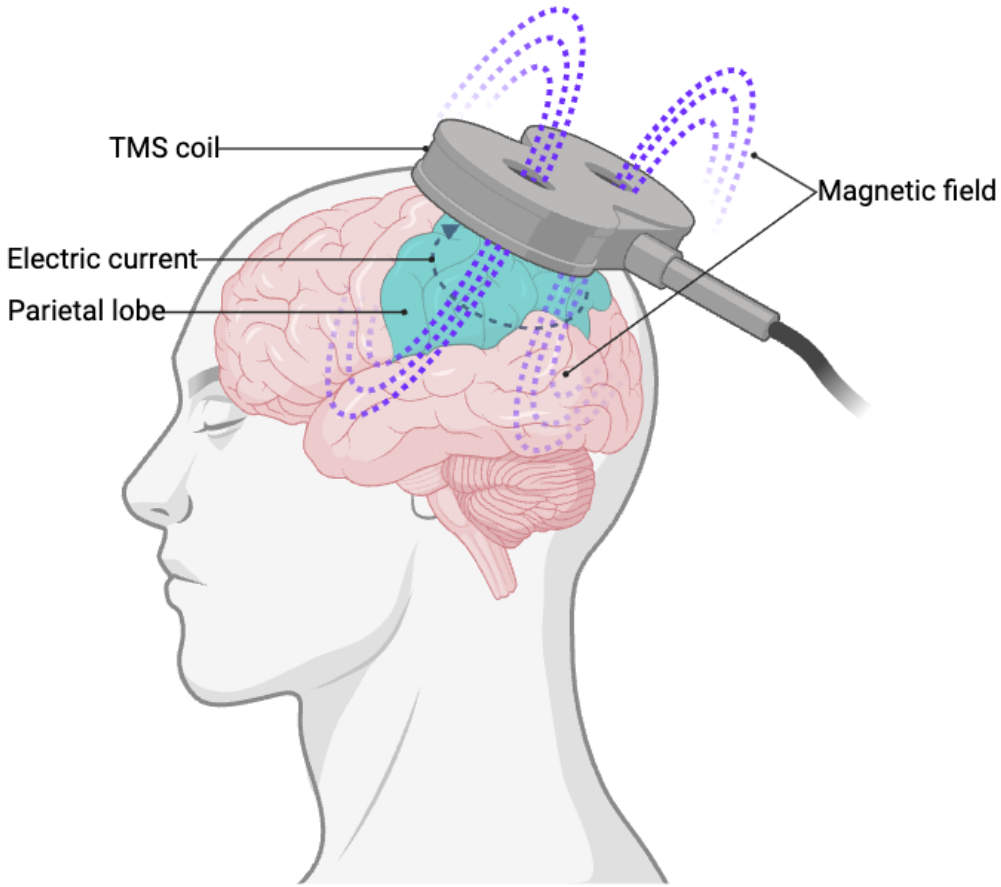
- TMS operates based on Faraday's electromagnetic induction principle
- A changing electric field will produce a magnetic field, and vice versa



1. TMS coil – Acts as a Magnetic Field Generator

2. Creates an intense magnetic field ranging from 0.5 to 3 Tesla, penetrating the skull to reach brain tissues

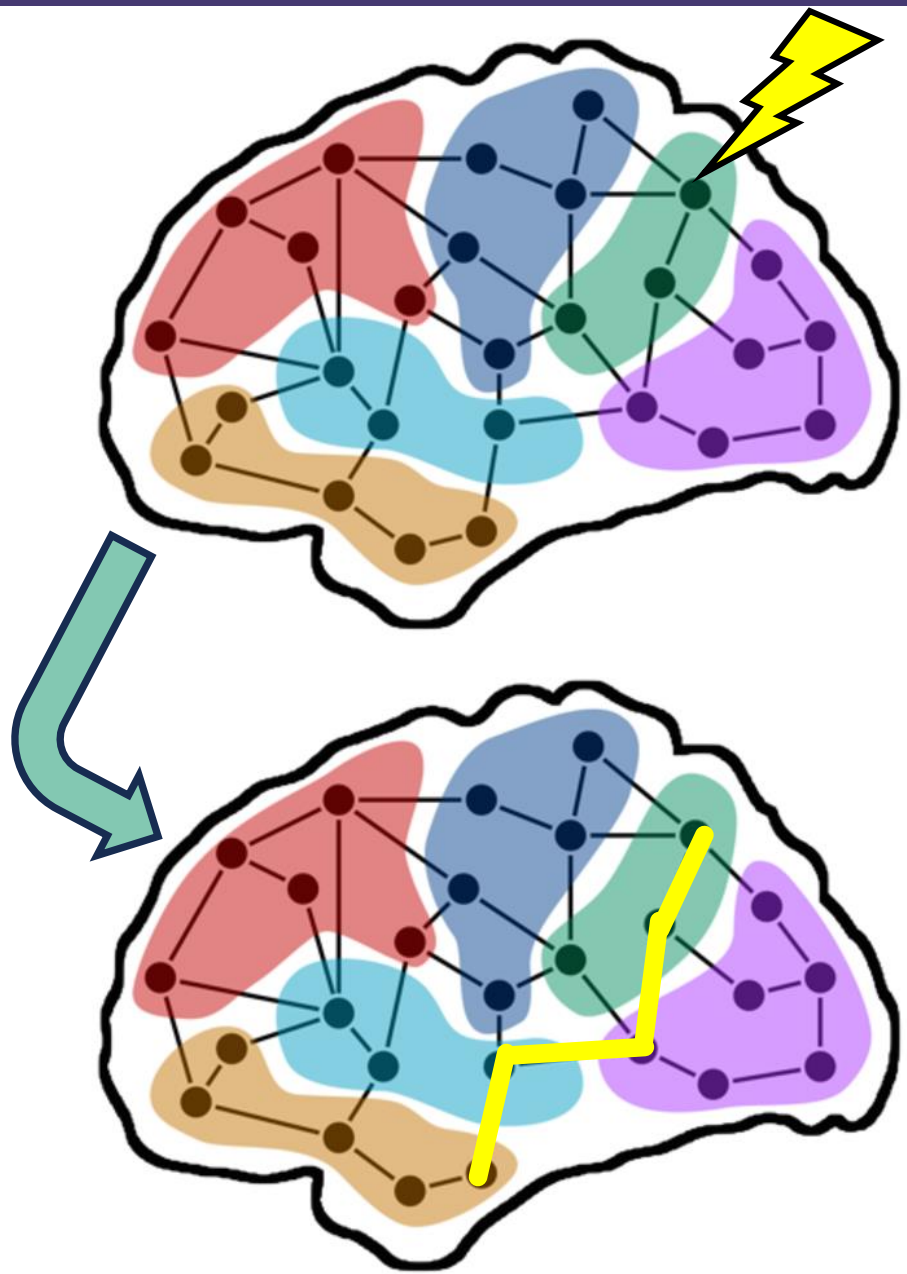
3. Induces a secondary electric field within the brain's conductive tissues



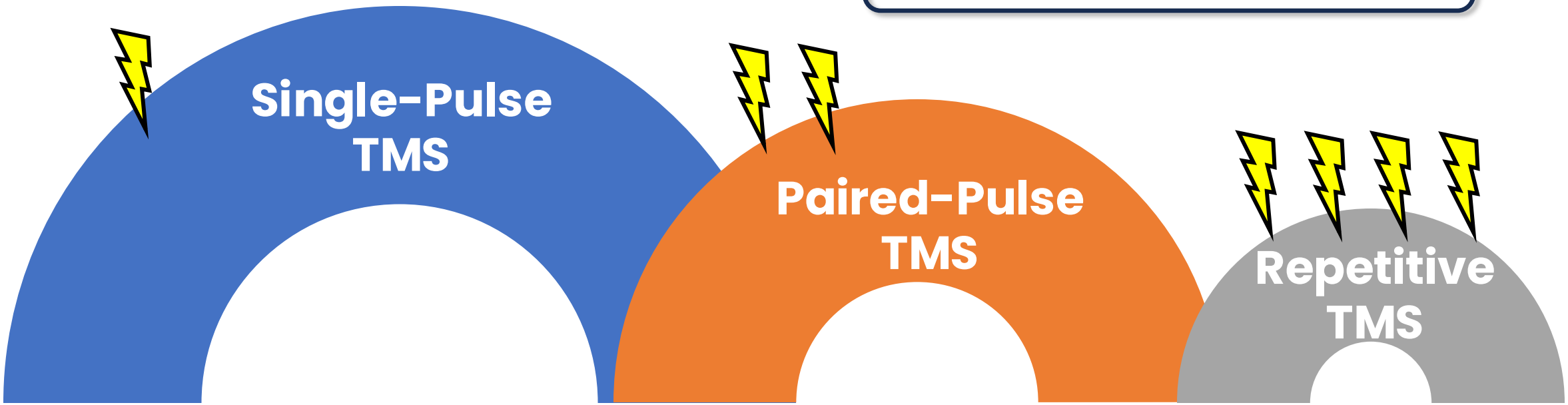
Illustrated by Chen (2023)

4. Triggers depolarization or hyperpolarization of neurons in the stimulated region

5. Initiates the spread of neural signals through networks of connected pathways



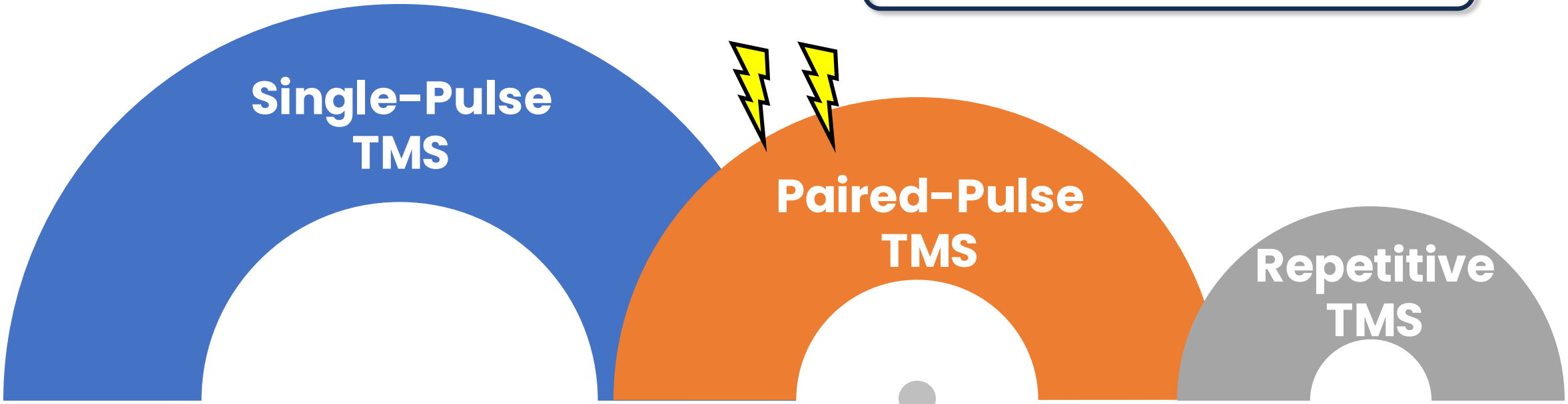
TMS PROTOCOLS



TMS PROTOCOLS

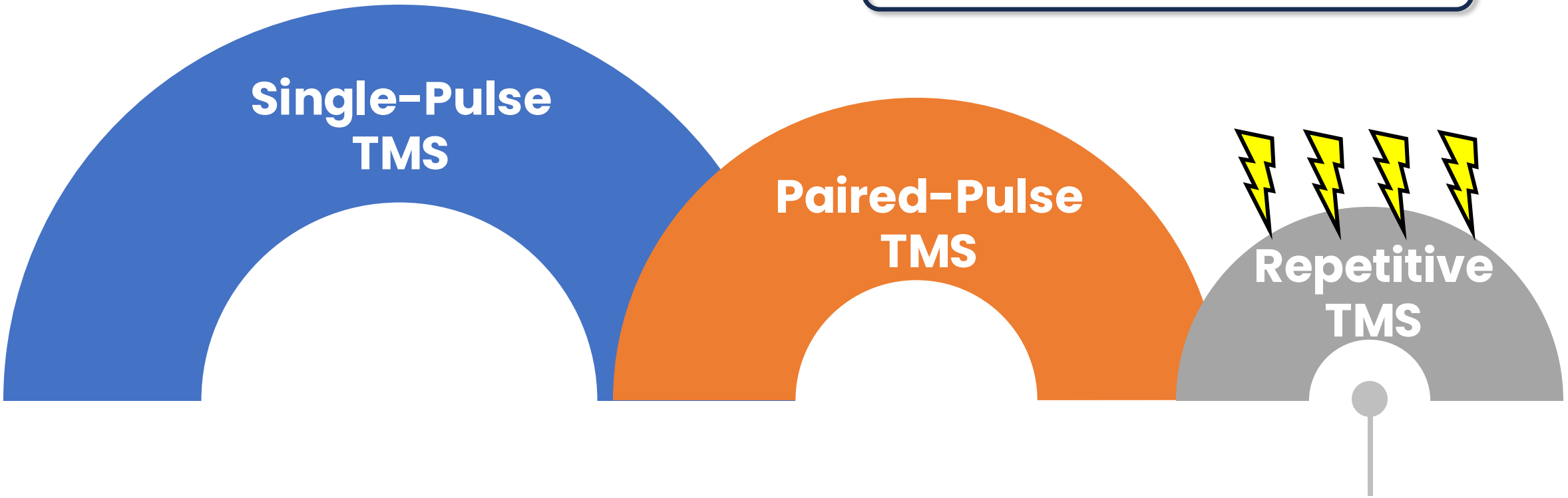
- Assesses Cortical Excitability and Brain-Behavior Relationships
- Utilized for Cortical Mapping

TMS PROTOCOLS



- Comprises a Conditioning and a Test Stimulus
- Measures Intracortical Facilitation/Inhibition
- Assesses Cholinergic Function

TMS PROTOCOLS



- High-frequency rTMS (> 1 Hz) typically has an excitatory effect
- Low-frequency rTMS (≤ 1 Hz) commonly exhibits inhibitory properties
- Investigates neural plasticity potential and applied in therapeutic contexts

TMS-BASED ASSESSMENT

	Protocol	Descrption	Physiology
Cortical Excitability	**Single-pulse TMS**	Minimum level of intensity required to produce a defined response	Conductivity of sodium channels
Cholinergic Function	**Paired-pulse TMS**	Paired-pulse TMS with ISI = 20-25 ms	Cholinergic circuits
Plasticity Potential	**Repetitive TMS**	EMG, fMRI, and EEG before and after rTMS	LTP-like or LTD-like plasticity

Badawy et al., 2012

Introducing TMS | TMS-based Assessment | Therapeutic TMS

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Review

Cortical excitability and plasticity in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis of transcranial magnetic stimulation studies

Ying-hui Chou [a,b,*], Mark Sundmana [a], Viet Ton That [a], Jacob Greena [a], Chrisopher Trapani [a]

[a] Brain Imaging and TMS Laboratory, Department of Psychology, University of Arizona, Tucson, USA
[b] Evelyn F McKnight Brain Institute, Arizona Center on Aging, and BIO5 Institute, University of Arizona, Tucson, USA

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique. When stimulation is applied over the primary motor cortex and coupled with electromyography measures, TMS can probe functions of cortical excitability and plasticity in vivo. The purpose of this meta-analysis is to evaluate the utility of TMS-derived measures for differentiating patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) from cognitively normal older adults (CN).

Methods: Databases searched included PubMed, Embase, APA PsycInfo, Medline, and CINAHL Plus from inception to July 2021.

Results: Sixty-one studies with a total of 2728 participants (1454 patients with AD, 163 patients with MCI, and 1111 CN) were included. Patients with AD showed significantly higher cortical excitability, lower cortical inhibition, and impaired cortical plasticity compared to the CN cohorts. Patients with MCI exhibited increased cortical excitability and reduced plasticity compared to the CN cohort. Additionally, lower cognitive performance was significantly associated with higher cortical excitability and lower inhibition. No seizure events due to TMS were reported, and the mild adverse response rate is approximately 3/1000 (i.e., 9/2728).

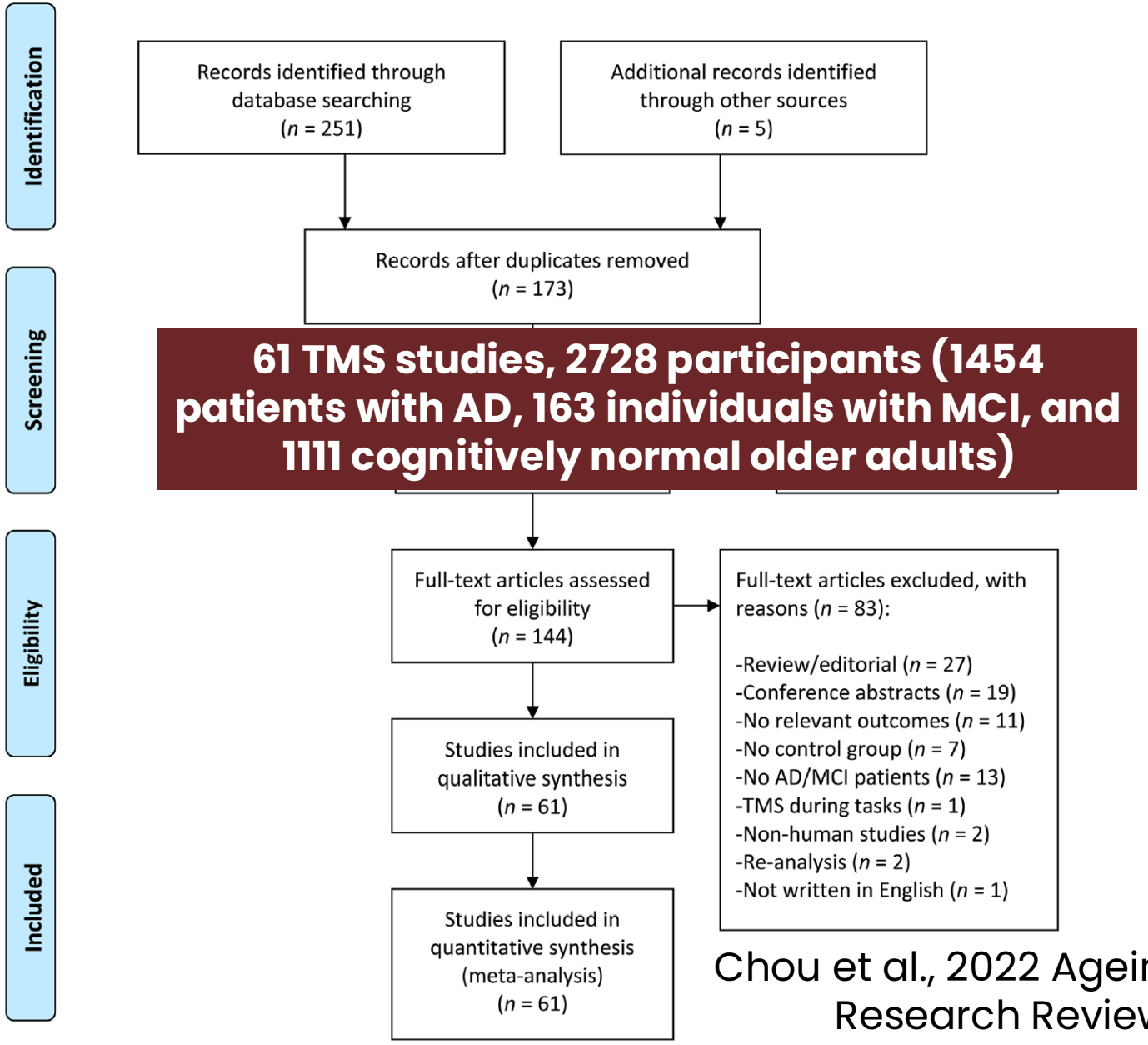
Conclusions: Findings of our meta-analysis demonstrate the potential of using TMS-derived cortical excitability and plasticity measures as diagnostic biomarkers and therapeutic targets for AD and MCI.

1. Intorduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that causes a continuous decline in memory, thinking and behavioral skills which ultimately disrupts a person's ability to function independently. The disease was traditionally defined by and diagnosed according to this relatively heterogenous clinical phenotype. During the past few years, however, there has been a shift to define AD biologically by neuropathological changes or biomarkers, including ß-amyloid deposition (A), pathologic tau (T), and neurodegeneration (N) based on the 2018 NIA-AA Research Framework (Jack et al., 2018). In this new NIA-AA framework, the hallmark cognitive symptoms of the disease do not factor into the initial diagnosis of AD, but are instead incorporated for staging the clinical severity of AD.

This paradigm shift towards a biological definition of AD coincides with recent advances in research indicating that the pathological onset of the disease can precede the clinical manifestation of AD by many years (Dubois et al., 2016). This extended preclinical phase may hold particular significance for disease modification, as potential therapies are likely to be most effective in the early, asymptomatic stages of AD. As such, it is important to identify useful and reliable biomarkers that can be used as leading indicators of disease to identify potential cases of preclinical AD before the neurodegenerative disease becomes medically refractory. Therefore, novel biomarkers that can be used to characterize the complementary pathophysiological features within the amyloid-tau-neurodegeneration (ATN) Research Framework (Jack et al., 2018) are urgently needed.

