2021

Effect of Targeted Transcranial Magnetic Stimulation on Hippocampal-Dependent Declarative Memory in Older Adults

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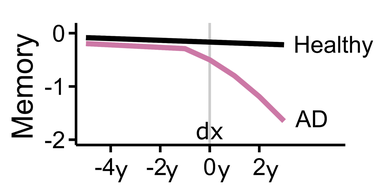
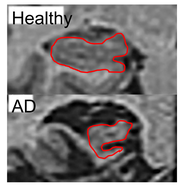
The research reported on this poster was supported by Great Plains IDeA-CTR, Fremont Area Alzheimer's Fund, UNMC DONS, and the UNMC MSSRP. The investigators retained full independence in the conduct of this research.

Background

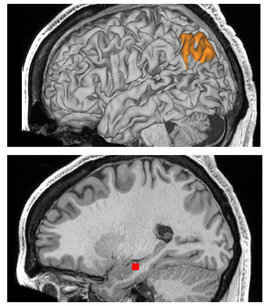
- Memory disorders affect patients, caregivers, and health care systems by reducing independence and degrading identity
- Healthy aging is related to slow declines in memory and hippocampal atrophy
- Pathological aging due to AD is associated with sharp declines in memory





- Restoring memory abilities could lessen debilitating effects of memory loss
- Non-invasive transcranial magnetic stimulation (TMS) has been identified as a possible treatment modality for the memory deficits typical of AD
- TMS has led to improved memory in healthy young adults but has not yet been applied to healthy and non-healthy older adults

Transcranial Magnetic Stimulation



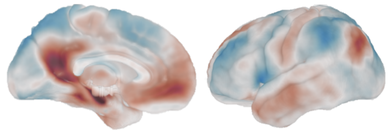
- TMS induces electric current in brain tissue using strong magnetic fields
- Stimulation can be excitatory or inhibitory
- TMS can only penetrate 3-4 cm beneath skull — no deep structures
- Repetitive TMS (rTMS) = stimulation delivered with a Nexstim 5.0 NBS at 20 Hz (2 sec stim, 28 sec pause, 20 min. per day for 5 consecutive days)

Connections from the lateral parietal cortex (targeted brain region) reach the hippocampus and its functional network
Hippocampal networks are imperative for storage and retrieval of relational memories (targeted cognitive ability)
Frequencies >1 Hz increase activity in the stimulated parietal region and its extended network

Specific Aims

(1) Declarative memory will be measured in older participants who are treated with repetitive TMS (rTMS). It is hypothesized that with rTMS, a significant positive change will occur in declarative memory performance when compared to those who receive placebo ("sham") stimulation.

(2) Specific brain networks related to memory will be measured using MRI in older adults who are treated with rTMS. It is hypothesized that those administered rTMS compared to a sham stimulation will show in increase in connectivity within brain networks related to memory abilities.



Left: Memory networks in the brain that are connected to the hippocampus

Hypothesis: A 5-day course of excitatory rTMS focused on one part of a target brain network will improve the connectivity of that network with associated improvements in memory abilities and tested via neuropsychological assessment and functional neuroimaging with MRI

Methods

- Participants drawn from the UNMC Mind Brain Health Registry and the UNMC DONS Memory Disorders Clinic and compensated for their time
- Age range from 65-85 years old
- Informed consent and screening prior to full enrollment
- Screening criteria: MoCA score of >26 in order to continue, confirm rTMS and MRI compatibility by ruling out implanted devices, claustrophobia, history of seizure, and excessive movement during MRI scanning

Table 1. Experimental protocol for the proposed study.

Day(s)	Phase	Note	Description
0	Informed Consent	—	Consent of recruited participants
	Post-consent Screening	—	MoCA, MRI screening, TMS screening, etc.
1	Memory Assessment	1st of 4	Behavioral measures of Hc-dependent memory abilities
	MRI exam	1st of 4	Structural and functional neuroimaging
2-6	rTMS protocol	1st of 2	rTMS (*real* or *sham*) for five consecutive days
7	MRI exam	2nd of 4	Structural and functional neuroimaging
	Memory Assessment	2nd of 4	Behavioral measures of Hc-dependent memory abilities
8-21	— *Break* —	2 wks	Two week break before continuing in next study phase
22	Memory Assessment	3rd of 4	Behavioral measures of Hc-dependent memory abilities
	MRI exam	3rd of 4	Structural and functional neuroimaging
23-27	rTMS protocol	2nd of 2	rTMS (*real* or *sham*) for five consecutive days
28	MRI exam	4th of 4	Structural and functional neuroimaging
	Memory Assessment	4th of 4	Behavioral measures of Hc-dependent memory abilities
	Debriefing & Payment	—	End of participation

Long-term memory → declarative memory → non-relational vs. relational memory
Relational memory includes: words, events, sequences, routes, and scenes
The hippocampus is necessary for normal relational memory.

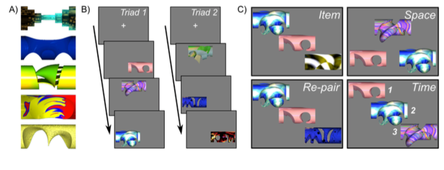
Neurocognitive Testing

Used to measure participant cognitive abilities at baseline
After rTMS, compare cognitive abilities to baseline abilities and determine if a relationships or improvement exists

spoon

Left: Example of face image used during recall and oral presentation of associated word after studying 20 different pairs

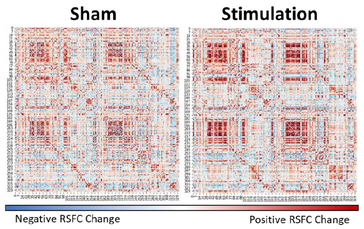
Right: Objects used in relational memory tasks that require hippocampal contributions



Status and Future Directions

Enrollment of healthy younger adults has been closed and completed
Preliminary data shows increased recall of more words with history of treatment with rTMS (in both younger and older adults)

Right: A cross correlation matrix from a healthy young adult showing the effects of sham and stimulatory rTMS.



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