

Macro and micro structural preservation of grey matter integrity after 24 weeks of rTMS in Alzheimer's disease patients: a pilot study

Mencarelli et al. (2024)

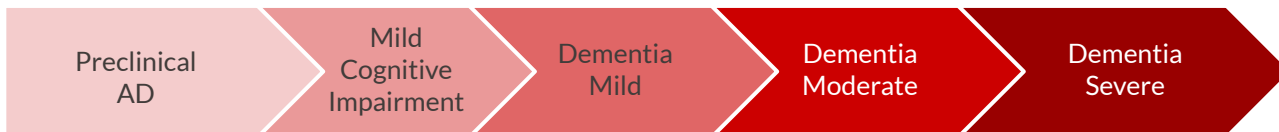
Gonçalo Braga, Julie Le Tallec & Matthew Morvan

Alzheimer's Disease (AD)

Definition and Prevalence

Progressive neurodegenerative disorder:

- ❑ memory loss
- ❑ cognitive decline
- ❑ behavioral changes



55 million people worldwide

> 65 years

Risk **doubles** every 5 years after 65

2023 Alzheimer's disease facts and figures

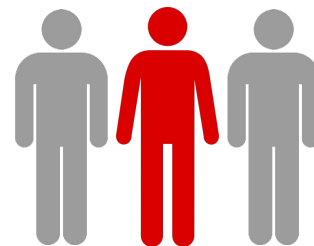
Alzheimer's Disease (AD) Definition and Prevalence

6TH
**LEADING CAUSE
OF DEATH**

in the USA

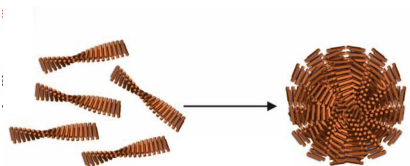


cannot be prevented,
cured or slowed

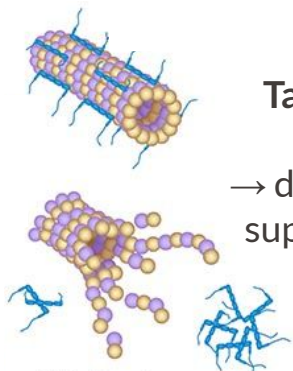


1 in 3 seniors dies with
AD or another dementia

Alzheimer's Disease (AD) Pathophysiology



Clumps of **beta-amyloid protein** accumulate between nerve cells



Tau protein forms tangles
→ disrupt the internal support structure of neurons

**progressive
neuron loss**



**brain
shrinkage**

(precuneus, DMN !)



Neuroinflammation and synaptic dysfunction

Alzheimer's Disease (AD)

Treatment Approaches

Existing Therapies

Pharmacological

- ❑ Cholinesterase inhibitors
- ❑ NMDA receptor antagonists

Non-pharmacological

- ❑ Cognitive stimulation therapy
- ❑ Psychosocial interventions
- ❑ ...



Just symptomatic relief
Efficacy
Side effects

Emerging Therapies

Neuromodulation Techniques

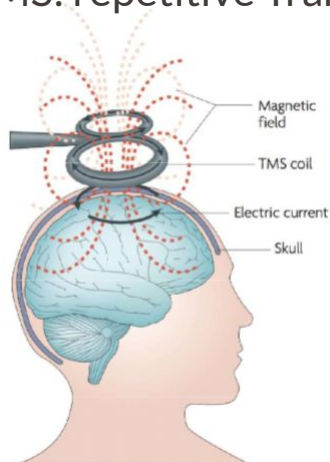


Gene therapy/Immunotherapy



rTMS principles

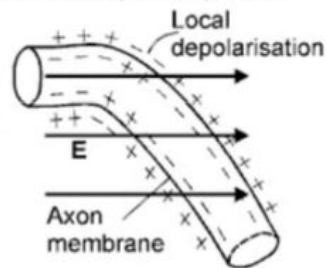
rTMS: repetitive Transcranial Magnetic Stimulation