Transcranial magnetic stimulation (TMS) is a versatile non-invasive brain stimulation tool that may have utility in this respect. TMS applies electromagnetic pulses to the brain with a coil that is carefully placed on the surface of the scalp over a targeted stimulation site (Barker et al., 1985). TMS leverages Faraday's law of electromagnetic induction



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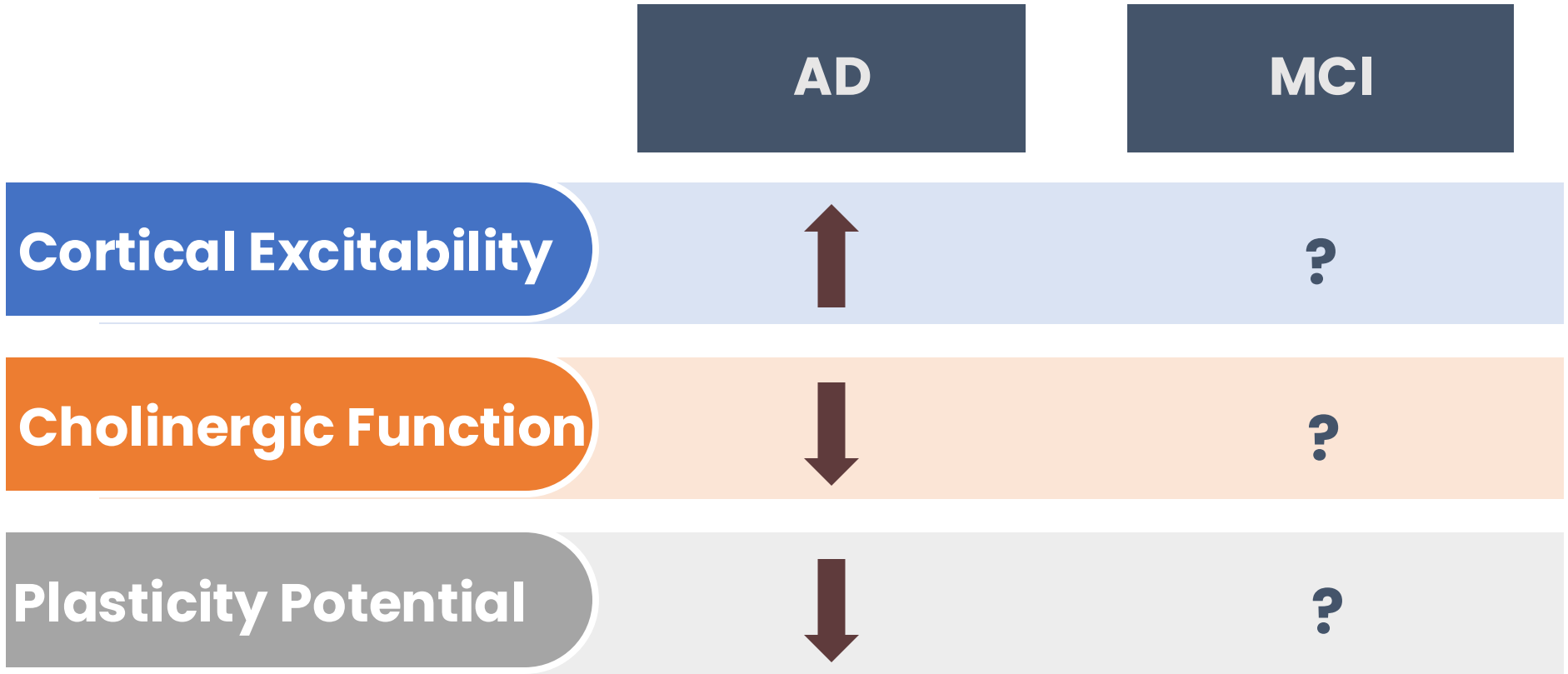

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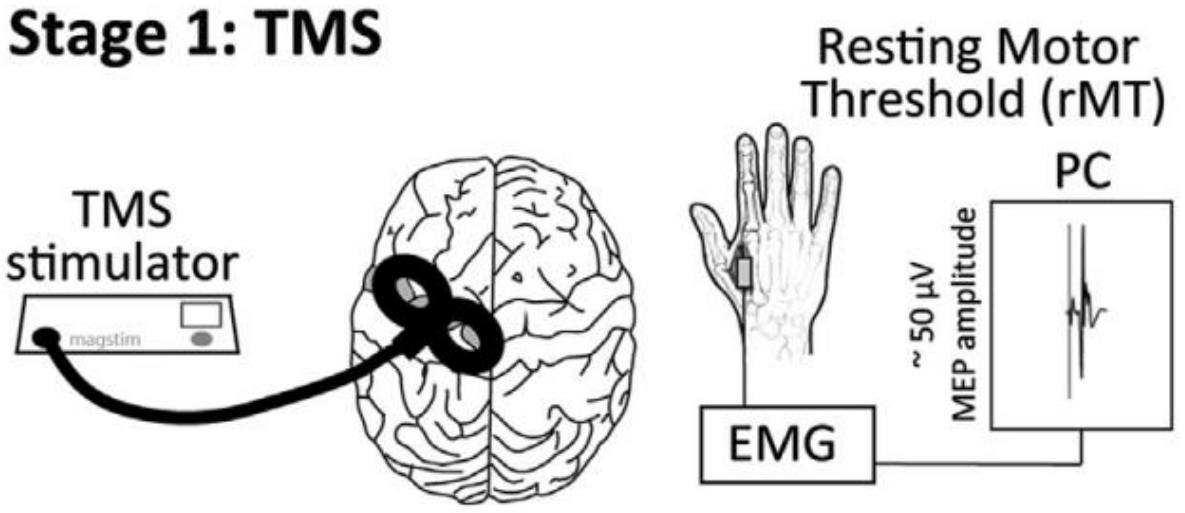

Labruna et al., 2023

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Letter to the editor

The (hyper)excitable brain: what can a ubiquitous TMS measure reveal about cognitive aging?

Dear Editor,

In their insightful work, Zadey et al. (2021) undertook a discerning re-examination of auxiliary resting motor threshold (rMT) data from previous Transcranial Magnetic Stimulation (TMS) trials encompassing a cognitively normal control group (n = 26), a discovery AD cohort (n = 22), and a larger validation Alzheimer's disease (AD) cohort (n = 129). Despite its well-described physiological relevance, rMT data are commonly overlooked as a constituent element of subsequent TMS protocols given its essential function as a calibration parameter for the determination of individualized TMS intensity. The obligatory ubiquity of this parameter has generated a sizeable cache of rMT data, and the authors have leveraged this underutilized data to establish a consistent finding across both their discovery and validation cohorts. Specifically, global cognitive dysfunction was significantly associated with reduced rMT, which reflects increased cortical excitability. This finding was exclusive to AD patients and was particularly robust in relation to memory impairment. Zadey et al.'s work serves as a compelling prompt for fellow researchers to similarly examine repositories of previously untapped rMT data to reveal insights into the neurobiological features of cognitive aging. In this short communication, we will briefly (1) contextualize their findings in the broader body of literature; (2) illuminate the neural components interrogated by rMT; and (3) share corroborative findings from our own data.

Though the primary motor cortex (M1) is not characteristically involved in the pathophysiology of AD, the findings reported by Zadey and colleagues fit into a mature corpus of M1-TMS literature that characterizes aberrant cortical excitability in the AD continuum. We recently published a meta-analysis comprising 2728 individuals, in which we reported that a wide array of single- and paired-pulse M1-TMS measures reflect hyperexcitability in AD (Chou et al., 2022). Specific to rMT, this parameter was significantly reduced both in patients with probable AD (effect size d = 1.05, p < 0.0001) and mild cognitive impairment (MCI) (effect size d = 0.39, p < 0.005) (Chou et al., 2022). Notably, however, the majority of reports among the 56 studies that reported rMT included the data as an ancillary measure (Chou et al., 2022). Zadey et al.'s work stands out for its deeper, more intentional examination of rMT data.

rMT is the minimum TMS intensity necessary to elicit a twitch in a targeted muscle at rest, which is operationally defined as a motor evoked electromyographic potential ≥ 50 µV in at least 50% of trials. Foundational work from Di Lazzaro and colleagues evaluated TMS-evoked descending volleys in patients with chronically implanted epidural electrodes to elucidate the cortical elements targeted by TMS stimuli. In sharp contrast to electrical stimulation that directly stimulate pyramidal tract axons, they concluded that peri-threshold TMS stimuli *indirectly* activate pyramidal tract neurons via synaptic inputs (Di Lazzaro et al., 2004). More specifically, subsequent investigations reached the consensus that inhibitory interneurons and presynaptic terminals are the cortical elements with the lowest threshold for TMS stimuli (Siebner et al., 2022; Spampinato et al., 2023). The cumulative input from these cortical elements can transynaptically depolarize pyramidal tract neurons, which propagates to evoke a motor response. When controlling for anatomical factors (e.g., skull thickness, cortical atrophy, etc.), a reduction in rMT implies a lowered energy requirement to transynaptically depolarize pyramidal tract neurons and reflects increased cortical excitability. Further delineating the neurobiological foundation of rMT, converging lines of evidence suggest that the parameter is an indirect proxy for neuronal membrane excitability. Pharmacologic-TMS data reveals that rMT is distinctly modulated by anti-epileptic drugs targeting voltage-gated sodium channels (VGSCs), which are crucial in regulating axonal excitability (Ziemann et al., 2015). Multiple trials report a dose-dependent relationship whereby rMT linearly increases with an increase in serum levels of lamotrigine, a VGSC antagonist designed to suppress neuronal membrane excitability (Tergau et al., 2003). Congruent with this inferred physiological relevance, rMT is notably insensitive to acute pharmacologic modulation of cortical excitability through drugs targeting gamma-aminobutyric acid-ergic signaling and neuromodulating neurotransmitter systems (e.g., dopamine, acetylcholine, etc.) (Paulus et al., 2008).

This proposed neurobiological underpinning of rMT is fitting in the context of AD, as neuronal hyperexcitability is a well characterized pathophysiological feature of the disease. While preclinical models report that hallmark AD pathology increases the density of VGSC expression (Wang et al., 2016), axonal hyperexcitability may also be derivative of unrelated pathophysiological changes. According to the size principle, for example, reduced neuronal cell sizes observed in AD could also increase excitability (Sosulina et al., 2021). Alternatively, other preclinical work suggests that metabolic deficits may be a causal factor leading to an increase in cortical excitability (Macauley et al., 2015). Though mechanistically nonspecific, neuronal hyperexcitability is also more crudely observed in clinical populations, where epileptiform activity is approximately ten times more common in AD than age-matched controls and reportedly corresponds with exacerbated cognitive dysfunction (Voglein et al., 2020). This is congruent with the findings of Zadey et al., as their

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal adults; GABA, gamma-aminobutyric acid; M1, primary motor cortex; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; NACC UDS, National Alzheimer's Coordinating Center Uniform Data Set; rMT, resting motor threshold; TMS, transcranial magnetic stimulation; VGSC, Voltage-Gated Sodium Channel

https://doi.org/10.1016/j.neurobiolaging.2023.09.007

Figure 1: rMT and Global Cognition

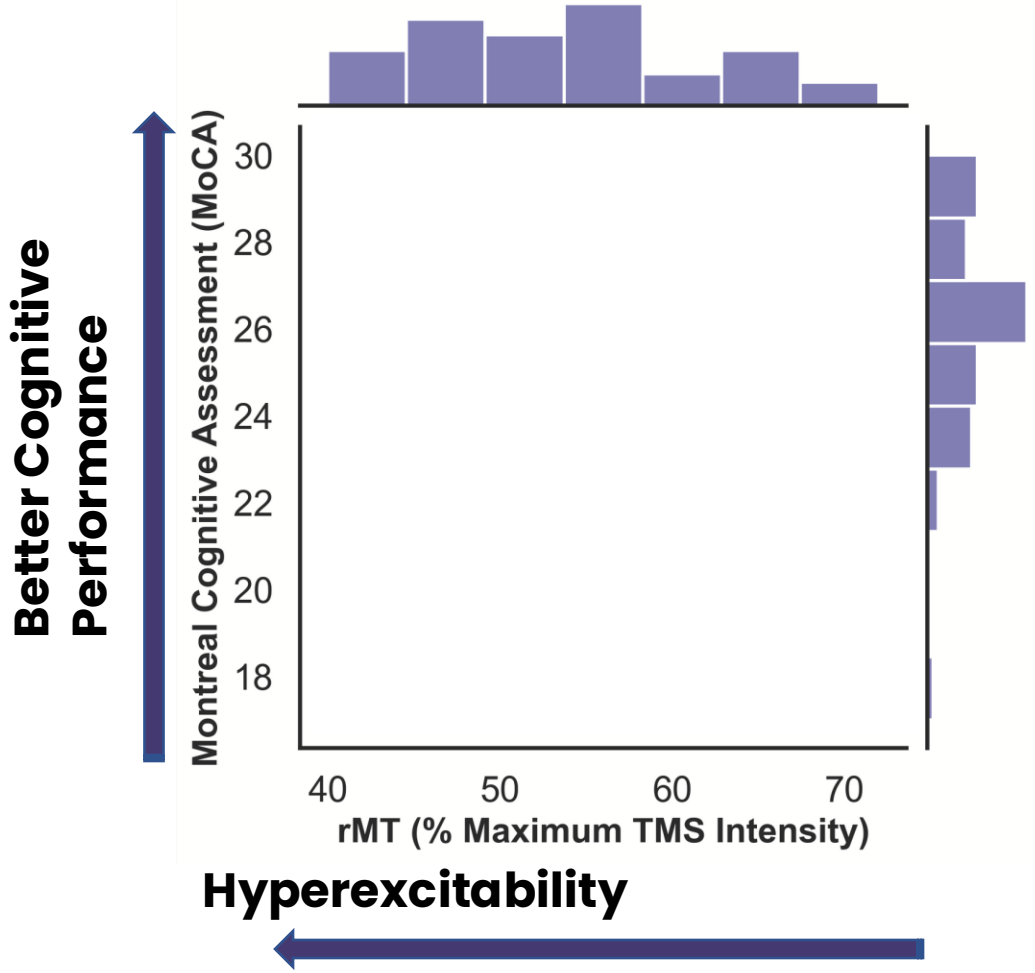
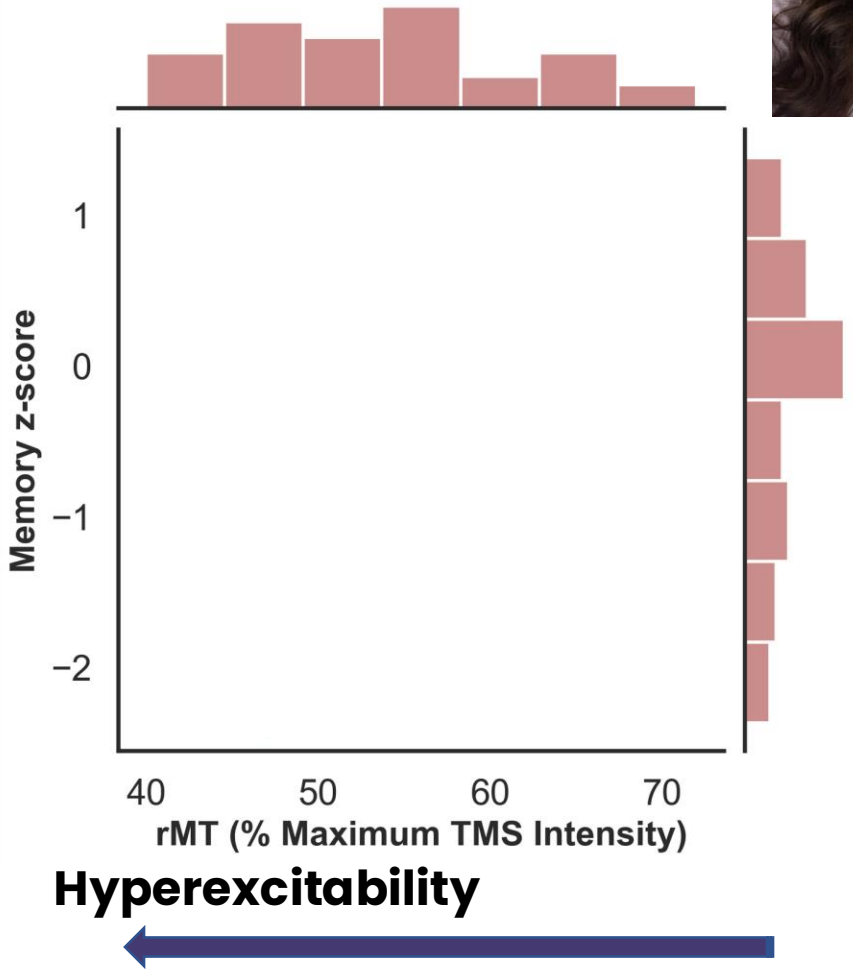


Figure 2: rMT and Memory



Sundman, Avila De Vault et al., 2023 Neurobiology of Aging

Figure 1: rMT and Global Cognition

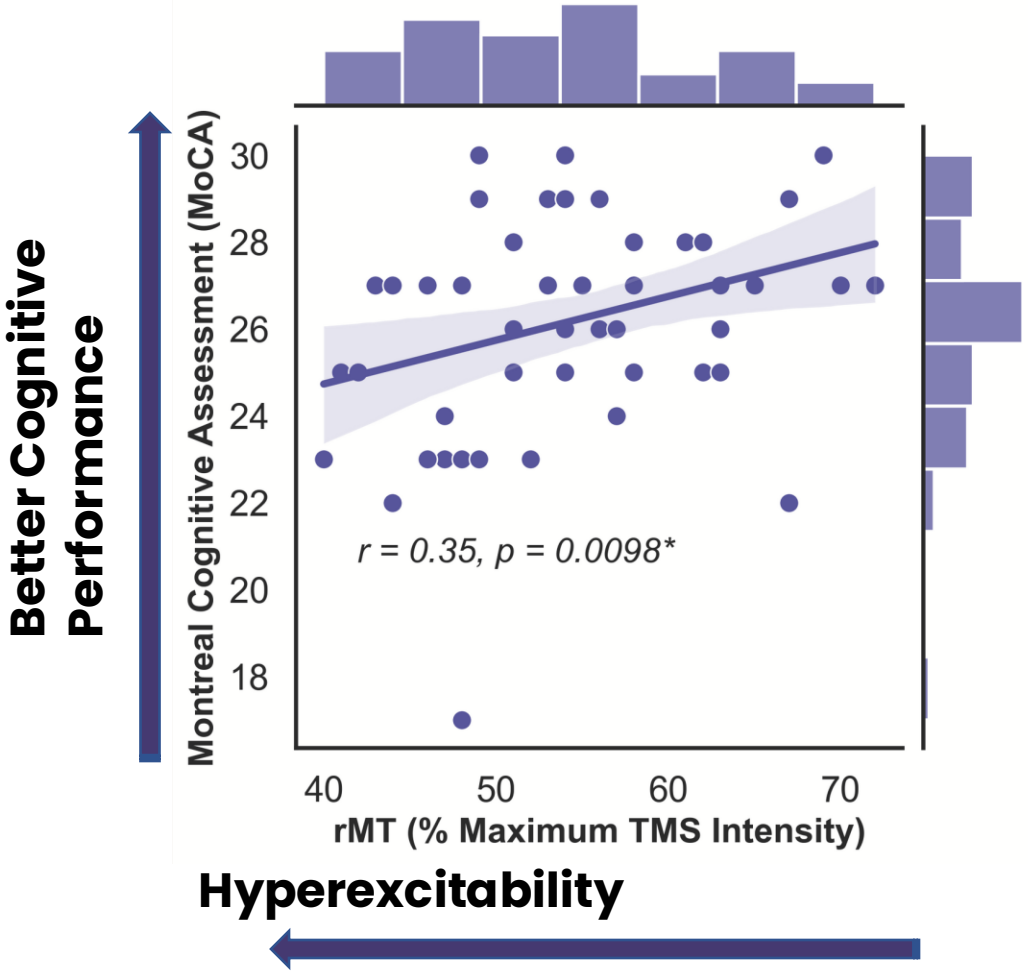
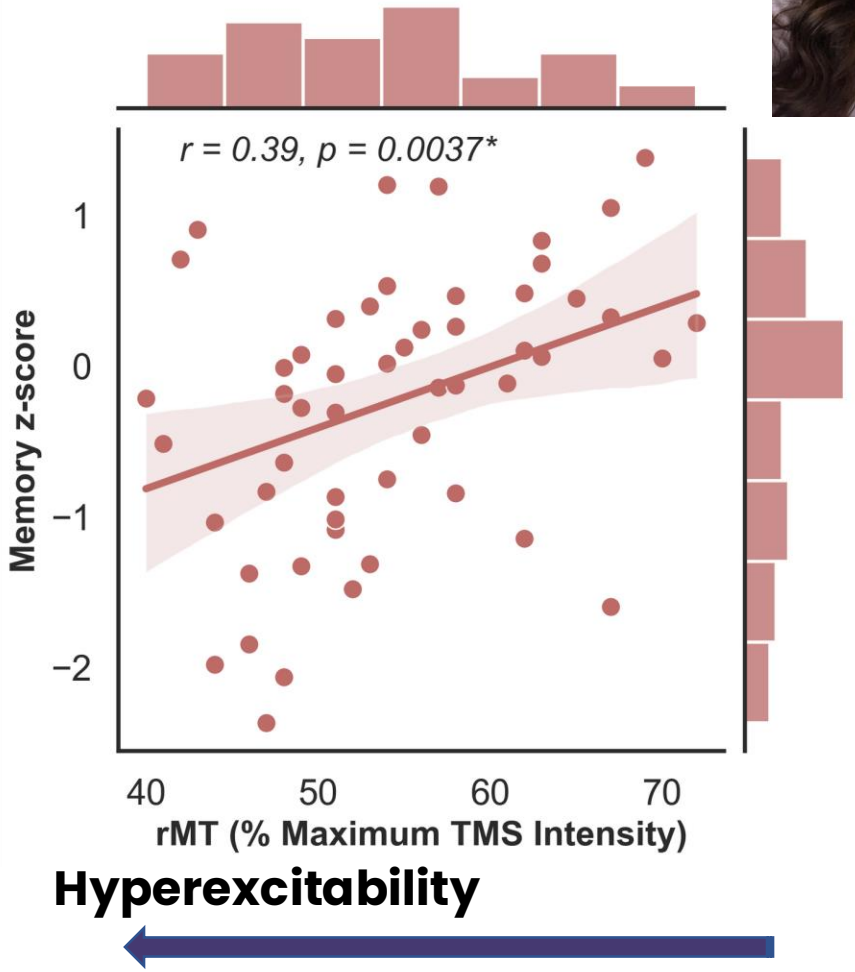


Figure 2: rMT and Memory



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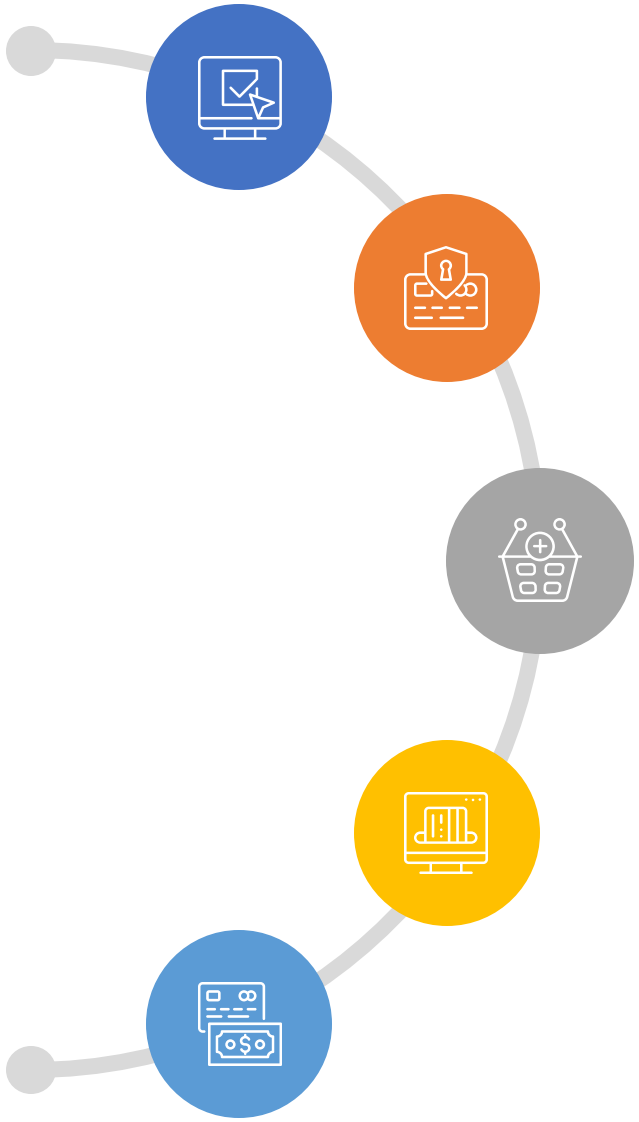
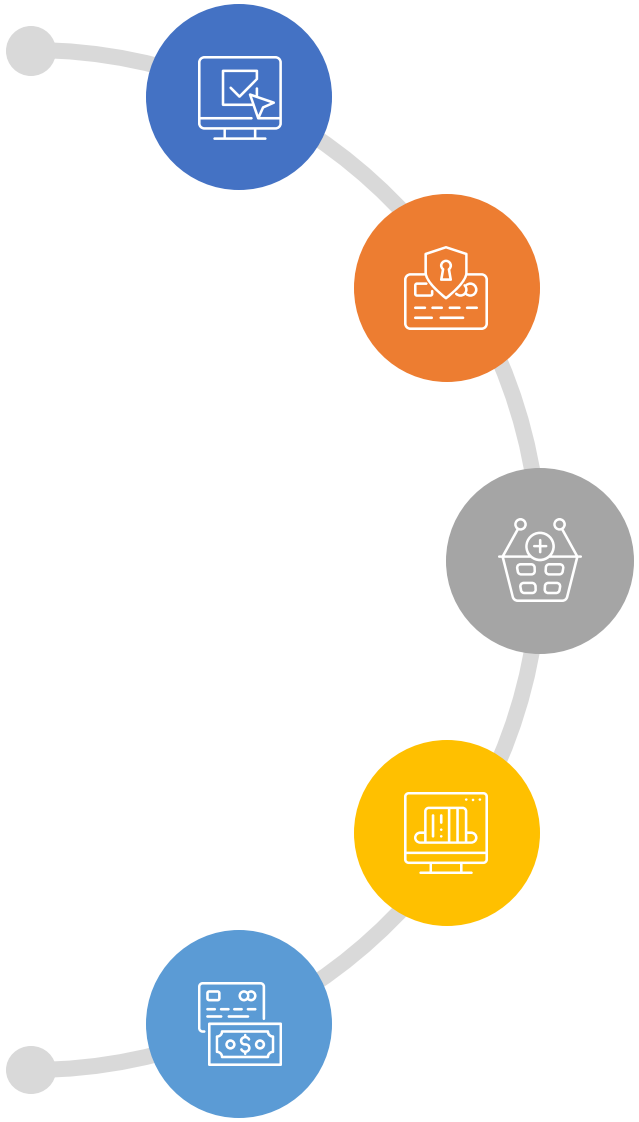
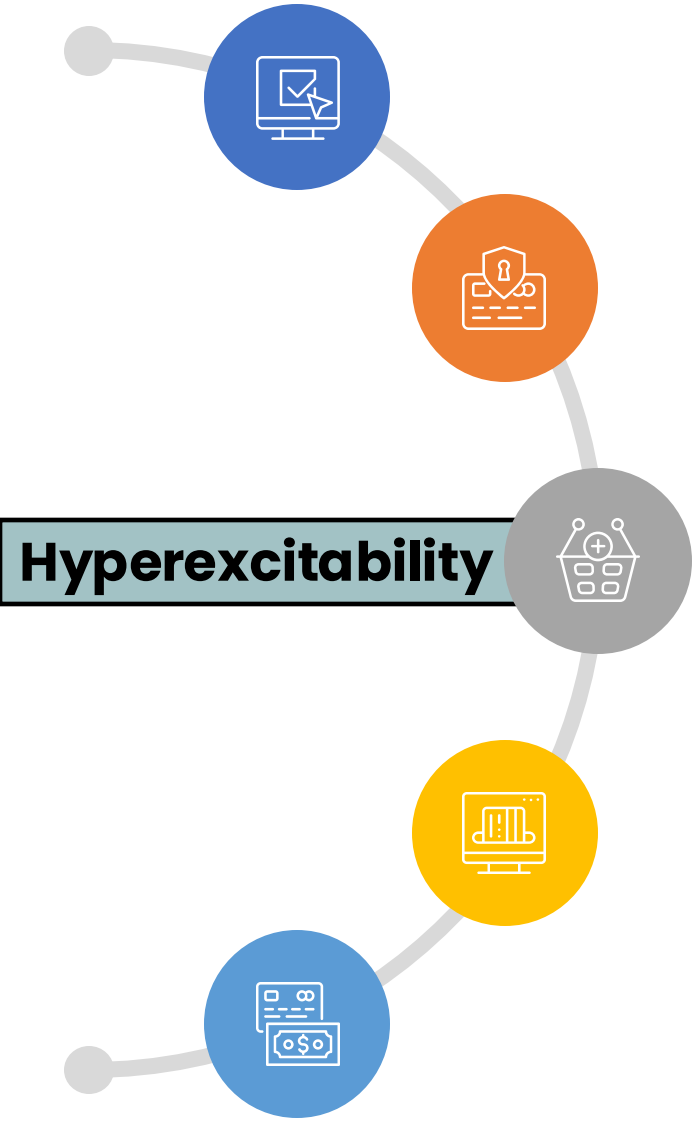


- Hyperexcitability is characterized by neurons' increased action potential frequency and lowered firing threshold (Anastacio et al., 2022)
- Detected in animal models before AD symptoms and pathology onset (Anastacio et al., 2022)



- Associated with memory deficits and global cognitive impairment (Sundman et al., 2023) and heightened seizure risk in later AD stages (Miranda et al., 2014)
- Controversy over whether hyperexcitability is a response to amyloid-beta deposits (Busche et al., 2020) or a precursor to AD pathology (Kazim et al., 2021)

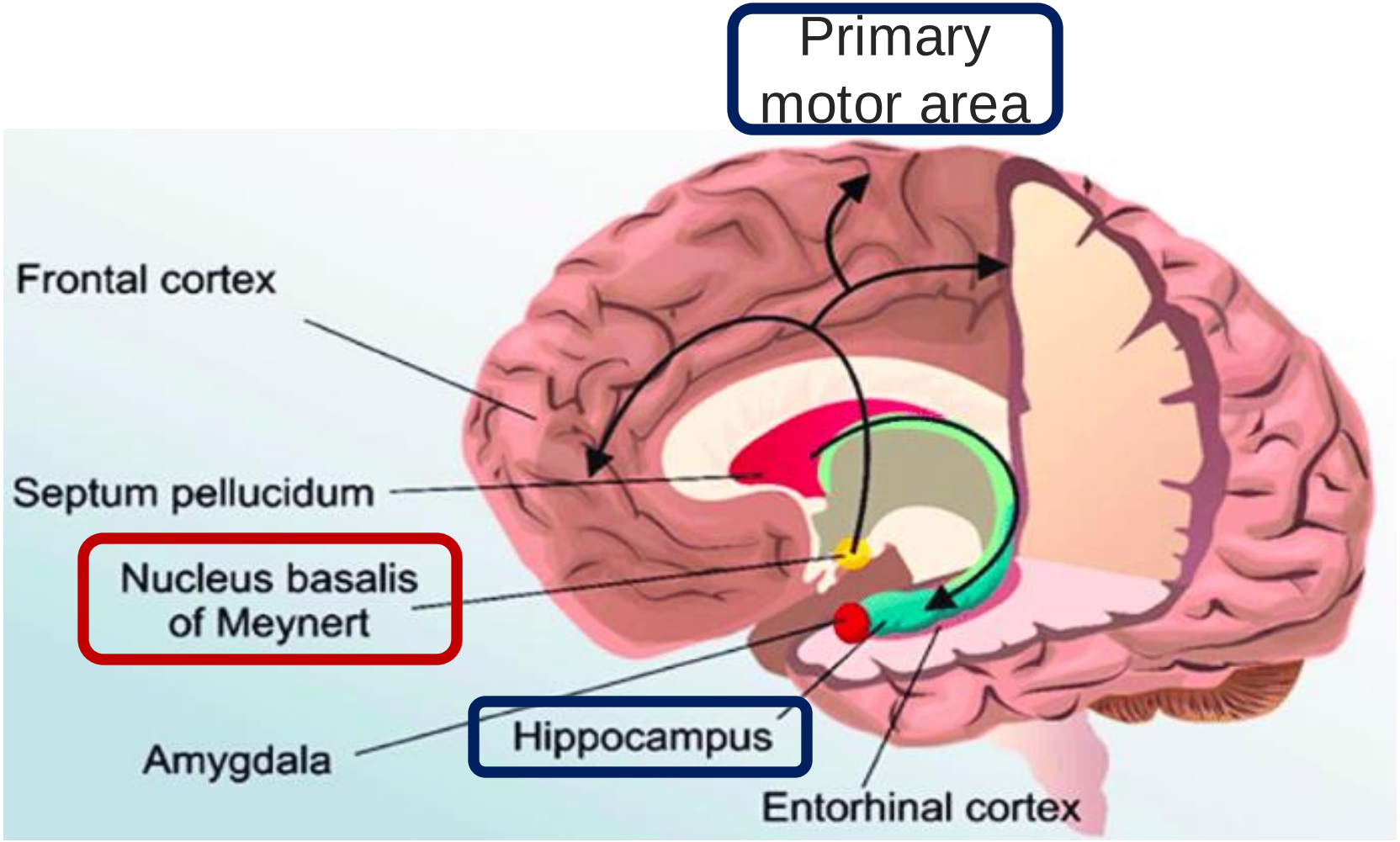


- **Treatments aimed at hyperexcitability show promise in reducing AD pathological markers and enhancing memory, highlighting its importance in AD research and therapy**

Cholinergic System and AD

- Cholinergic system's critical role in brain homeostasis, neural plasticity, and higher cognitive functions (Auerbach et al., 1996; Perry et al., 1999)
- Early cholinergic lesions in the basal forebrain, such as the Nucleus basalis of Meynert, play a significant role in AD cognitive decline (cholinergic hypothesis of AD)
- Cholinesterase inhibitor therapies have provided notable symptomatic improvement in patients with AD (Summers et al., 1986)
- Lack of reliable biomarkers for detecting cholinergic system deficits in AD's asymptomatic stages

The Nucleus Basalis of Meynert Pathway



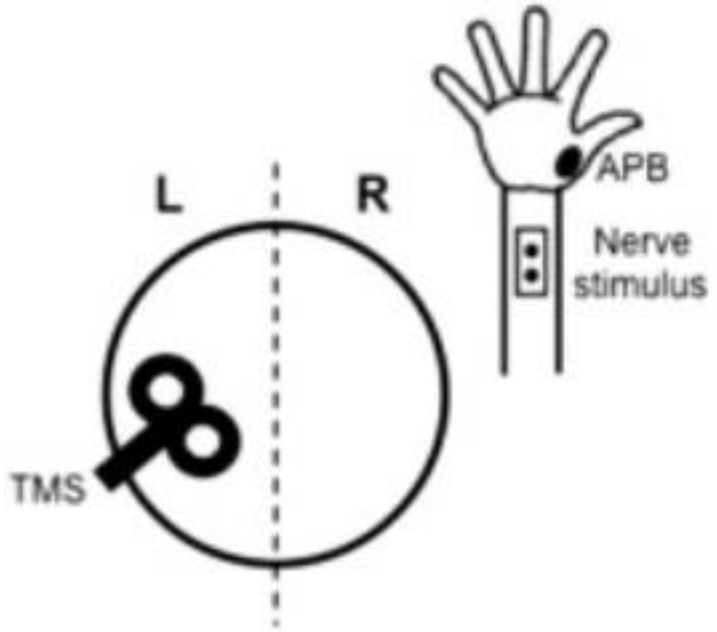
The nucleus basalis of Meynert (NBM) is a pivotal cholinergic center, projecting widespread innervation to the primary motor cortex and the hippocampus (Chen et al., 2023; Liu et al., 2015).

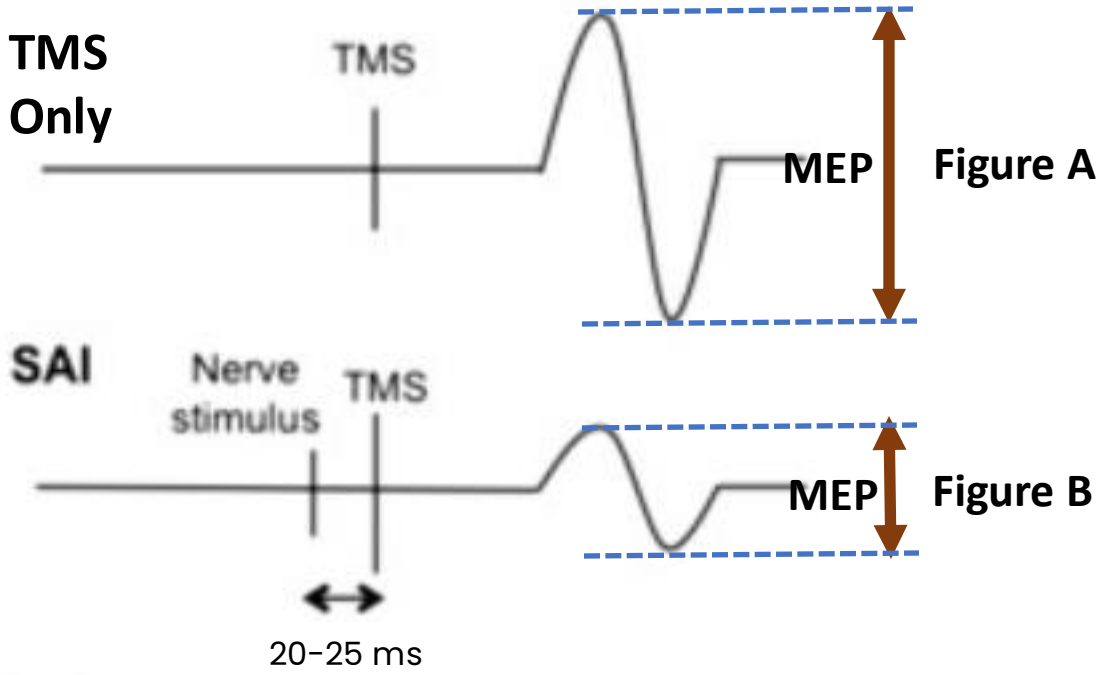
TMS and Cholinergic System

A specific paired-pulse TMS protocol, called Short-latency Afferent Inhibition (SAI), can be used to probe cholinergic function (Tokimura et al., 2000; Turco et al., 2018).

Short-Interval Afferent Inhibition (SAI)

- Peripheral median nerve stimulation is applied non-invasively 20-25 ms before a TMS pulse to the primary motor cortex
- The pre-stimulation leads to a suppression of the MEP
- The degree of MEP inhibition serves as an indicator of the functional integrity of central cholinergic pathways.





SAI and Cholinergic System

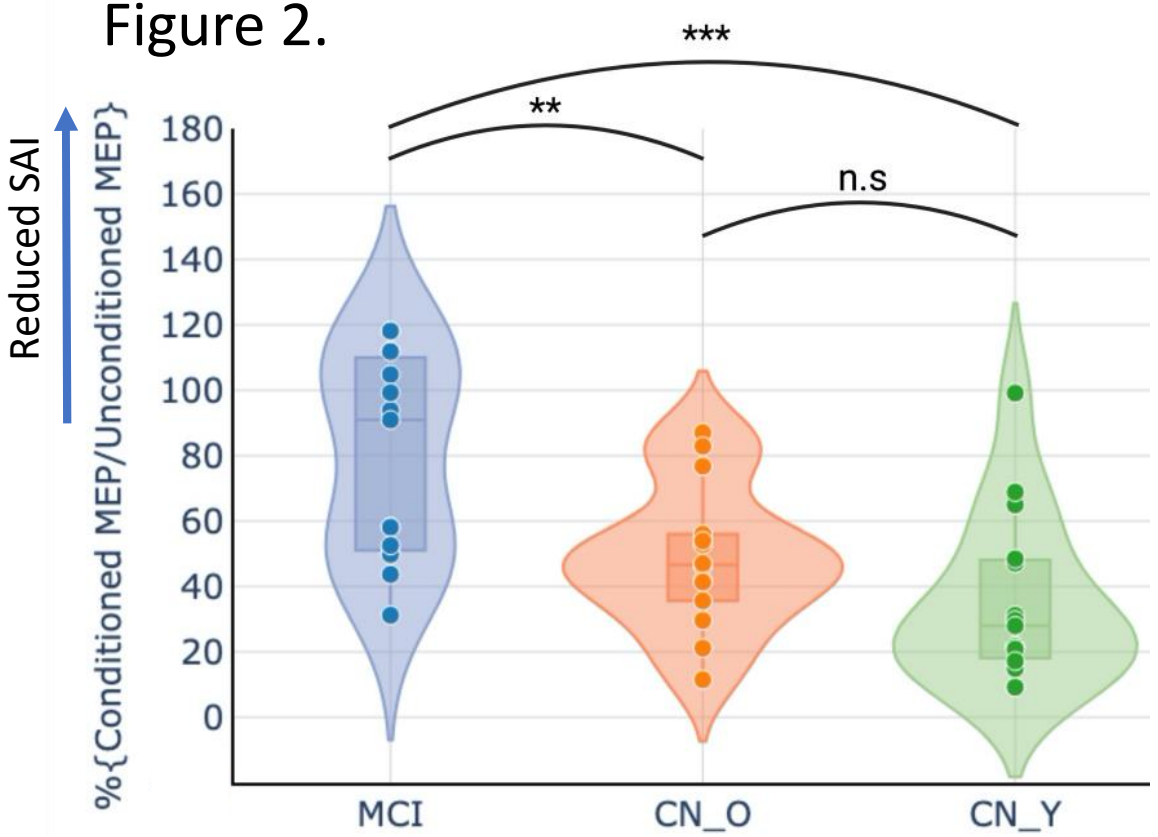
- There is strong evidence from TMS-pharmacological studies to support the role of acetylcholine in the generation of SAI (a review by Turco et al., 2018). For example:

- Muscarinic antagonists (e.g., scopolamine) reduce SAI and induce short-term memory impairment in healthy younger adults (Di Lazzaro et al., 2000).

- Acetylcholinesterase inhibitors (e.g., donepezil) increase SAI (Fujiki et al., 2006; Di Lazzaro et al., 2005).

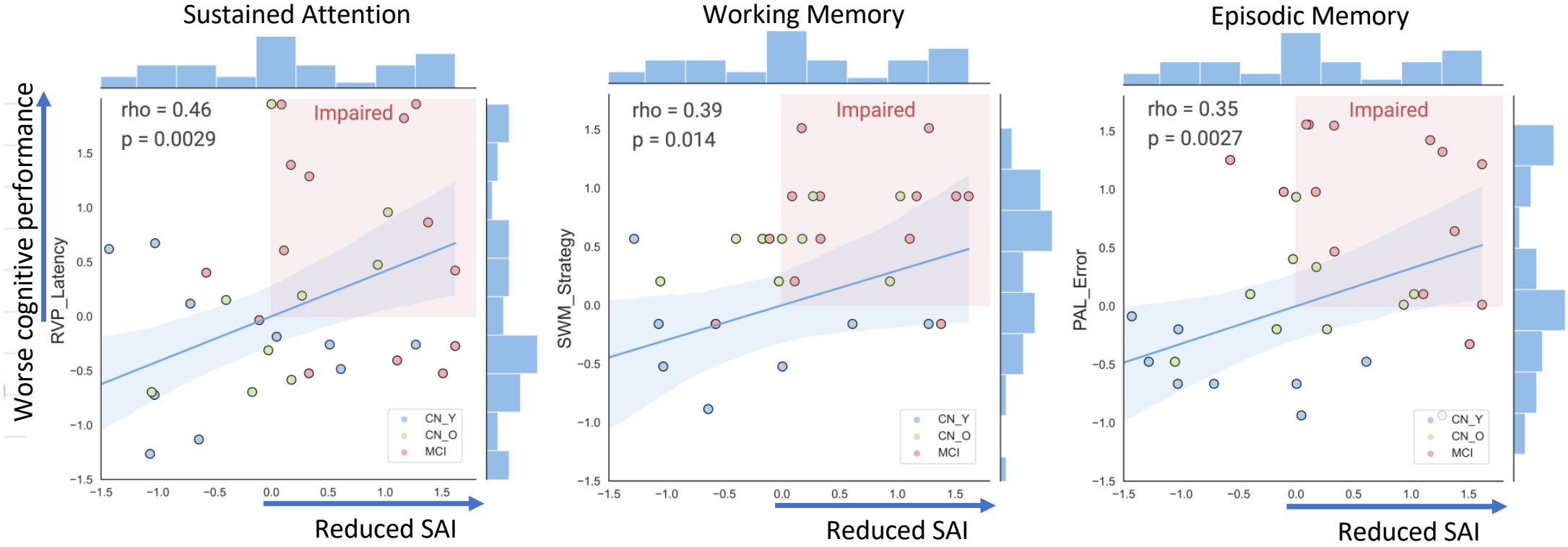
SAI was significantly reduced in the MCI group compared to both the CN older and CN younger adults, suggesting impaired cholinergic function in MCI.

Figure 2.



SAI = (Conditioned MEP / Non-Conditioned MEP) x 100

Sundman et al., 2024 Aging Brain



Significant correlations between diminished SAI and deficits in sustained attention, working memory, and episodic memory

Sundman et al., 2024 Aging Brain

doi:10.1093/braincomms/fcaa203 BRAIN COMMUNICATIONS 2020: Page 1 of 15 | 1

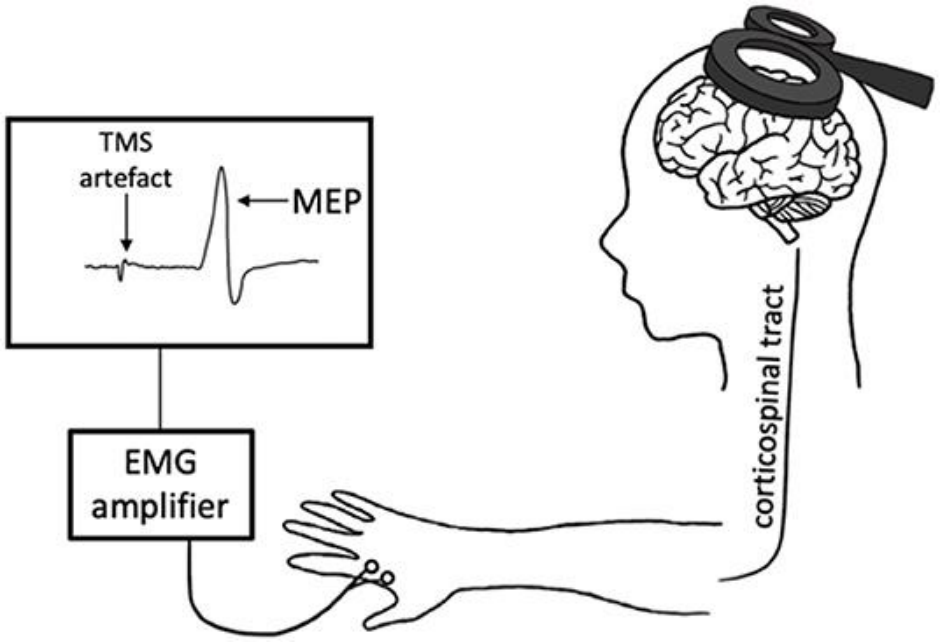
BRAIN COMMUNICATIONS

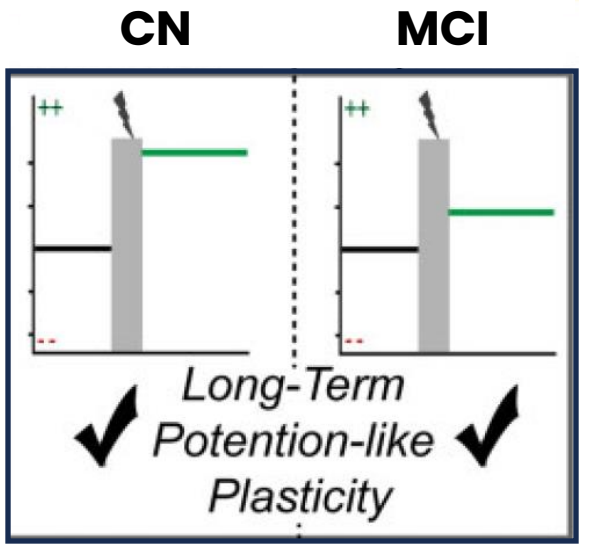
Transcranial magnetic stimulation reveals diminished homoeostatic metaplasticity in cognitively impaired adults

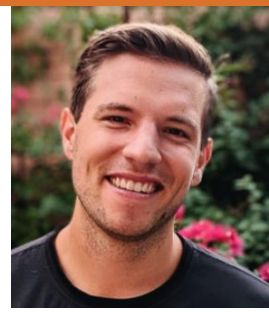
Mark H. Sundman,[1] Koeun Lim,[1] Viet Ton That,[1] Jack-Morgan Mizell,[1] Chidi Ugonna,[2,3] Rudolph Rodriguez,[1] Nan-Kuei Chen,[2,3] Andrew J. Fuglevand,[4,5] Yilin Liu,[1] Robert C. Wilson,[1] Jean-Marc Fellous,[1,2] Steven Rapcsak[1,6] and Ying-Hui Chou[1,7]

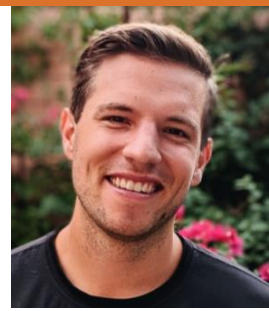
Homoeostatic metaplasticity is a neuroprotective physiological feature that counterbalances Hebbian forms of plasticity to prevent network destabilization and hyperexcitability. Recent animal models highlight dysfunctional homoeostatic metaplasticity in the pathogenesis of Alzheimer's disease. However, the association between homoeostatic metaplasticity and cognitive status has not been systematically characterized in either demented or non-demented human populations, and the potential value of homoeostatic metaplasticity as an early biomarker of cognitive impairment has not been explored in humans. Here, we report that, through pre-conditioning the synaptic activity prior to non-invasive brain stimulation, the association between homoeostatic metaplasticity and cognitive status could be established in a population of non-demented human subjects (older adults across cognitive spectrums; all within the non-demented range). All participants ($n = 40$; age range, 65–74, 47.5% female) underwent a standardized neuropsychological battery, magnetic resonance imaging and a transcranial magnetic stimulation protocol. Specifically, we sampled motor-evoked potentials with an input/output curve immediately before and after repetitive transcranial magnetic stimulation to assess neural plasticity with two experimental paradigms: one with voluntary muscle contraction (i.e. modulated synaptic activity history) to deliberately introduce homoeostatic interference, and one without to serve as a control condition. From comparing neuroplastic responses across these experimental paradigms and across cohorts grouped by cognitive status, we found that (i) homoeostatic metaplasticity is diminished in our cohort of cognitively impaired older adults and (ii) this neuroprotective feature remains intact in cognitively normal participants. This novel finding suggests that (i) future studies should expand their scope beyond just Hebbian forms of plasticity that are traditionally assessed when using non-invasive brain stimulation to investigate cognitive ageing and (ii) the potential value of homoeostatic metaplasticity in serving as a biomarker for cognitive impairment should be further explored.

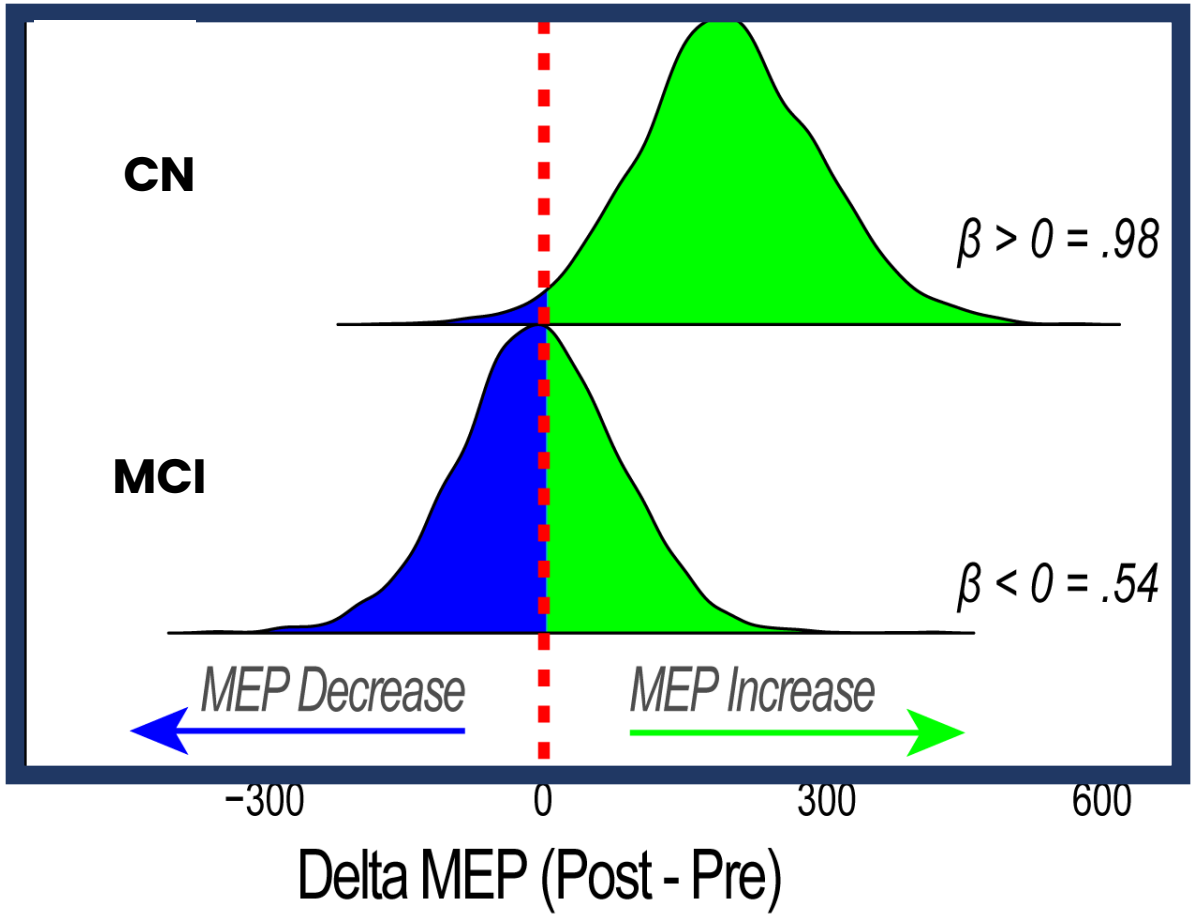
1 Department of Psychology, University of Arizona, Tucson, AZ 85721, USA
2 Department of Biomedical Engineering, University of Arizona, Tucson, AZ 85721, USA
3 Department of Medical Imaging, University of Arizona, Tucson, AZ 85721, USA
4 Department of Physiology, College of Medicine, University of Arizona, Tucson, AZ 85721, USA
5 Department of Neuroscience, College of Medicine, University of Arizona, Tucson, AZ 85721, USA
6 Department of Neurology, University of Arizona, Tucson, AZ 85721, USA
7 Evelyn F. McKnight Brain Institute, Arizona Center on Aging, and BIO5 Institute, University of Arizona, Tucson, AZ 85721, USA











The CN group displayed a heightened response to excitatory rTMS relative to the MCI group, indicating reduced plasticity potential in individuals with MCI.

› Brain Connect. 2023 Feb;13(1):39-50. doi: 10.1089/brain.2021.0180. Epub 2022 Jun 27.

Association Between Responsiveness to Transcranial Magnetic Stimulation and Interhemispheric Functional Connectivity of Sensorimotor Cortex in Older Adults

Yilin Liu [1], Koeun Lim [1], Mark H Sundman [1], Chidi Ugonna [1 2], Viet Ton That [1], Stephen Cowen [1 3], Ying-Hui Chou [1 3]

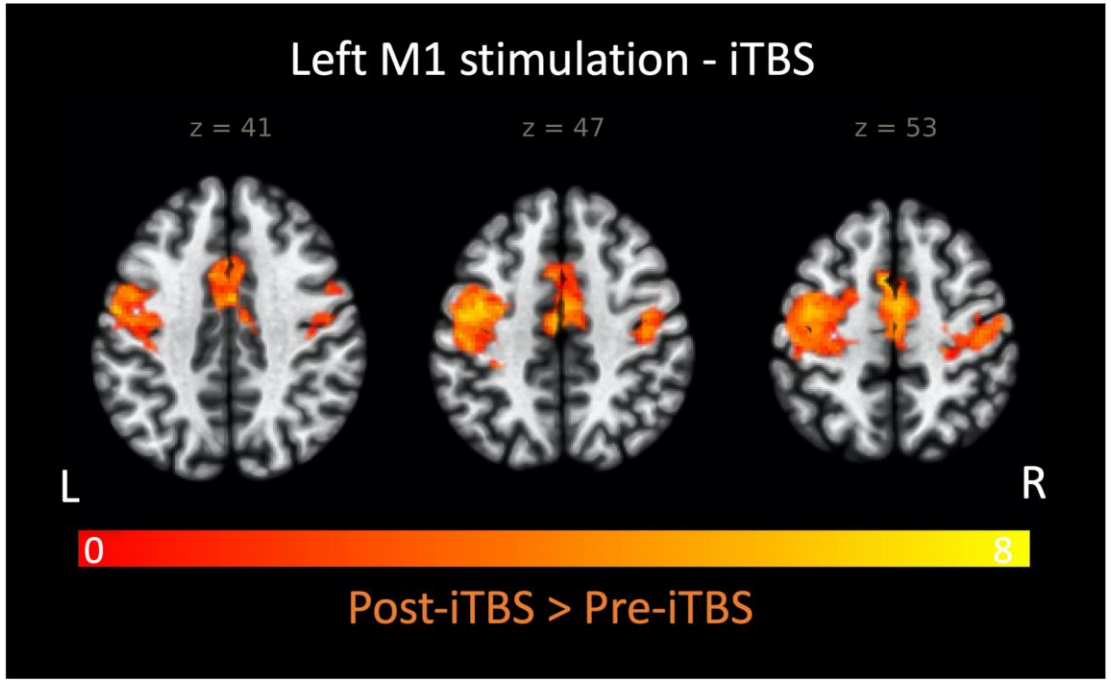
Affiliations + expand

PMID: 35620910 PMCID: PMC9942174 (available on 2024-02-01)

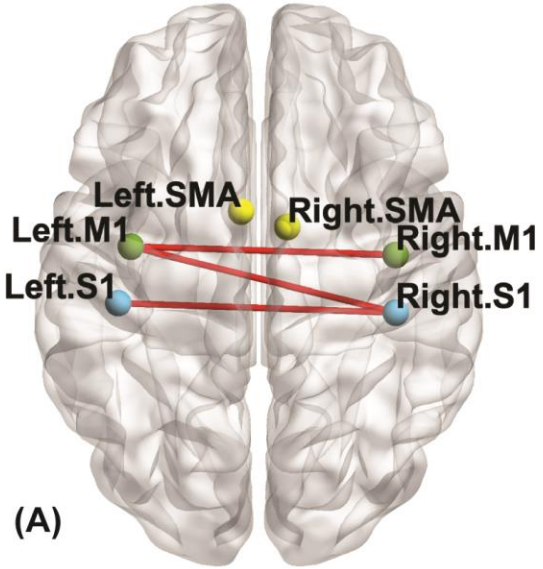
DOI: 10.1089/brain.2021.0180 Paperpile

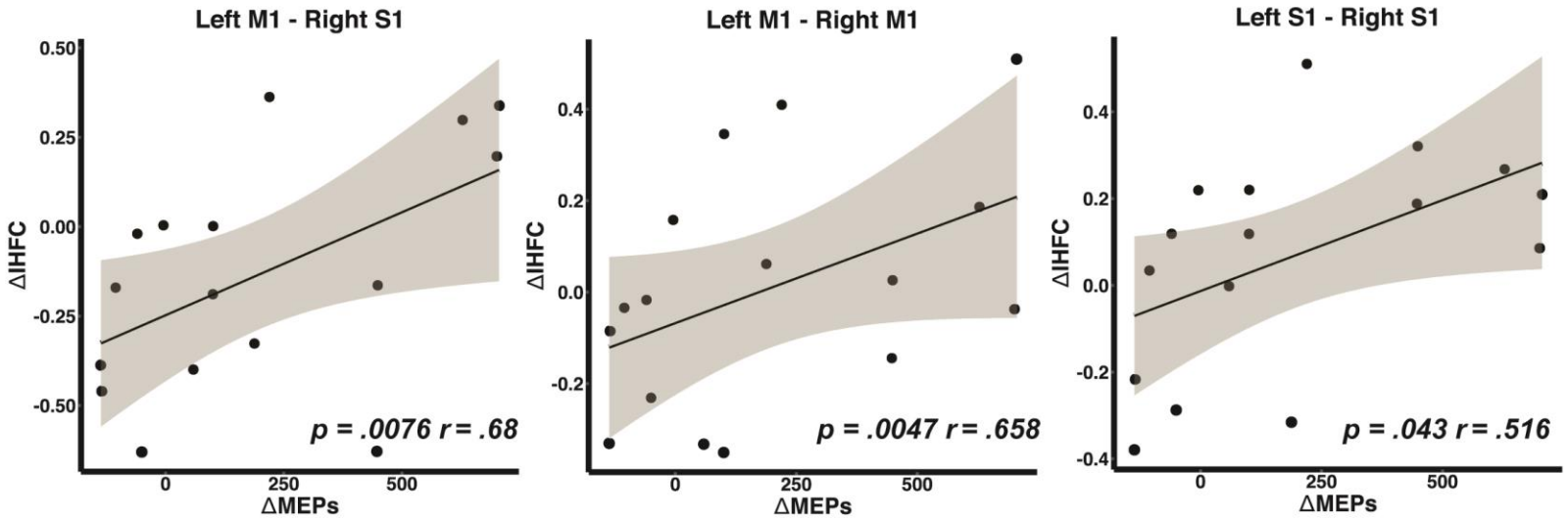
Abstract

Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a promising therapeutic technique, and is believed to accomplish its effect by influencing the stimulated and remotely connected areas. However, responsiveness to rTMS shows high interindividual variability, and this intersubject variability is particularly high in older adults. It remains unclear whether baseline resting-state functional connectivity (rsFC) contributes to this variability in older adults. The aims of this study are to (1) examine rTMS effects over the primary motor cortex (M1) in older adults, and (2) identify baseline network properties that may contribute to the interindividual variability. ***Methods:*** We tested response to intermittent theta burst stimulation (iTBS), an effective rTMS protocol, over M1 by using both electromyography and resting-state functional magnetic resonance imaging in older adults. Outcome measures included motor-evoked potential (MEP) elicited by single-pulse transcranial magnetic stimulation and rsFC before and after an iTBS session. ***Results:*** iTBS significantly increased MEP amplitudes and rsFC between the stimulation site, sensorimotor cortex, and supplementary motor area (SMA) in older adults. iTBS-induced changes in MEP amplitude were positively correlated with increases in interhemispheric rsFC after iTBS. Furthermore, older adults with lower baseline interhemispheric rsFC between sensorimotor cortex and SMA exhibited stronger MEP response after iTBS. ***Discussion:*** Findings of the study suggest that different levels of interhemispheric communication during resting state might contribute to the response heterogeneity to iTBS in older adults. Interhemispheric rsFC may have great potential serving as a useful marker for predicting iTBS responsiveness in older adults. ClinicalTrials.gov ID: 1707654427 Impact statement Factors contributing to interindividual variability of the responsive to repetitive transcranial magnetic stimulation (rTMS) in older adults remain poorly understood. In this study, we examined the effects of rTMS over the primary motor cortex in older adults, and found that response to rTMS is associated with prestimulation interhemispheric connectivity in the sensorimotor and premotor areas. Findings of the study have great potential to be translated into a connectivity-based strategy for identification of responders for rTMS in older adults.



Excitatory rTMS applied to the M1 significantly enhanced both MEP amplitudes and resting-state functional connectivity within the sensorimotor cortex and the supplementary motor area.





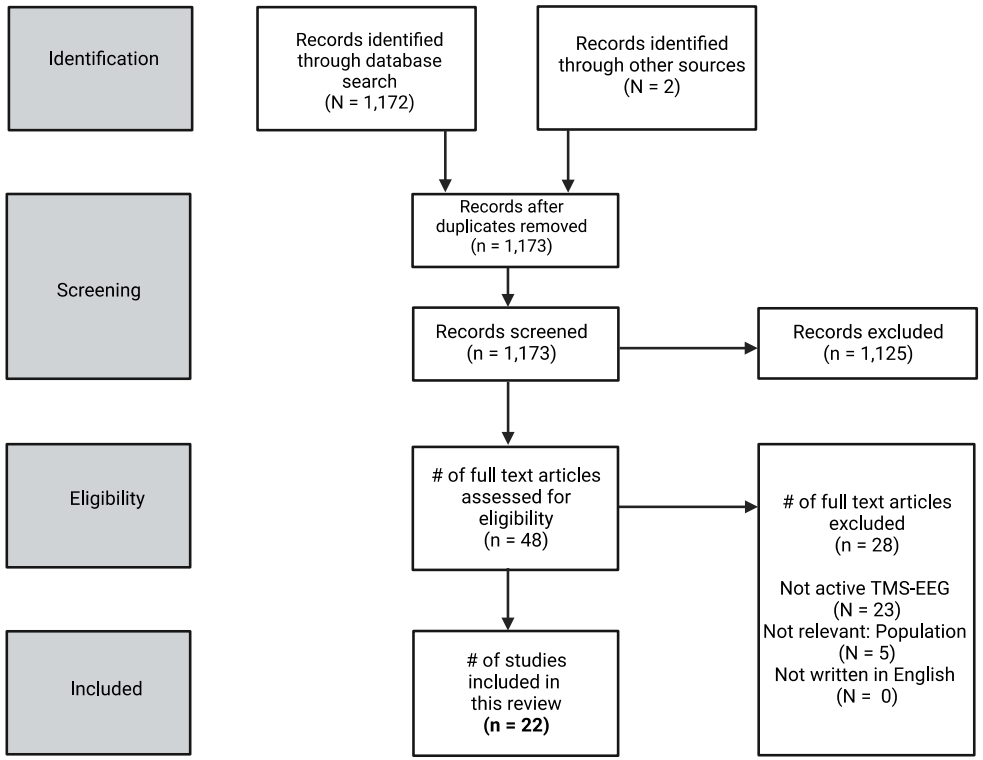
Increases in MEP amplitude induced by excitatory rTMS were found to be positively correlated with enhanced interhemispheric resting-state functional connectivity after excitatory rTMS application.

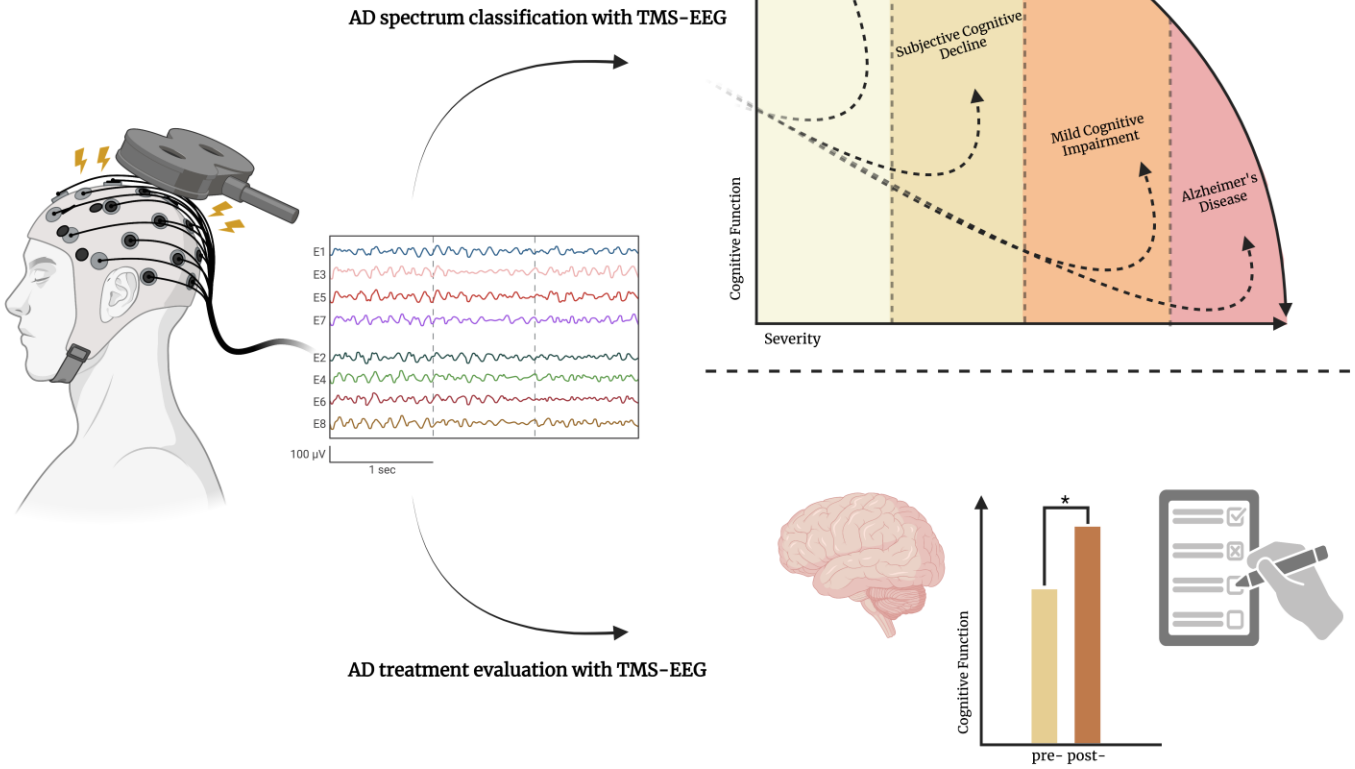
Introducing TMS | TMS-based Assessment | Therapeutic TMS

Diagnostic Biomarkers

Prognostic Biomarkers

Response Biomarkers





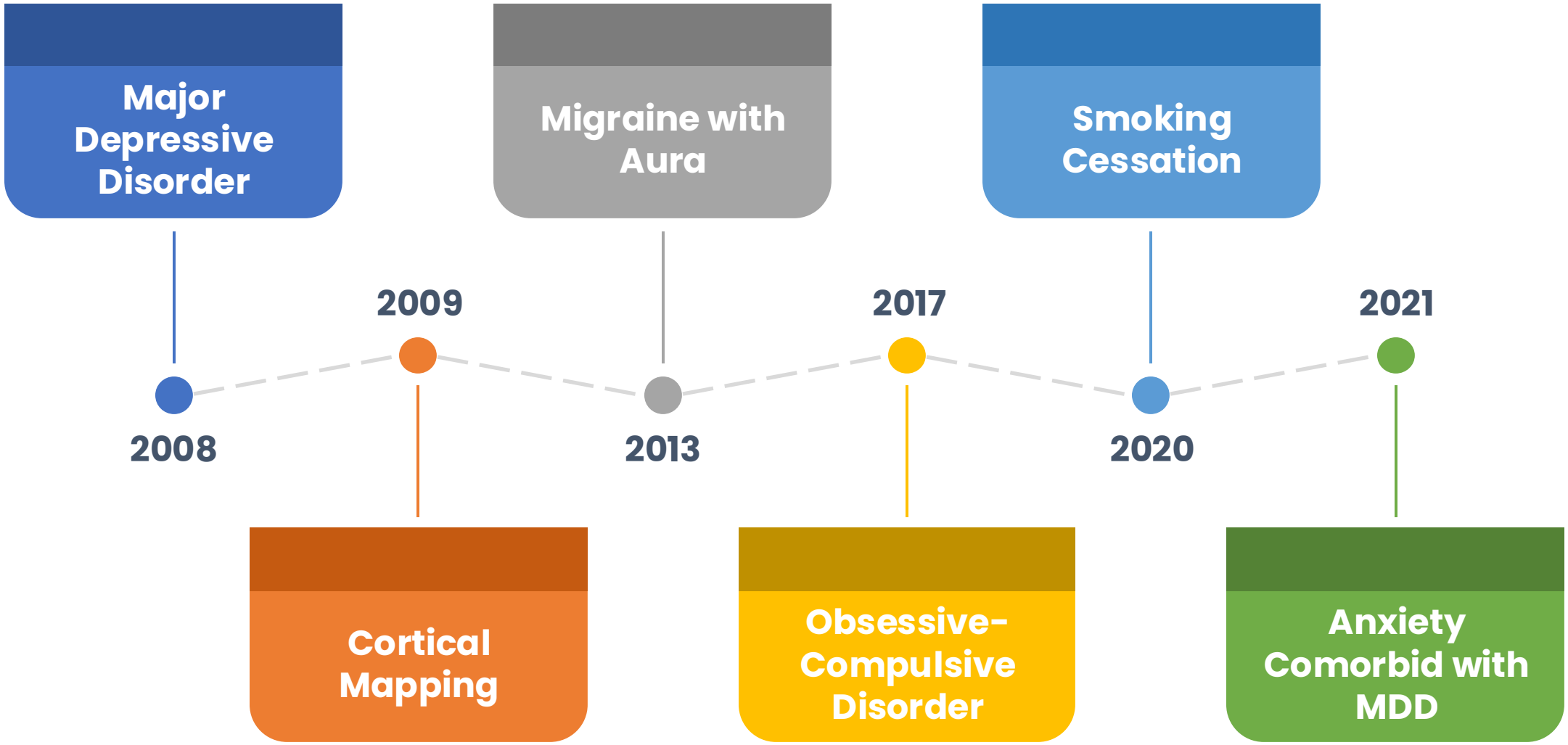
Hall et al., 2024 GeroScience

TMS-base Assessment Research Highlights

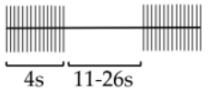
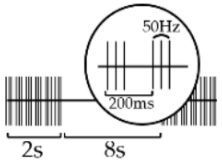
- TMS can be combined with EMG, fMRI, and EEG to evaluate neurophysiological functions in AD and MCI.
- TMS-derived parameters have demonstrated correlations with cognitive performance.
- TMS-based assessment reveals increased cortical excitability, diminished cholinergic function, and reduced neuroplasticity potential in individuals with AD and MCI compared to cognitively normal older adults.
- TMS metrics have the potential to serve as measurable health outcomes, augment existing biomarkers, and assist in the early identification of AD.

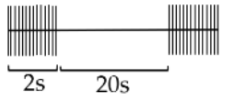
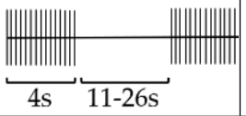
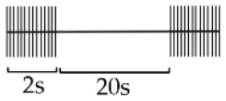
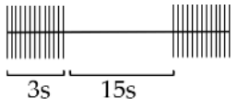
INTERVENTIONAL TMS

Timeline of US FDA Milestones for TMS Devices



FDA-Cleared TMS Protocols/Devices

Disorder	Frequency	Ses. Pulses (Duration)	Schedule (No Ses.)	Target Region	Examples of TMS Manufacturers (Coils)
Major Depressive Episode	10Hz rTMS 	3000 (18′ 48″ to 37′ 30″)	1/d (20–30d)	L-DLPFC	NeuroStar 
				L-DLPFC	Magstim (e.g., HORIZON® Coils) 
				BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
				L-DLPFC	Magventure (e.g., B65 coil) 
	Intermittent Theta Burst 	600 (3′ 9″)	1/d (20–30 d)	L-DLPFC	NeuroStar  Magstim  Magventure 
		18000 (9′ 27′)	Accelerated: 10/d (5 d)	L-DLPFC	Magventure (B65 coil) 

Disorder	Frequency	Ses. Pulses (Duration)	Schedule (No Ses.)	Target Region	Examples of TMS Manufacturers (Coils)
With Comorbid Anxiety	20Hz rTMS 	1980 (20′ 12″)	1st: 1/d (20 d) 2nd: 2/w (12 w)	BL-DLPFC (L-DLPFC)	Brainsway (H1 coil) 
	10Hz rTMS 	3000 (18′ 48″)	1st: 1/d (30 d) 2nd: ~2/w (3 w)	L-DLPFC	NeuroStar 
Obsessive Compulsive Disorder	20Hz rTMS 	2000 (18′)	1/day (29 d)	ACC/mPFC	Brainsway (H7 coil) 
				ACC/mPFC	Magventure (DB-80 coil) 
Smoking Cessation	10Hz rTMS 	1800 (17′ 48″)	1st: 1/d (15d) 2nd: 1/w (3 w)	BL-lPFC BL-Insula	Brainsway (H4 coil) 

Cotovio et al., 2023

Neurobiology of Aging 86 (2020) 1–10

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Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

A systematic review and meta-analysis of rTMS effects on cognitive enhancement in mild cognitive impairment and Alzheimer's disease

Ying-hui Chou [a,b,*], Viet Ton That [a], Mark Sundman [a]

[a] Department of Psychology, Brain Imaging and TMS Laboratory, University of Arizona, Tucson, USA
[b] Everlyn F McKnight Brain Institute, Arizona Center on Aging, and BIO5 Institute, University of Arizona, Tucson, USA

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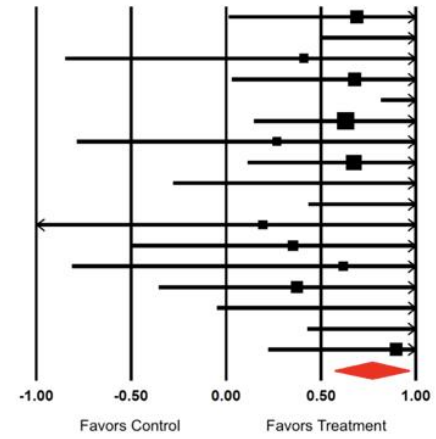
Dorsolateral prefrontal cortex
Intervention
Memory
Treatment
Therapy
Cognition

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation technique, has emerged as a promising treatment for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Currently, however, the effectiveness of this therapy is unclear because of the low statistical power and heterogeneity of previous trials. The purpose of the meta-analysis was to systematically characterize the effectiveness of various combinations of rTMS parameters on different cognitive domains in patients with MCI and AD. Thirteen studies comprising 293 patients with MCI or AD were included in this analysis. Random-effects analysis revealed an overall medium-to-large effect size (0.77) favoring active rTMS over sham rTMS in the improvement of cognitive functions. Subgroup analyses revealed that (1) high-frequency rTMS over the left dorsolateral prefrontal cortex and low-frequency rTMS at the right dorsolateral prefrontal cortex significantly improved memory functions; (2) high-frequency rTMS targeting the right inferior frontal gyrus significantly enhanced executive performance; and (3) the effects of 5–30 consecutive rTMS sessions could last for 4–12 weeks. Potential mechanisms of rTMS effects on cognitive functions are discussed.

13 studies, 293 patients with MCI and AD

Study name	Sample size	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Drumond et al., 2015	34	0.689	0.344	0.118	0.015	1.363	2.003	0.045
Turriziani et al., 2012	8	1.527	0.520	0.271	0.507	2.547	2.935	0.003
Eliasova et al., 2014	10	0.410	0.640	0.410	-0.846	1.665	0.640	0.522
Sole-Padulles et al., 2006	39	0.678	0.329	0.109	0.032	1.324	2.058	0.040
Padala et al., 2018	9	2.033	0.619	0.383	0.819	3.246	3.284	0.001
Anderkova et al., 2015	20	0.630	0.245	0.060	0.149	1.111	2.568	0.010
Koch et al., 2018	14	0.268	0.537	0.288	-0.785	1.320	0.498	0.618
Wu et al., 2015	52	0.674	0.285	0.081	0.115	1.233	2.364	0.018
Rutherford et al., 2015	10	1.046	0.674	0.455	-0.276	2.367	1.551	0.121
Ahmed et al., 2012a	21	1.398	0.490	0.241	0.436	2.359	2.850	0.004
Ahmed et al., 2012b	9	0.194	0.674	0.454	-1.127	1.515	0.288	0.773
Ahmed et al., 2012c	22	0.353	0.431	0.186	-0.493	1.198	0.818	0.414
Ahmed et al., 2012d	8	0.619	0.729	0.532	-0.811	2.048	0.848	0.396
Zhao et al., 2017	30	0.375	0.372	0.138	-0.353	1.104	1.010	0.312
Cotelli et al., 2011	10	1.325	0.698	0.488	-0.044	2.693	1.897	0.058
Cotelli et al., 2008a	12	1.162	0.374	0.140	0.430	1.894	3.110	0.002
Cotelli et al., 2008b	12	0.897	0.343	0.117	0.225	1.569	2.618	0.009
Across Studies	293	0.770	0.100	0.010	0.574	0.967	7.686	0.000



Active rTMS is more effective than sham rTMS

Effect size = 0.77, $p < .0001$

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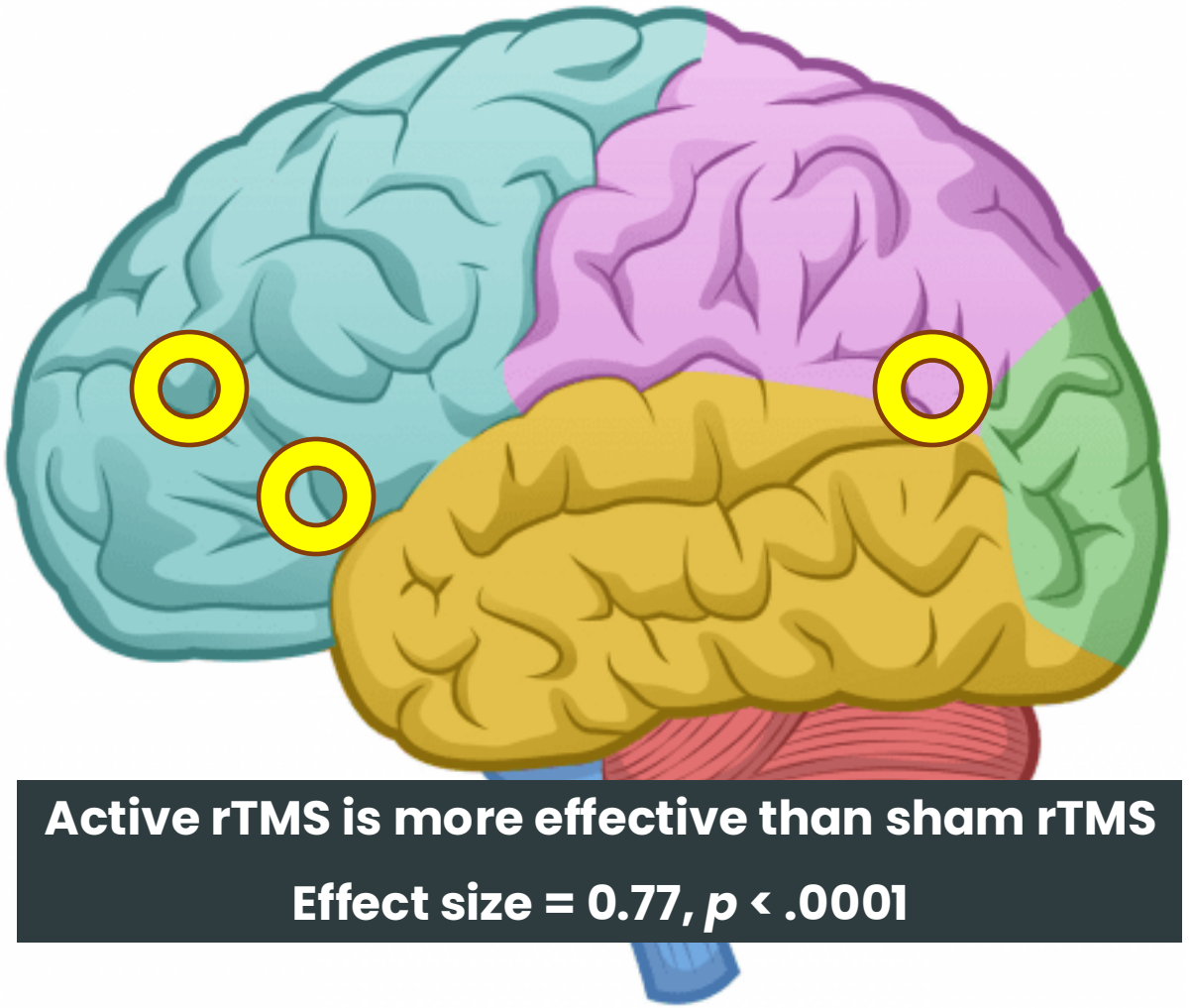
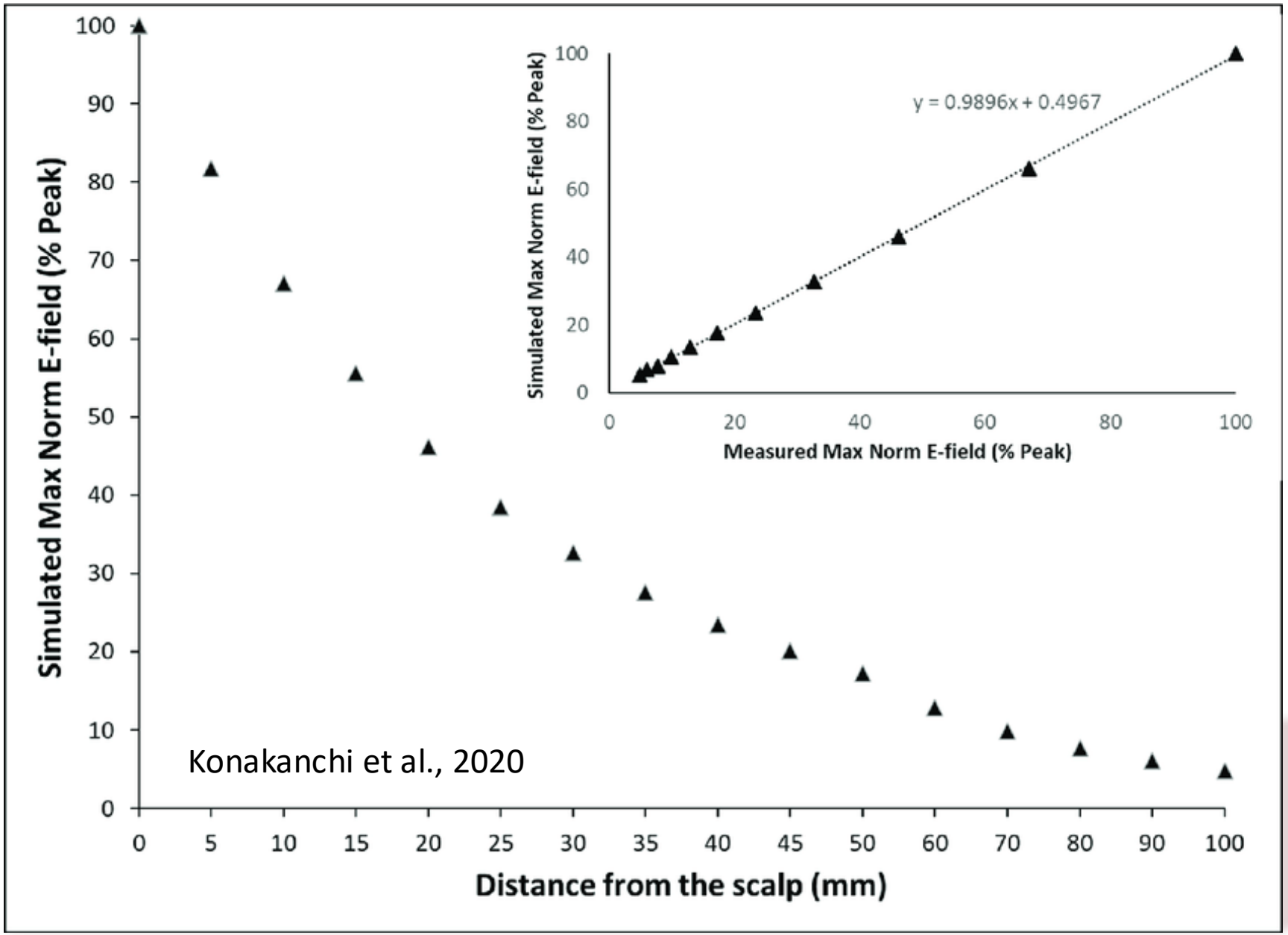


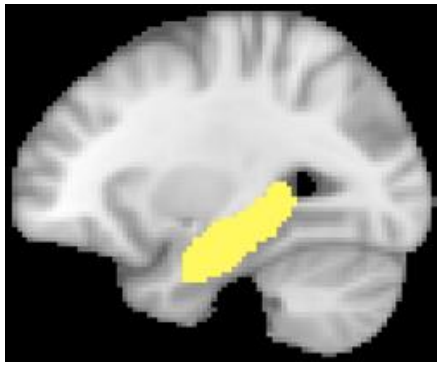
Active rTMS is more effective than sham rTMS

Effect size = 0.77, $p < .0001$

Why didn't the researchers directly stimulate the hippocampus with TMS?

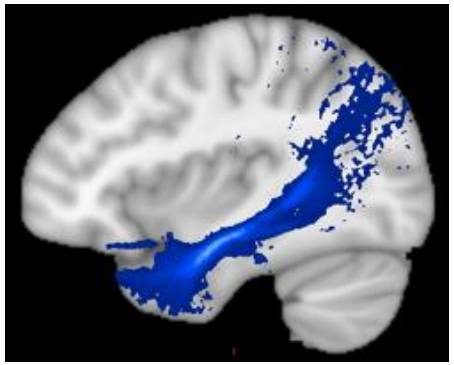

Simulated Max Norm E-field (% Peak)
Distance from the scalp (mm)
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30
35
40
45
50
60
70
80
90
100
Simulated Max Norm E-field (% Peak)
Measured Max Norm E-field (% Peak)
y = 0.9896x + 0.4967
0
20
40
60
80
100
Konakanchi et al., 2020

01



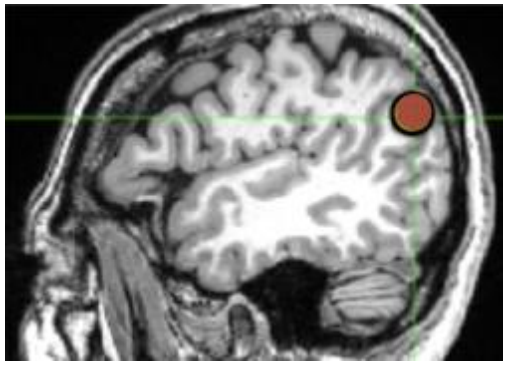
Starting with the left hippocampus as a seed

02

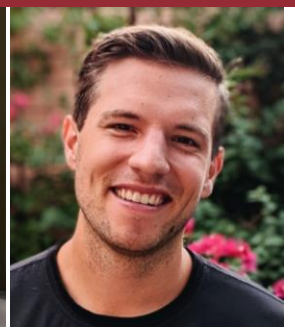


Mapping white matter pathways or resting-state fMRI connections from the left hippocampus to cortical surface regions

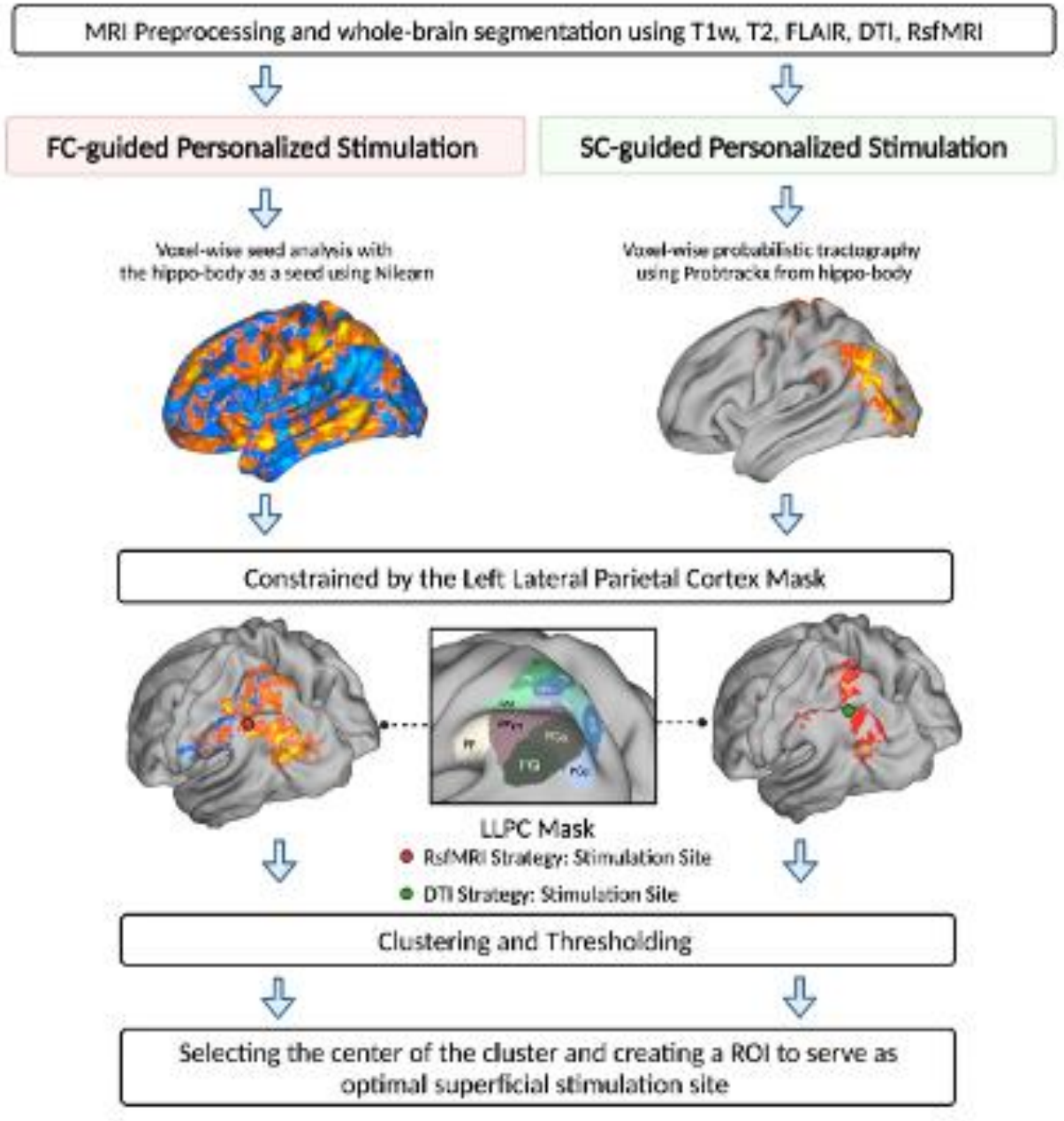
03



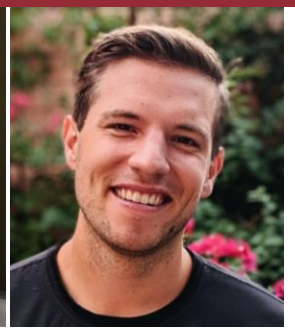
Pinpointing a personalized superficial stimulation site

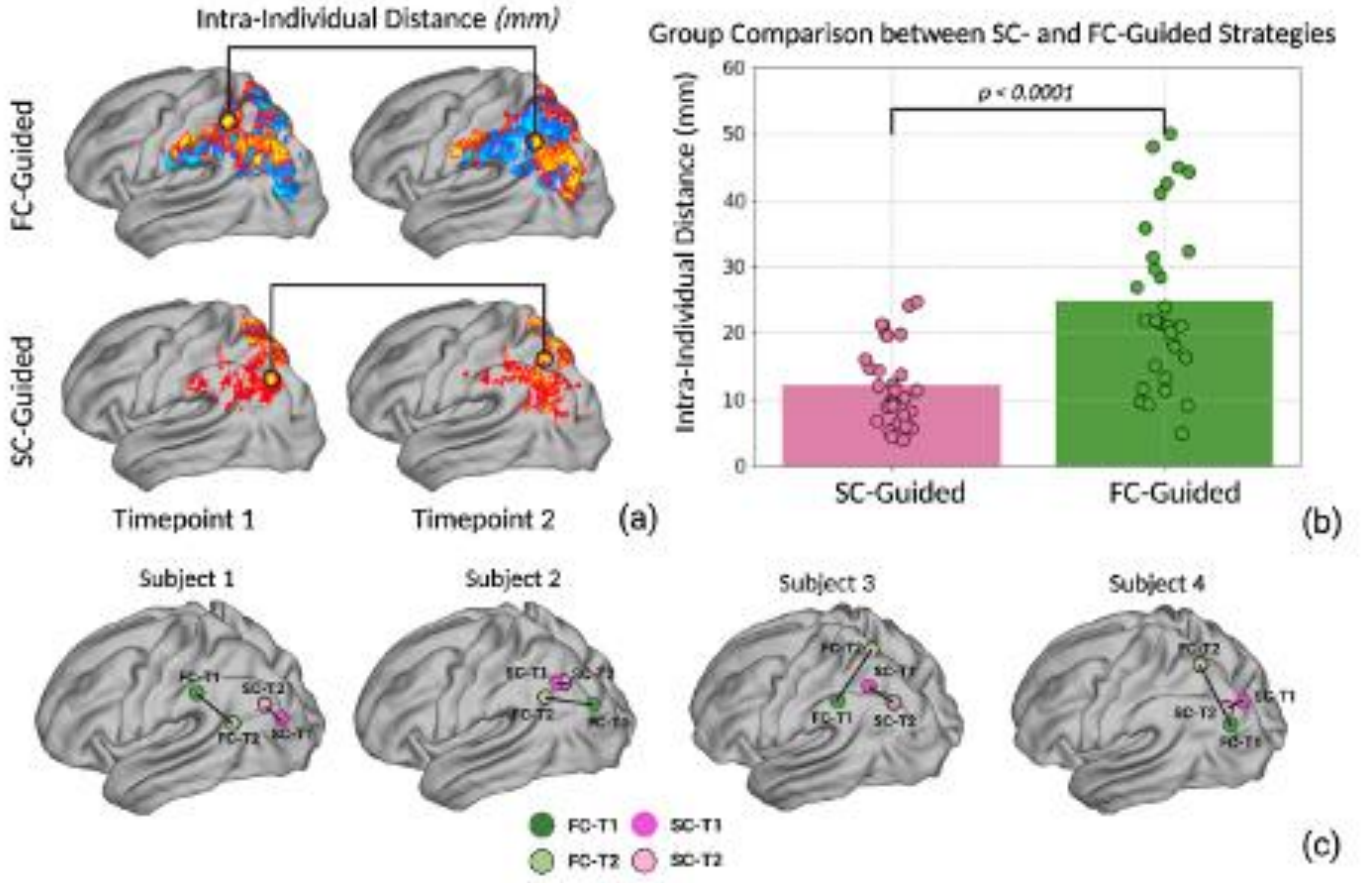
dMRI (1)→ dMRI (2)
fMRI (1) → fMRI (2)



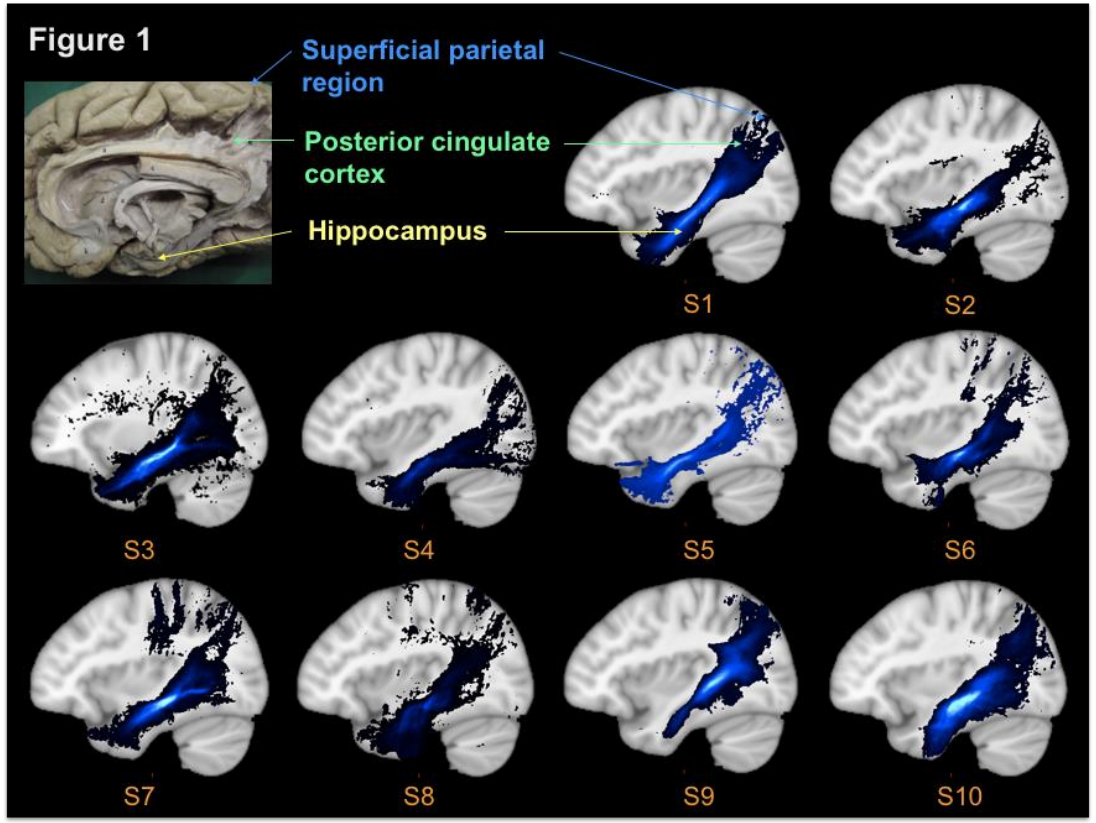
Liu and Sundman et al., 2024 Frontiers in Human Neuroscience – Brain Imaging and Stimulation



DTI-guided strategy is more reproducible compared to resting-state fMRI-guided strategy



Liu and Sundman et al., 2024 Frontiers in Human Neuroscience – Brain Imaging and Stimulation



PNAS RESEARCH ARTICLE | PSYCHOLOGICAL AND COGNITIVE SCIENCES NEUROSCIENCE

Diffusion MRI–guided theta burst stimulation enhances memory and functional connectivity along the inferior longitudinal fasciculus in mild cognitive impairment

Yu-Chin Chen[a], Viet Ton That[a], Chidi Ugonna[a], Yilin Liu[a], Lynn Nadel[a,b,1], and Ying-hui Chou[a,b,c,1]

Contributed by Lynn Nadel; received July 27, 2021; accepted April 16, 2022; reviewed by Isabelle Buard, Joy Taylor, and Anthony Wagner

Mild cognitive impairment (MCI) during aging is often a harbinger of Alzheimer's disease, and, therefore, early intervention to preserve cognitive abilities before the MCI symptoms become medically refractory is particularly critical. Functional MRI–guided transcranial magnetic stimulation is a promising approach for modulating hippocampal functional connectivity and enhancing memory in healthy adults. Here, we extend these previous findings to individuals with MCI and leverage theta burst stimulation (TBS) and white matter tractography derived from diffusion-weighted MRI to target the hippocampus. Our preliminary findings suggested that TBS could be used to improve associative memory performance and increase resting-state functional connectivity of the hippocampus and other brain regions, including the occipital fusiform, frontal orbital cortex, putamen, posterior parahippocampal gyrus, and temporal pole, along the inferior longitudinal fasciculus in MCI. Although the sample size is small, these results shed light on how TBS propagates from the superficial cortex around the parietal lobe to the hippocampus.

transcranial magnetic stimulation | theta burst stimulation | mild cognitive impairment | magnetic resonance imaging | memory

Mild cognitive impairment (MCI) lies somewhere between the expected cognitive decline of normal aging and Alzheimer's disease (AD). Although cognitive changes in individuals with MCI are not severe enough to interfere with daily function, people with MCI are at an increased risk of developing AD. Approximately 10 to 15% of individuals with MCI convert to AD every year (1). Individuals with amnestic MCI (aMCI), a subtype of MCI with memory impairment, have an even higher rate of conversion (1–3). Currently, pharmacological approaches are the mainstream of therapy for AD and MCI, and those interventions have demonstrated only moderate effects in reducing clinical symptoms for relatively short periods (4, 5). Therefore, we need nonpharmacological approaches, particularly treatment for memory dysfunction, for individuals with MCI before the cognitive impairments become medically refractory.

Significance

Noninvasive theta burst stimulation (TBS) guided by brain white matter tractography is a promising approach to strengthen resting-state functional connectivity of the hippocampus and increase associative memory performance in individuals with mild cognitive impairment. With this approach, our findings add insight into how TBS propagates from the superficial stimulation site to the hippocampus along the inferior longitudinal fasciculus. Results of this study provide an innovative platform for developing a noninvasive hippocampal stimulation protocol that has great potential in enhancing memory function in mild cognitive impairment.

Design and Outcomes

Double-blind

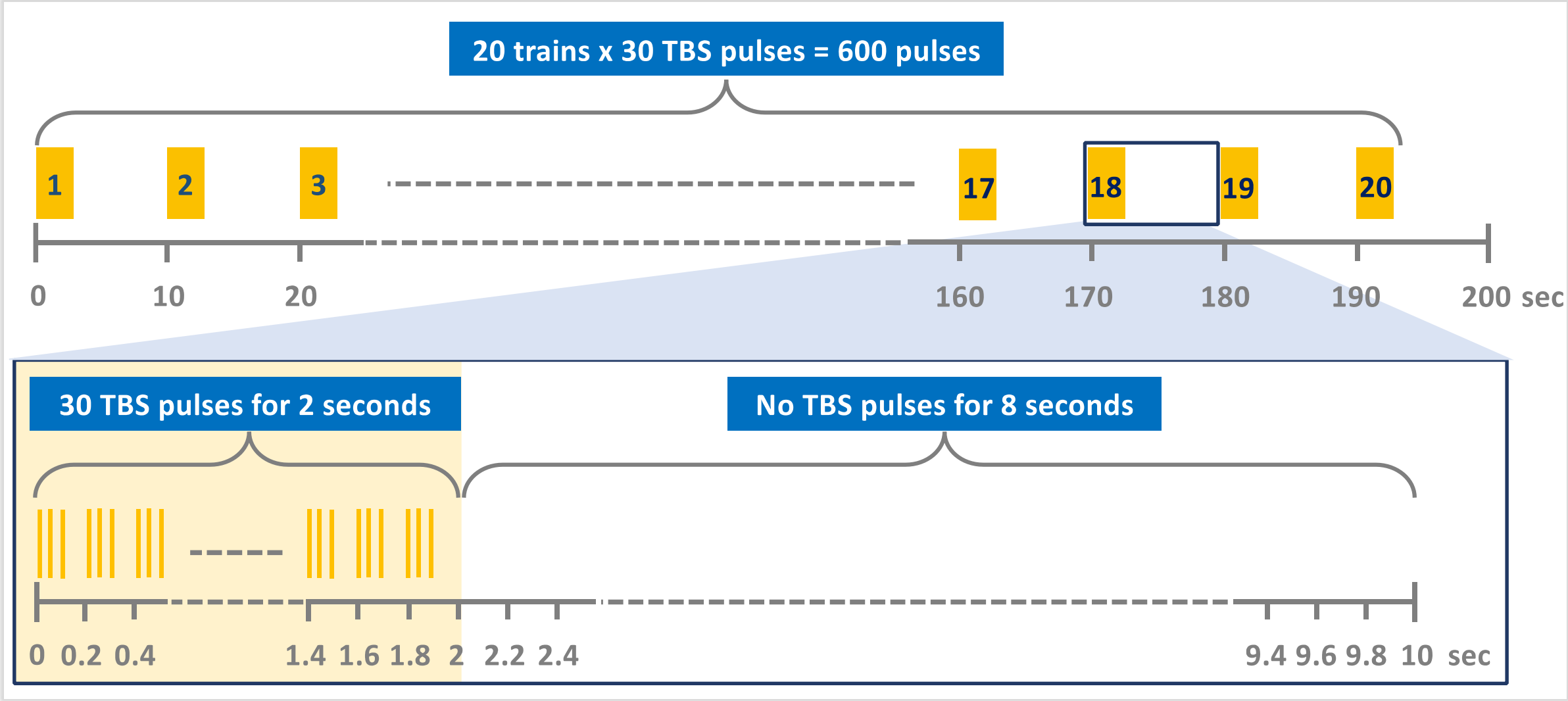
Randomized

Sham-Controlled

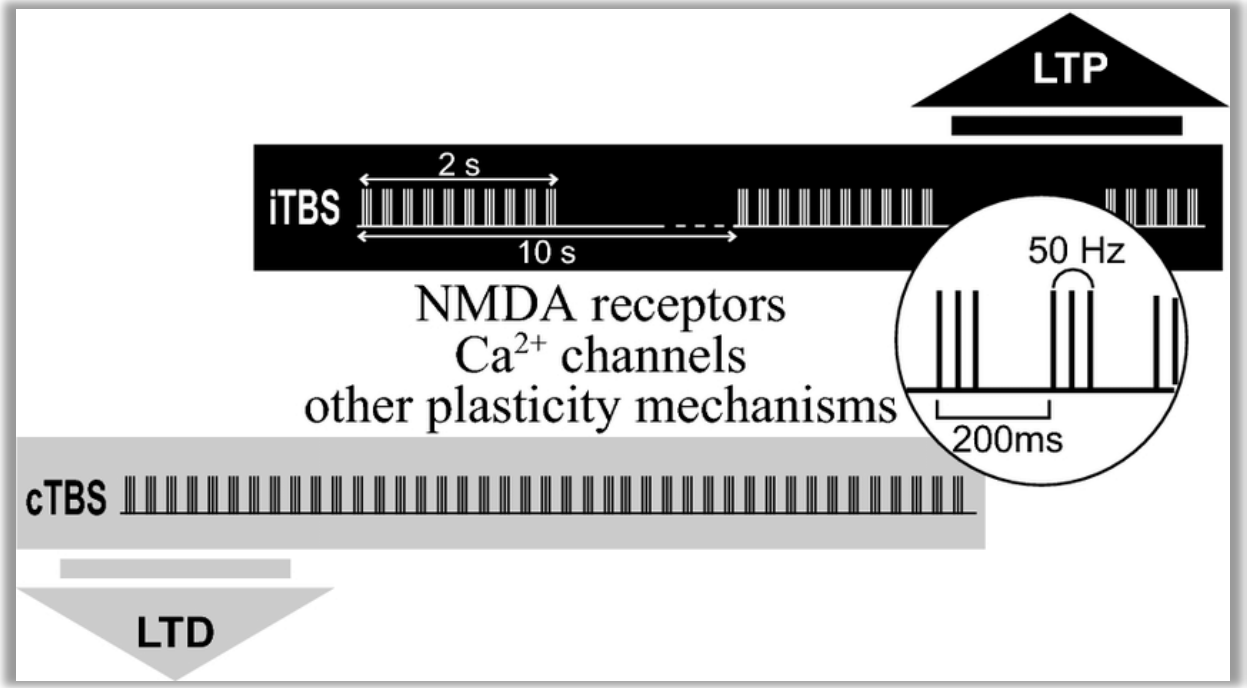
Crossover

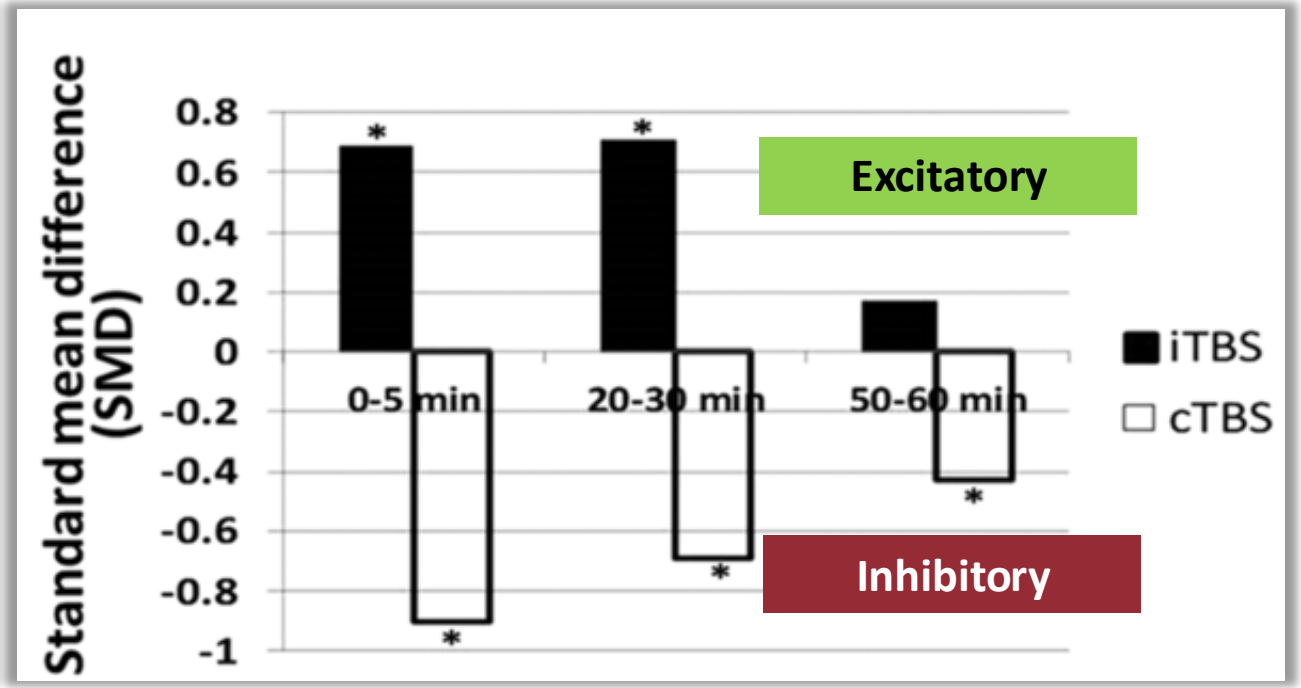
Test the efficacy of theta burst stimulation (TBS) on memory function in 60 individuals with mild cognitive impairment (MCI)

Intermittent Theta Burst Stimulation (TBS)

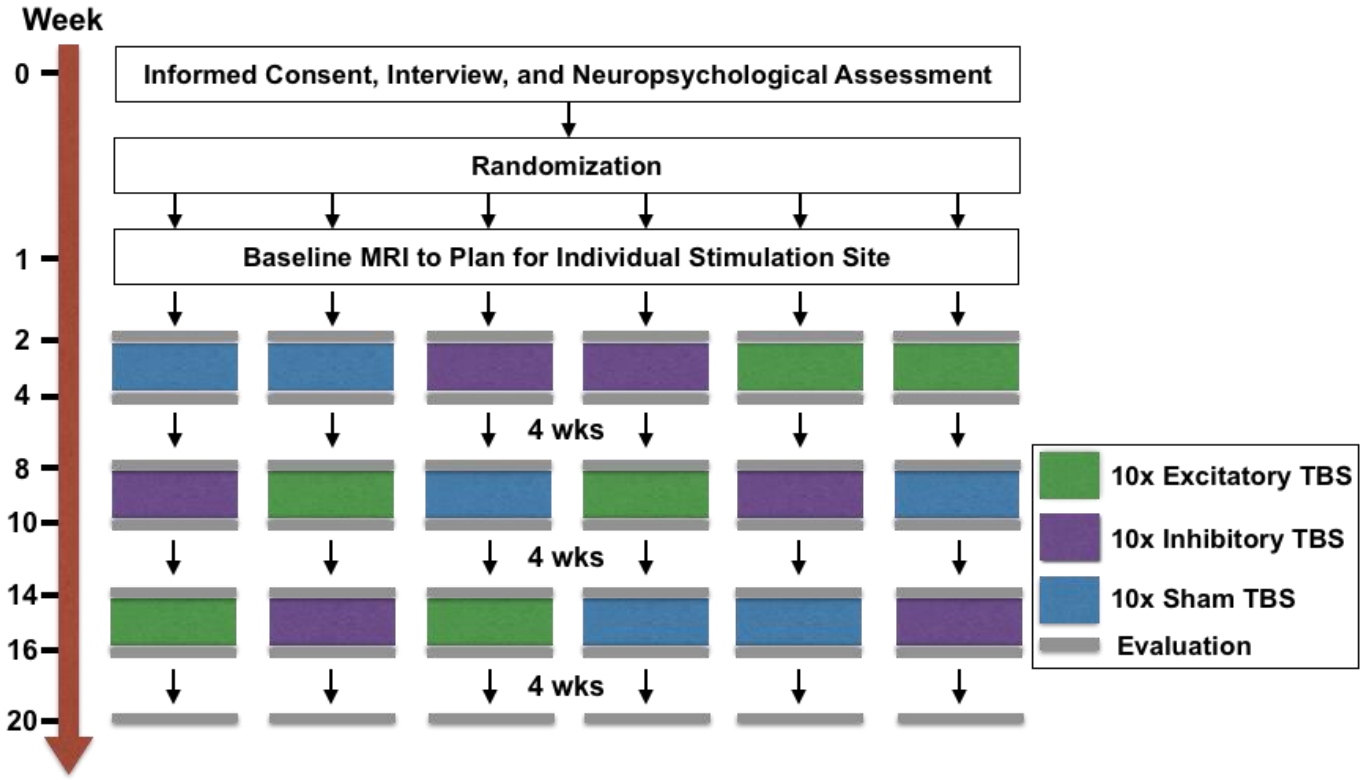


Huang et al., 2005



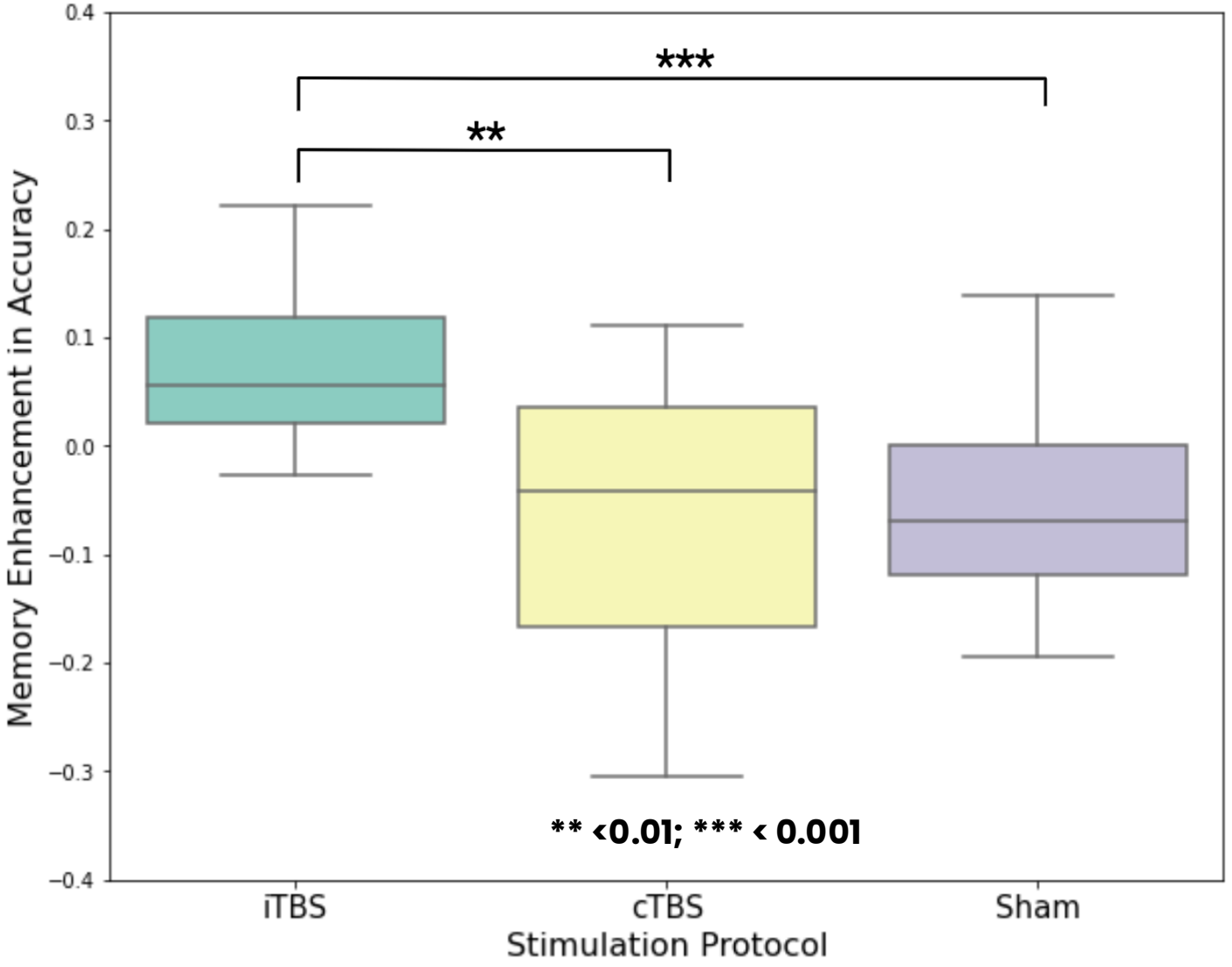


Rounis et al., 2020
Li et al., 2019

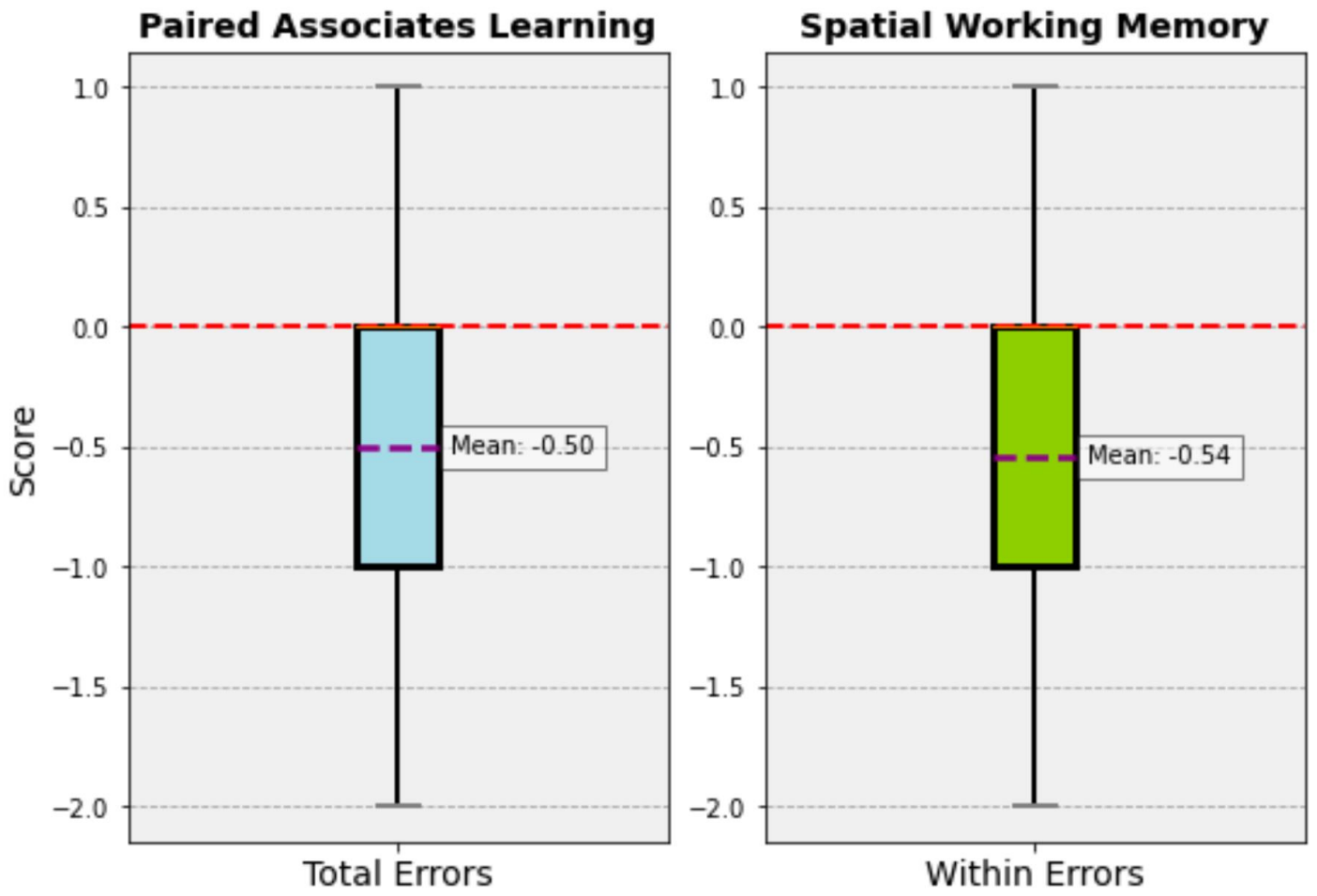


Day 0	Screening for Eligibility: Interview and Neuropsychological Assessment (2 hours)
Day 1	MRI (60 mins)
Day 8	MRI (60 mins) + Cognitive Tasks (1 hour)
Days 8-12	Daily TBS condition A (15 mins)
Days 15-19	Daily TBS condition A (15 mins)
Day 19	MRI (60 mins) + Cognitive Tasks (1 hour)
Day 50	MRI (60 mins) + Cognitive Tasks (1 hour)
Days 50-54	Daily TBS condition B (15 mins)
Days 57-61	Daily TBS condition B (15 mins)
Day 61	MRI (30 mins) + Cognitive Tasks (1 hour)
Day 92	MRI (60 mins) + Cognitive Tasks (1 hour)
Days 92-96	Daily TBS condition C (15 mins)
Days 99-103	Daily TBS condition C (15 mins)
Day 103	MRI (60 mins) + Cognitive Tasks (1 hour)

iTBS improved associative memory relative to both cTBS and sham TBS

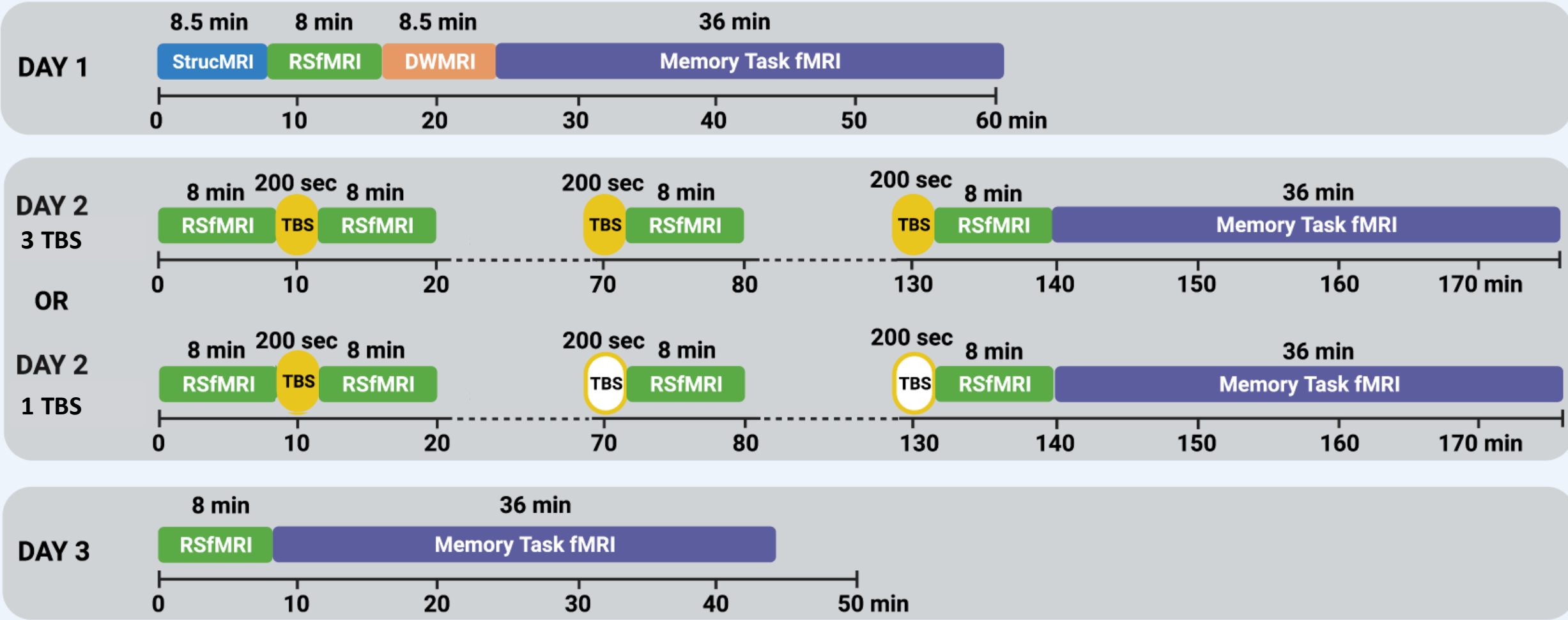


iTBS reduced errors on learning and spatial working memory tests compared to sham TBS.

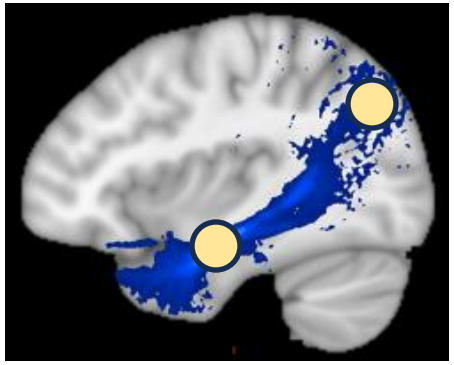


Score = (Post_iTBS – Pre_iTBS) – (Post_shamTBS – Pre_shamTBS)

Figure 1

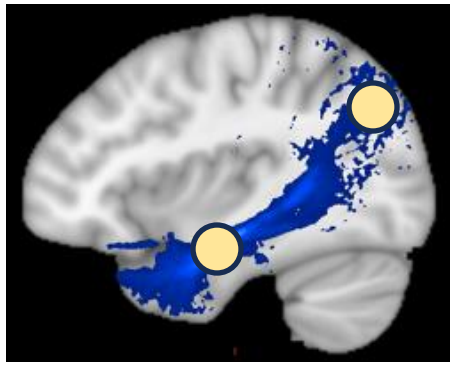


Note. DWMRI = diffusion-weighted MRI; RSfMRI = resting-state fMRI; StrucMRI = structural T1 MPRAGE and T2 FLAIR MRI; TBS = theta burst stimulation

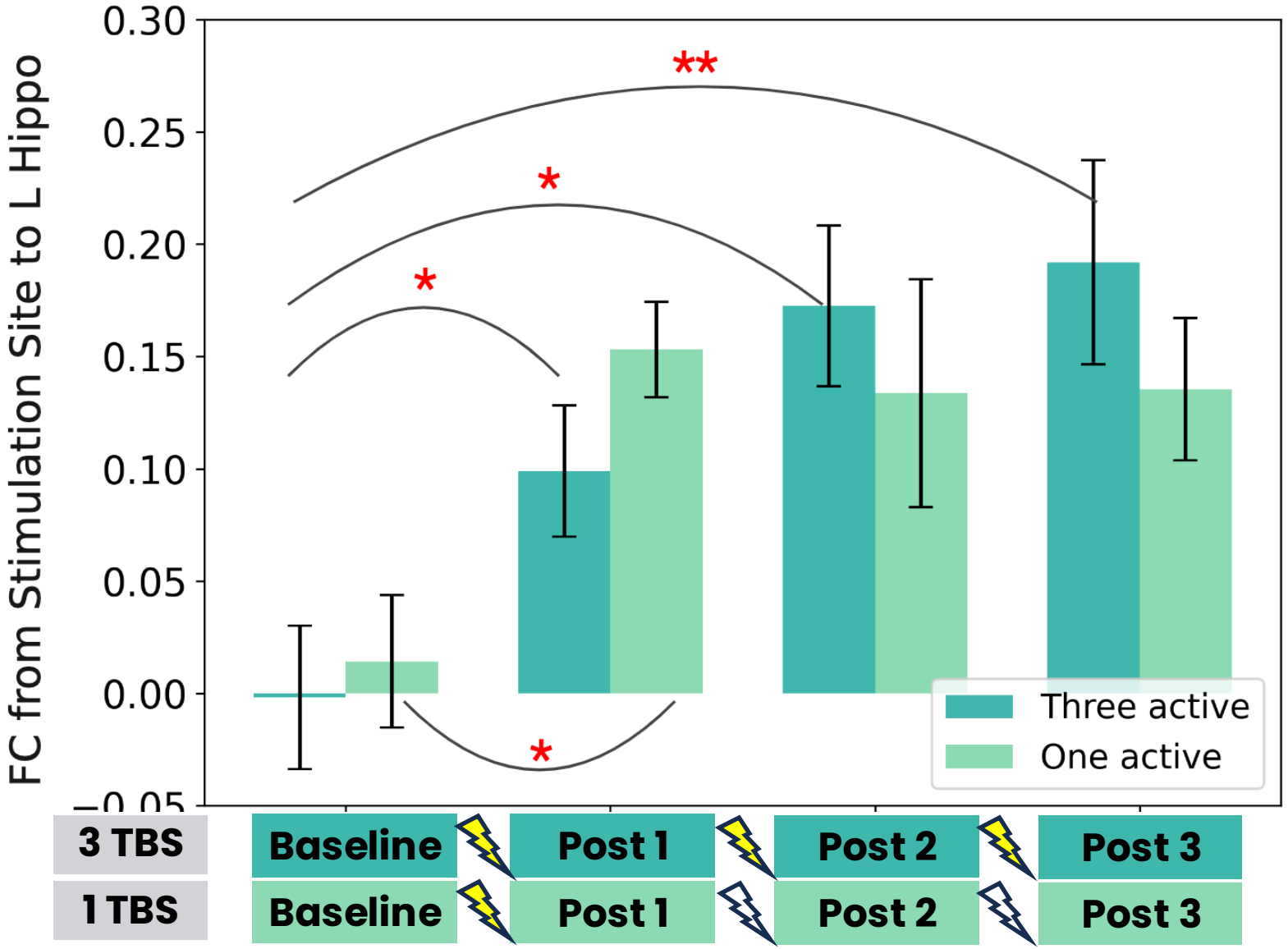


STIMULATION SITE

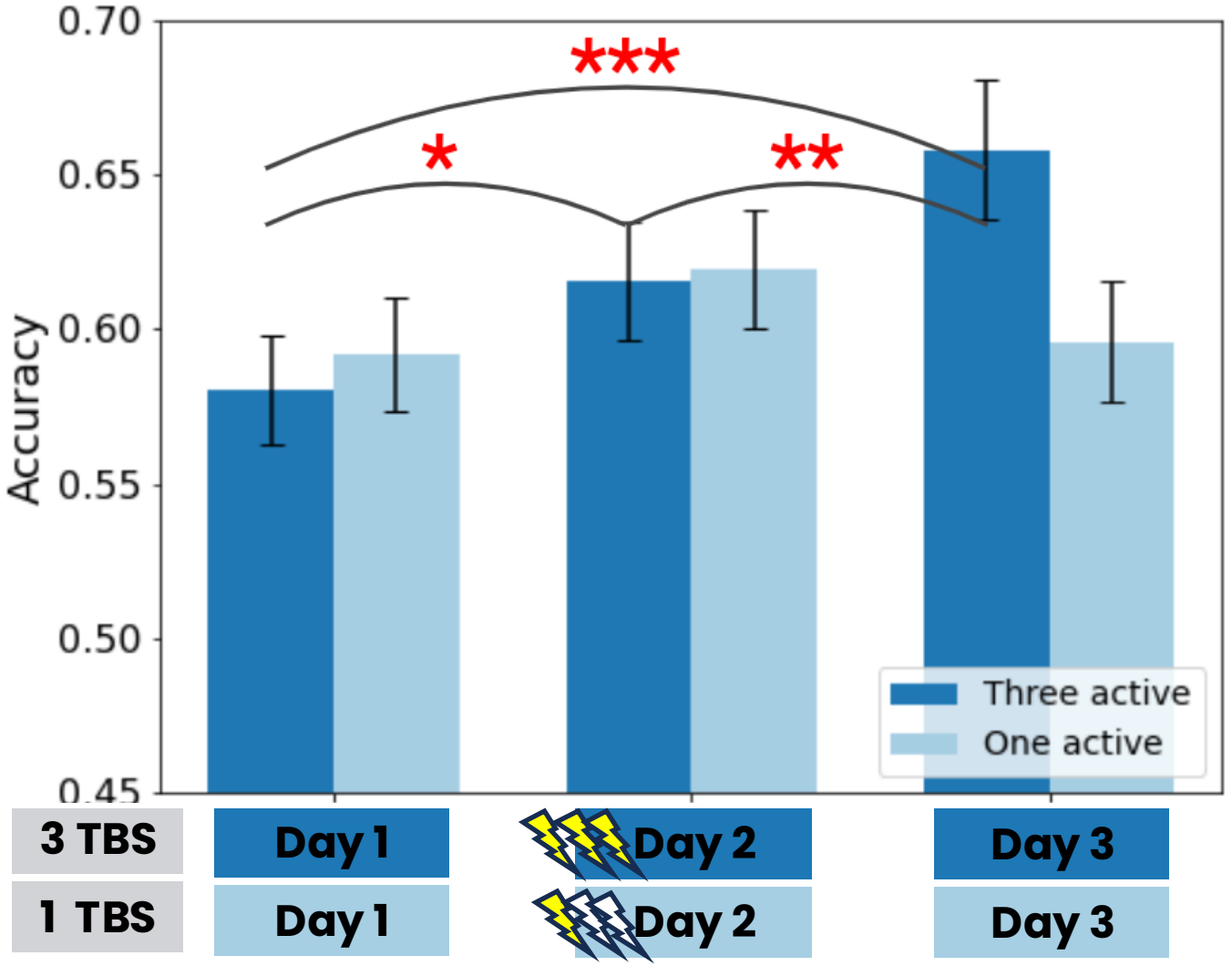
HIPPOCAMPUS – TARGET BRAIN REGION



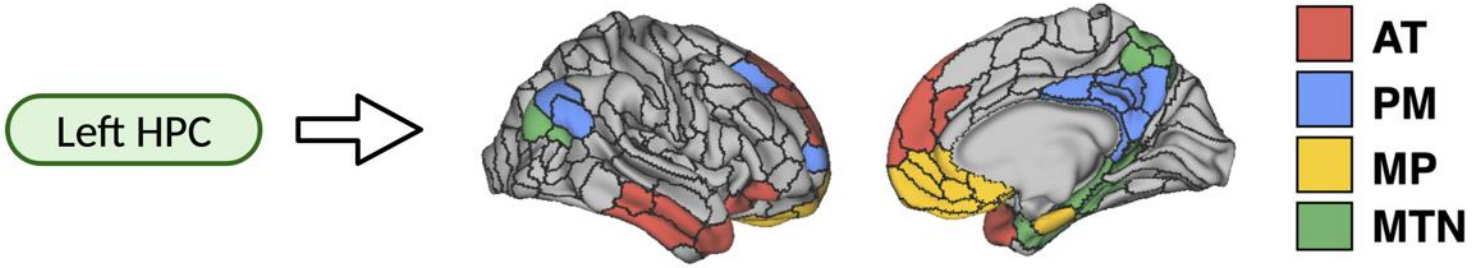
3 iTBS sessions enhanced functional connectivity compared to a single TBS session



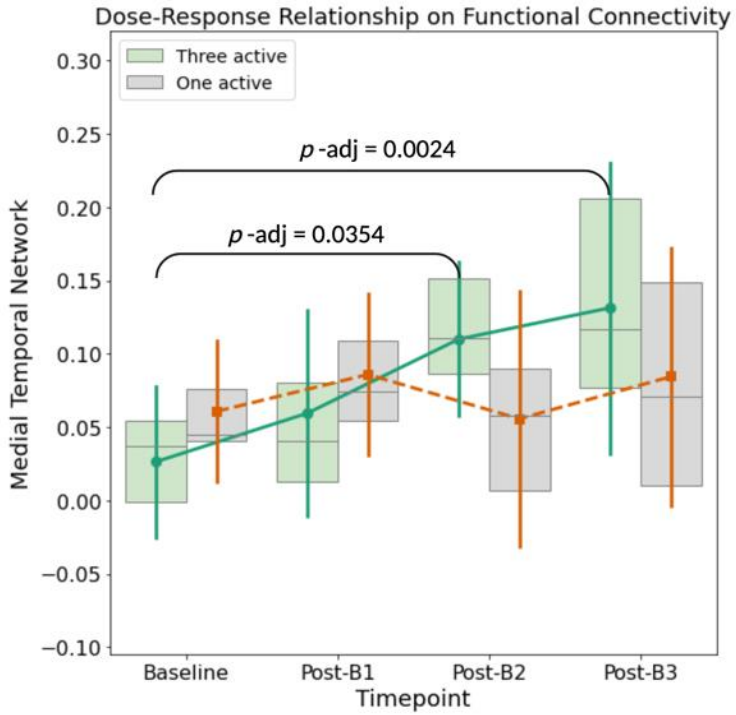
The impact of 3 TBS sessions on associative memory performance has been observed to persist for at least 24 hours following the stimulation.



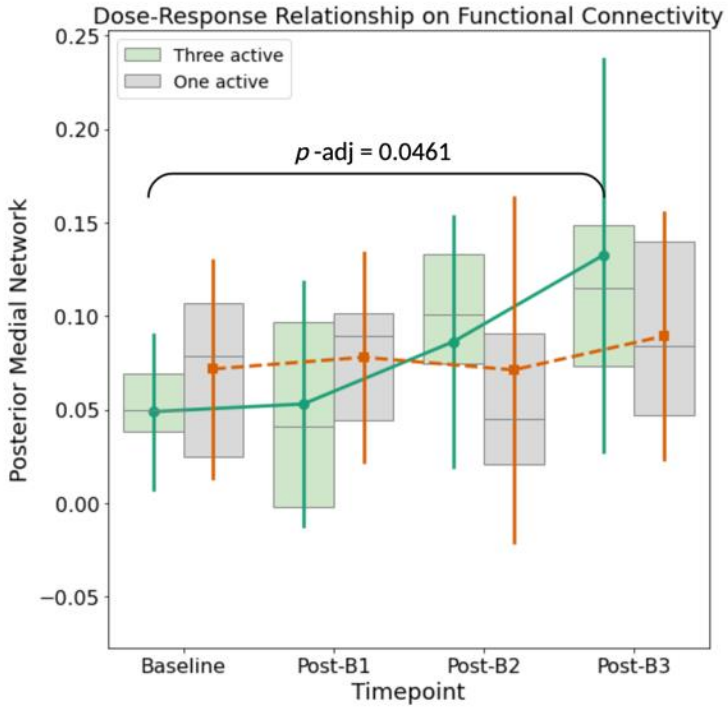
3 iTBS sessions increased functional connectivity between hippocampus and other brain networks.



Medial Temporal Network (MT)

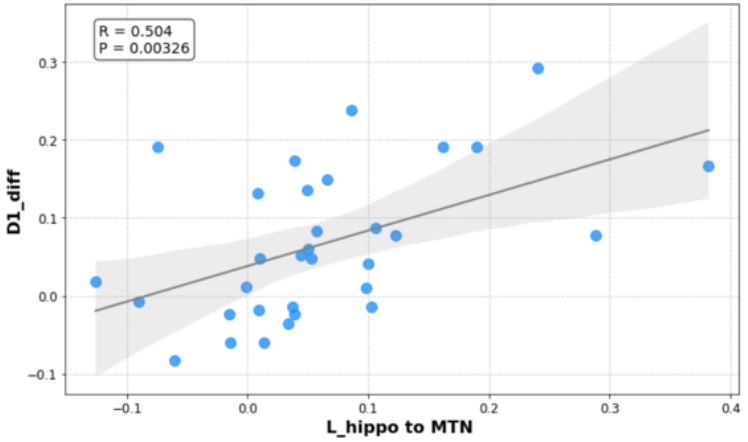


Posterior Medial Network (PM)

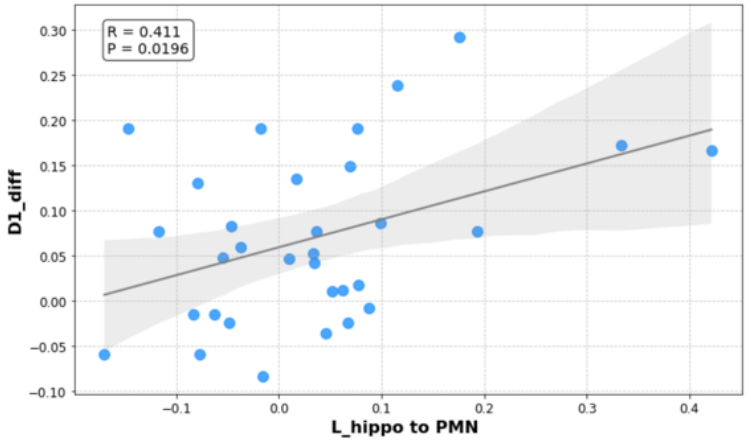


The changes in functional connectivity induced by iTBS were positively linked to improvements in memory.

Medial Temporal Network (MT)

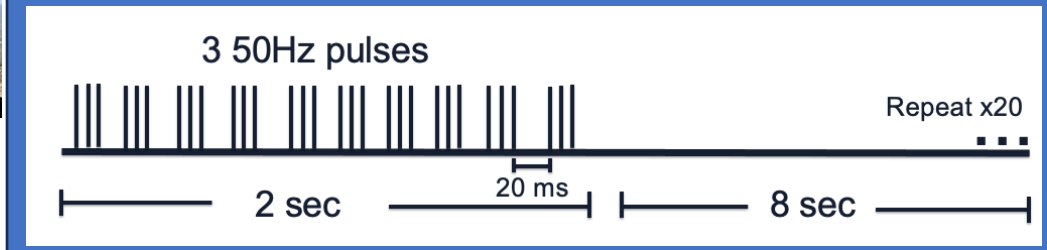


Posterior Medial Network (PM)



Introducing TMS | TMS-based Assessment | Therapeutic TMS

Accelerated intermittent TBS Protocol



Pulses per block: 600 iTBS
Total pulses: 1800 iTBS; ~30 spTMS

Day 0

Preparation

- Mnemonic Similarity Task (intro) — 30 min.
- Structural MRI — 60 min.
- Neuropsychological Assessment — 120 min.

Day 1

Cognitive Task | Block 1 | Block 2 | Block 3 | Cognitive Task

- Mnemonic Similarity Task — 15 min.
- Block 1: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- rest — 50 min.
- Block 2: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- rest — 50 min.
- Block 3: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- Mnemonic Similarity Task — 15 min.

1 month

Day 2

Cognitive Task | Block 1 | Block 2 | Block 3 | Cognitive Task

- Mnemonic Similarity Task — 15 min.
- Block 1: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- rest — 50 min.
- Block 2: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- rest — 50 min.
- Block 3: Resting State EEG — 6 min. | iTBS/Sham — 3 min. | Resting State EEG — 6 min.
- Mnemonic Similarity Task — 15 min.

Research

Original Investigation

Effects of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson Disease
A Systematic Review and Meta-analysis

Ying-hui Chou, ScD; Patrick T. Hickey, DO; Mark Sundman, BS; Allen W. Song, PhD; Nan-kuei Chen, PhD

IMPORTANCE Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been closely examined as a possible treatment for Parkinson disease (PD). However, results evaluating the effectiveness of rTMS in PD are mixed, mostly owing to low statistical power or variety in individual rTMS protocols.

OBJECTIVES To determine the rTMS effects on motor dysfunction in patients with PD and to examine potential factors that modulate the rTMS effects.

DATA SOURCES Databases searched included PubMed, EMBASE, Web of Knowledge, Scopus, and the Cochrane Library from inception to June 30, 2014.

STUDY SELECTION Eligible studies included sham-controlled, randomized clinical trials of rTMS intervention for motor dysfunction in patients with PD.

DATA EXTRACTION AND SYNTHESIS Relevant measures were extracted independently by 2 investigators. Standardized mean differences (SMDs) were calculated with random-effects models.

MAIN OUTCOMES AND MEASURES Motor examination of the Unified Parkinson's Disease Rating Scale.

RESULTS Twenty studies with a total of 470 patients were included. Random-effects analysis revealed a pooled SMD of 0.46 (95% CI, 0.29-0.64), indicating an overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms ($P < .001$). Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46-1.08; $P < .001$) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13-0.87; $P = .008$) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (ie, high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, −0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, −0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, we characterized the quality of evidence presented in this meta-analysis as moderate quality.

CONCLUSIONS AND RELEVANCE The pooled evidence suggests that rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of rTMS effects. The findings of our meta-analysis may guide treatment decisions and inform future research.

Supplemental content at jamaneurology.com

Author Affiliations: Brain Imaging and Analysis Center, Duke University Medical Center, Durham, North Carolina (Chou, Sundman, Song, Chen); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina (Chou); Department of

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Effect of Repetitive Transcranial Magnetic Stimulation on fMRI Resting-State Connectivity in Multiple System Atrophy

Ying-hui Chou,[1,2] Hui You,[3] Han Wang,[4] Yan-Ping Zhao,[3] Bo Hou,[3] Nan-kuei Chen,[1,5] and Feng Feng[3]

Abstract

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been used to treat neurological and psychiatric conditions. Although results of rTMS intervention are promising, so far, little is known about the rTMS effect on brain functional networks in clinical populations. In this study, we used a whole-brain connectivity analysis of resting-state functional magnetic resonance imaging data to uncover changes in functional connectivity following rTMS intervention and their association with motor symptoms in patients with multiple system atrophy (MSA). Patients were randomized to active rTMS or sham rTMS groups and completed a 10-session 5-Hz rTMS treatment over the left primary motor area. The results showed significant rTMS-related changes in motor symptoms and functional connectivity. Specifically, (1) significant improvement of motor symptoms was observed in the active rTMS group, but not in the sham rTMS group; and (2) several functional links involving the default mode, cerebellar, and limbic networks exhibited positive changes in functional connectivity in the active rTMS group. Moreover, the positive changes in functional connectivity were associated with improvement in motor symptoms for the active rTMS group. The present findings suggest that rTMS may improve motor symptoms by modulating functional links connecting to the default mode, cerebellar, and limbic networks, inferring a future therapeutic candidate for patients with MSA.

Key words: cerebellar network; default mode network; limbic network; Monte-Carlo simulation; multiple system atrophy; repetitive transcranial magnetic stimulation; resting-state functional connectivity; Unified Multiple System Atrophy Rating Scale

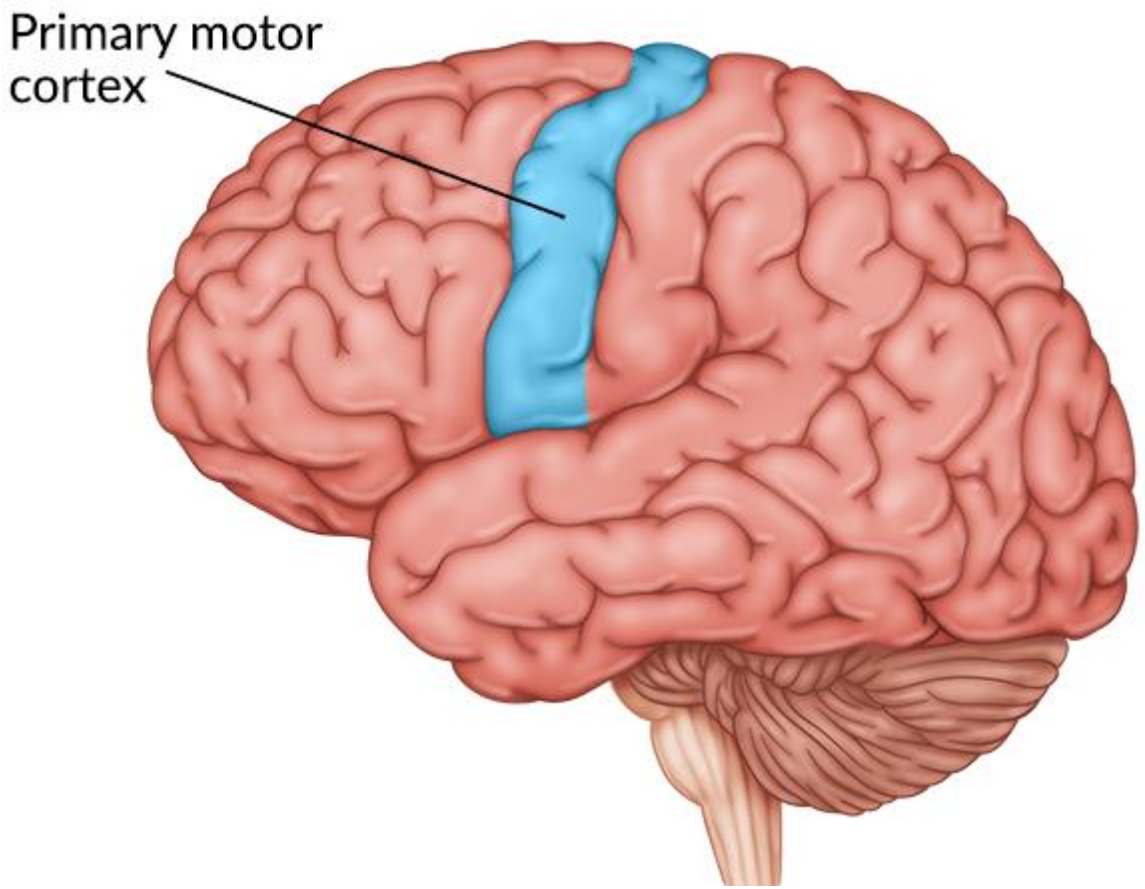
Introduction

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) is a noninvasive neuromodulation technique that has been closely examined as a possible treatment for neurodegenerative diseases (Chou et al., 2015; Nardone et al., 2012). It delivers repeated magnetic pulses through a stimulation coil placed over the scalp to generate a relatively focal electromagnetic field capable of triggering action potentials in neurons (Barker et al., 1985; Rothwell, 1991). Although accumulating evidence suggests that rTMS can stimulation site and how these changes correlate with improvement of symptoms.

Resting-state functional connectivity measured by functional magnetic resonance imaging (fMRI) has played an essential role in understanding brain functional networks and diseases (Fox and Greicius, 2010). Measures of resting-state functional connectivity refer to temporal correlations of fMRI signals between spatially distinct brain regions when participants are not performing a perceptual or behavioral task (Biswal et al., 1995). Neuroimaging studies have identified functional networks, such as the default

Excitatory rTMS over the primary motor cortex improved motor symptoms in patients with Parkinson's disease (Chou et al., 2015; ES = 0.77)

Excitatory rTMS targeting the primary motor cortex led to improvement in motor symptoms for patients with Multiple System Atrophy (Chou et al., 2015)



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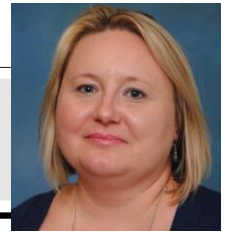

Efficacy of repetitive transcranial magnetic stimulation in treating stroke aphasia: Systematic review and meta-analysis

Aneta Kielar [a,*], Dianne Patterson [a], Ying-hui Chou [b]

[a] Department of Speech and Language Sciences, University of Arizona, AZ, USA
[b] Department of Psychology, University of Arizona, AZ, USA

See Editorial, pages 165–166

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HIGHLIGHTS

- Repetitive Transcranial Magnetic Stimulation (rTMS) can facilitate rehabilitation of language skills in post-stroke aphasia.
- Individual clinical characteristics, rTMS parameters, and language skills moderated treatment effects.
- Low frequency rTMS administered 20–40 min per day over right BA45 improved language abilities for up to 12 months.

ABSTRACT

Objective: This meta-analysis examined the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) in treating post-stroke aphasia with a goal to identify parameters that are associated with successful treatment outcomes.
Methods: Following PRISMA guidelines, ten electronic databases were searched from inception till June 4th 2020. A total of 24 studies (out of 1971 records) with 567 participants met selection criteria and were included in the meta-analysis.
Results: The overall pooled meta-analysis revealed a significant medium effect size in favor of rTMS treatment: Standard mean difference (SMD) of 0.655 (95% CI = [0.481, 0.830], $z = 7.369$, $p < 0.001$). Moderator subgroup analyses indicated that participants' clinical characteristics and rTMS parameters moderated treatment effects. The strongest effects were observed for naming, followed by speech production, repetition and comprehension. The results indicate that with 10 to 15 sessions of 1-Hz rTMS administered 20–40 min per day over right BA45 (Brodmann's area 45), significant language improvements can be observed for up to 12 months.
Conclusions: Our findings suggest that the rTMS technique can enhance rehabilitation of language skills in post-stroke aphasia when administered according to the established safety parameters.
Significance: Our results have implications for treatment of post-stroke aphasia. In subacute aphasia, low frequency rTMS over right BA45 improved naming, repetition, speech fluency and writing but not comprehension, whereas in chronic aphasia naming and speech production improved, but repetition and comprehension showed smaller gains.

1. Introduction

Stroke to the perisylvian brain regions often causes aphasia. Aphasia is debilitating because it can affect speech production and/or comprehension as well as reading and writing. Persistent language impairments prevent return to work, and lead to social

* Corresponding author at: Department of Speech, Language and Hearing Sciences, University of Arizona, 1131 E 2nd St, Tucson, AZ 85719, USA.
E-mail address: akielar@email.arizona.edu (A. Kielar).

Inhibitory rTMS targeting the right BA45 enhances language skills in post-stroke Broca's aphasia (Kielar et al., 2022)

Improving Sleep with Continuous Theta Burst Transcranial Magnetic Stimulation (TMS) of the Default Mode Network

William D. S. Killgore, Samantha Jankowski, Kimberly Henderson-Arredondo, Lindsey Hildebrand, Christopher Trapani, Heidi Elledge, Daniel A. Lucas, Emmet J. Suckow, Melissa Reich-Fuehrer, Gabriela Franca, Deva Reign, Alisa Huskey, Yu-Chin Chen, Ying-Hui Chou, & Natalie S. Dailey

[1]University of Arizona, Tucson, AZ

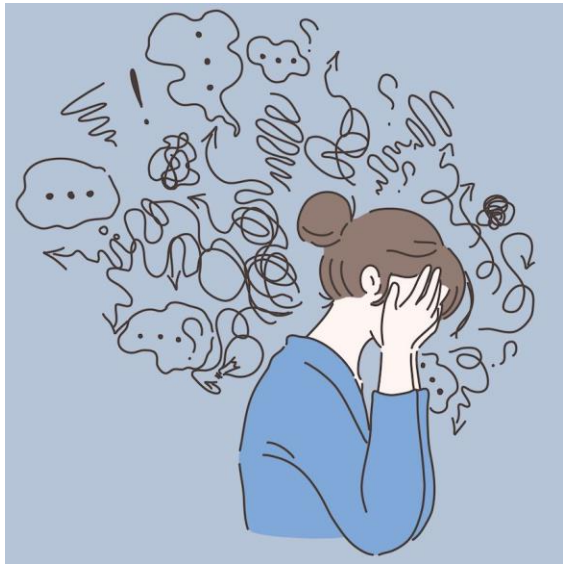
Objective: Nearly one in three Americans struggle with chronic insomnia, a disorder associated with increased cognitive arousal. Insomnia is also associated with activation/connectivity within the default mode network (DMN) of the brain, consistent with the hyperarousal theory. We hypothesized that suppression of the DMN with a type of repetitive transcranial magnetic stimulation (rTMS) known as continuous theta burst stimulation (cTBS) would lead to improved overnight sleep.

Methods: Twenty participants (12 female; age=26.9, SD=6.6 years) meeting criteria for insomnia/sleep disorder completed a counterbalanced sham-controlled crossover design in which they served as their own controls on two separate nights of in-laboratory polysomnography (PSG) monitored sleep on separate weeks. Sessions included two resting state functional magnetic resonance imaging (fMRI) sessions separated by a brief 40 second cTBS rTMS session applied over an easily accessible cortical surface node of the DMN located at the left inferior parietal lobe. After scanning/stimulation, participants were allowed an 8-hour sleep opportunity from 2300 to 0700 monitored with PSG.

Results: One session of active cTBS produced a significant alteration of functional connectivity ($p<.05$, FDR corrected) within the DMN, while the sham condition produced no changes in functional connectivity from pre- to post-treatment. After controlling for age and IQ, active treatment was associated with significant ($p<.05$) improvements in PSG measured Total Sleep Time (TST; $\eta_p^2=.28$), latency to Slow Wave Sleep (SWS; $\eta_p^2=.23$), Sleep Efficiency (SE; $\eta_p^2=.28$), and a lower Arousal Index ($\eta_p^2=.22$). Overall, individuals obtained 16 minutes more sleep after active cTBS compared to sham. Moreover, changes in brain connectivity following cTBS significantly ($p<.05$) predicted sleep outcomes, including TST, sleep latency, SE, minutes of wake, SWS, number of awakenings, arousals, and arousal index.

Conclusions: Findings suggest that brief targeted 40-second stimulation with cTBS can alter DMN brain functioning and was associated with improved PSG measured sleep outcomes during the night following stimulation. The effect sizes often exceed those observed for other established treatments such as cognitive behavioral therapy for insomnia or hypnotic sleep medications. Further work involving multiple stimulations over several days or weeks will be necessary to demonstrate the potential utility of this approach as a treatment for insomnia.

10 rTMS sessions targeting the left dorsolateral prefrontal cortex have potential to alleviate cognitive impairment associated with chemobrain



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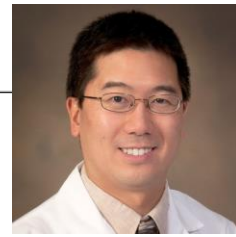

Case Report

Transcranial Magnetic Stimulation for the Treatment of Chemo Brain

Phillip H. Kuo [1,*], Allison Yu-Chin Chen [2], Rudolph J. Rodriguez [3], Carol Stuehm [4], Pavani Chalasani [5], Nan-Kuei Chen [6] and Ying-Hui Chou [7]

1 Departments of Medical Imaging, Medicine, and Biomedical Engineering, University of Arizona, Tucson, AZ 85721, USA
2 Brain Imaging and TMS Laboratory, Department of Psychology, University of Arizona, Tucson, AZ 85721, USA; yuchinchen@arizona.edu
3 Department of Physics, University of Colorado, Boulder, CO 80301, USA; rudolph.rodriguez@colorado.edu
4 Department of Medical Imaging, University of Arizona, Tucson, AZ 85721, USA; carols@arizona.edu
5 Division of Hematology-Oncology, George Washington Cancer Center, Washington, DC 20037, USA; pavani.chalasani@gwu.edu
6 Department of Biomedical Engineering, University of Arizona, Tucson, AZ 85721, USA; nkchen@arizona.edu
7 Brain Imaging and TMS Laboratory, Department of Psychology, Evelyn F McKnight Brain Institute, Arizona Center on Aging, BIO5 Institute, University of Arizona, Tucson, AZ 85721, USA; yinghuichou@email.arizona.edu
* Correspondence: pkuo@email.arizona.edu; Tel.: +1-520-626-1957; Fax: +1-520-626-1945

Abstract: This pilot feasibility study aimed to evaluate the effects of transcranial magnetic stimulation (TMS) on chemotherapy-related cognitive impairment (CRCI), and we report here on the first patient. Background: Deleterious cognitive changes due to chemotherapy or CRCI are commonly referred to as "chemo brain". With the increasing survival of cancer patients, this poorly understood and inadequately treated condition will likewise have an increasing toll on individuals and society. Since there is no approved treatment for chemo brain, we have initiated a therapeutic trial using transcranial magnetic stimulation (TMS), a non-invasive brain stimulation technique approved in many countries for the treatment of neurologic and psychiatric conditions like migraine and depression. Case presentation: A 58-year-old woman, diagnosed 7 years prior with left breast cancer, underwent partial mastectomy with sentinel lymph node biopsy. She then received four cycles of adjuvant chemotherapy followed by radiation therapy. Afterwards, she was on tamoxifen for 4 years and then switched to aromatase inhibitors. The patient's CRCI started during chemotherapy and severely impaired her quality of life for an additional two years. In the third year after chemotherapy, the CRCI partially cleared to stabilize to the level at the time of presentation for this trial. The patient continues to have memory difficulties and decreased concentration, which makes multi-tasking very difficult to impossible. She is reliant on memory aids at work and at home. The participant underwent 10 consecutive sessions of TMS during weekdays for 2 weeks. Stimulation was directed to the left dorsolateral prefrontal cortex. After TMS, the participant significantly improved in memory function on neuropsychological testing. While she reported no subjective differences in concentration or memory, she did report an improvement in her sleep. Functional magnetic resonance imaging of the brain before and after TMS showed increased resting-state functional connectivity between the stimulation site and several brain regions. Remarkably, after 6 years of chemo brain and remaining in the same position at work due to her inability to concentrate and multi-task, she applied for and received a promotion 5–6 months after her TMS treatments. Conclusions: This first patient in the phase 1 clinical trial testing of TMS for the treatment of "chemo brain" provided important lessons for feasibility and insights into mechanisms of potential benefit.

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Therapeutic TMS Research Highlights

- Multiple TMS devices have received FDA clearance for the treatment of depression, migraine, OCD, and smoking cessation.
- Evidence suggests diffusion MRI-guided TMS improves memory and bolsters parietal-hippocampal network functional connectivity.
- Multiple TMS sessions daily may yield more sustained memory enhancement benefits.
- TMS can be used to induce neuroplasticity and holds promise as a treatment for conditions such as MCI, AD, stroke aphasia, chemobrain, and insomnia.

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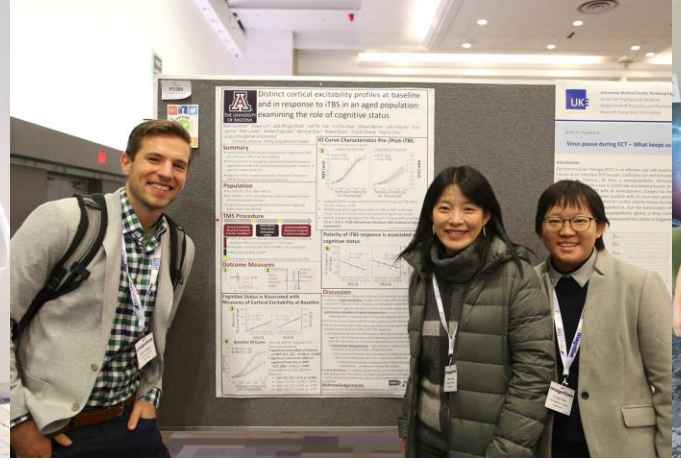
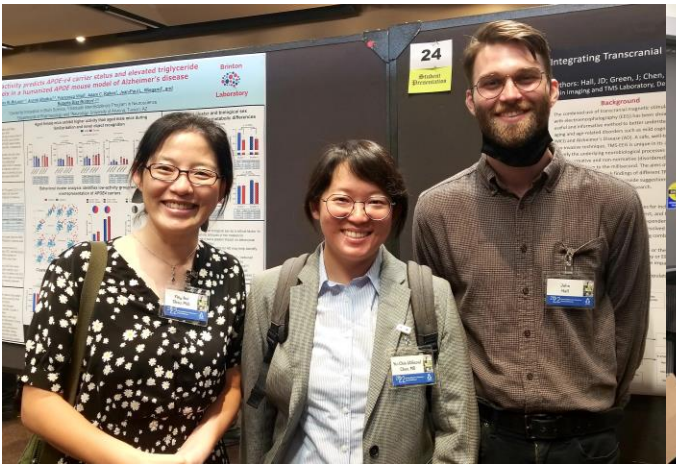
yinghuichou@arizona.edu


Distinct cortical excitability profiles at baseline and in response to iTBS in an aged population: examining the role of cognitive status
Summary
Population
TMS Procedure
Outcome Measures
3D Curve Characteristics Pre-/Post-iTBS
Discussion
Acknowledgements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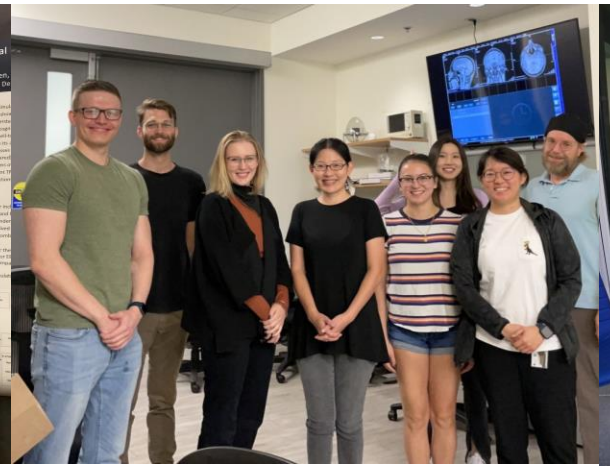
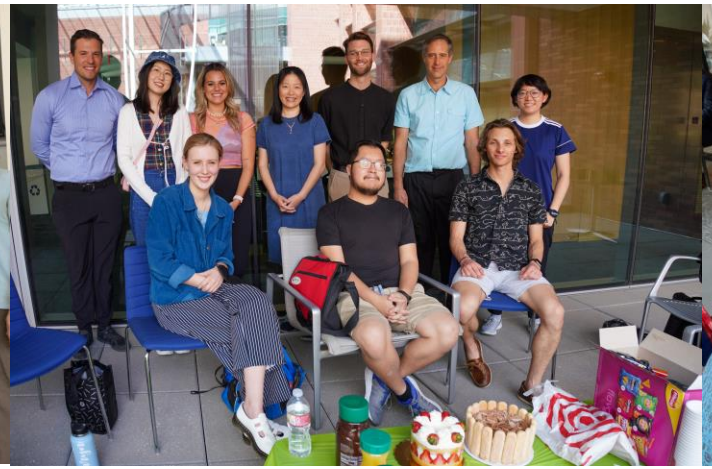
Integrating Transcranial
Laboratory



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