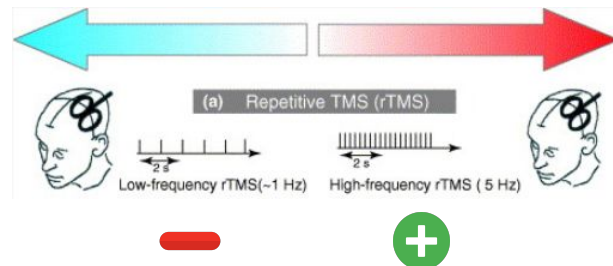
Ridding & Rothwell 2007 Nat Rev Neurosci

Neuromodulation with a directed magnetic field

Microscopic response



Mechanism: local depolarization of the axonal membrane



HF : Excitatory
LF : Inhibitory

Lefaucheur et al. (2014), Rosanova et al. (2011), Quartarone et al. (2006), Russo et al. (2017)

Scientific Gap: rTMS

PC-rTMS modulates
long-term memory in
healthy controls and AD
patients

Bonni S et al, 2015

Animal models:
rTMS increases
expression of neurogenic
properties

Choung JS et al, 2021



Cognitive modulation effects

Cotelli M et al, 2011



Impact on **neuroimaging**
Grey matter degeneration,
network activity and integration



rTMS enhances long-term
plasticity mechanisms

Hypotheses

1. PC-rTMS treatment **counteracts atrophy progression** in AD patients
 - macro structural level
 - micro structural level
2. PC-rTMS treatment leads to **changes in brain functional pathways**, that could influence network-to-network connectivity

Experimental Design



Mild to Moderate AD Patients
(n = 16)

=

Active PC-rTMS
(n = 8)

+

Sham PC-rTMS
(n = 8)

Week 1-2
(10 daily sessions)

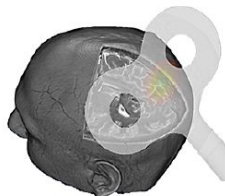
Week 3-24
(22 weekly sessions)

Intensive Phase

Maintenance Phase

Structural and
Functional MRI

Week 0 (W0)

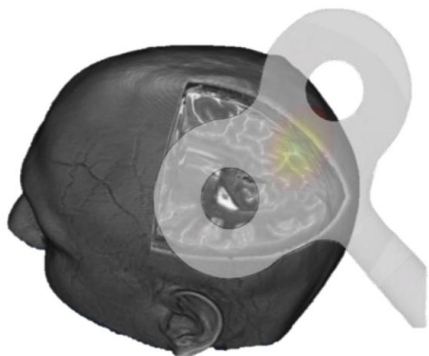


Structural and
Functional MRI

Week 24 (W24)

Mencarelli et al. (2024)

rTMS Stimulation Strategy



Target: Precuneus (PC)

Frequency: 20 Hz

Position: Parallel to midline
pointing up

Current: Posterior-anterior
directed current

Session duration: 20 min

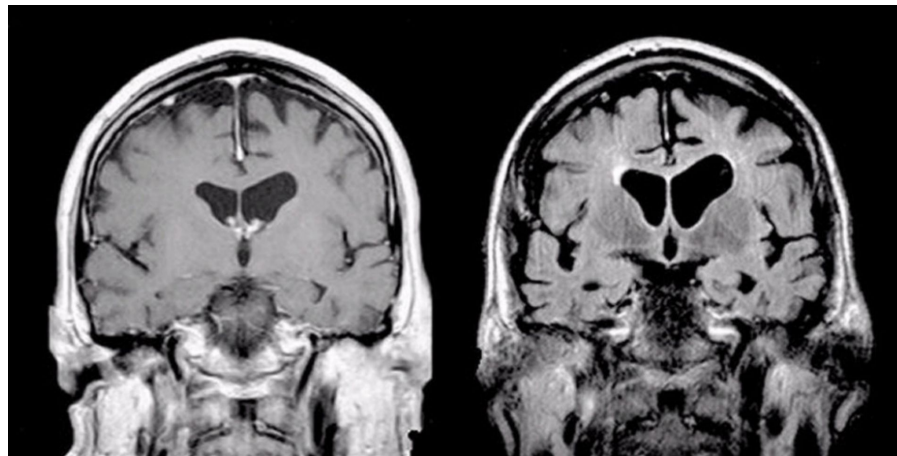
Mencarelli et al. (2024)

Analysis Methods (1)

Macro-structural

- T1-Weighted MRI
- Voxel based morphometry
- Changes in Grey Matter ?

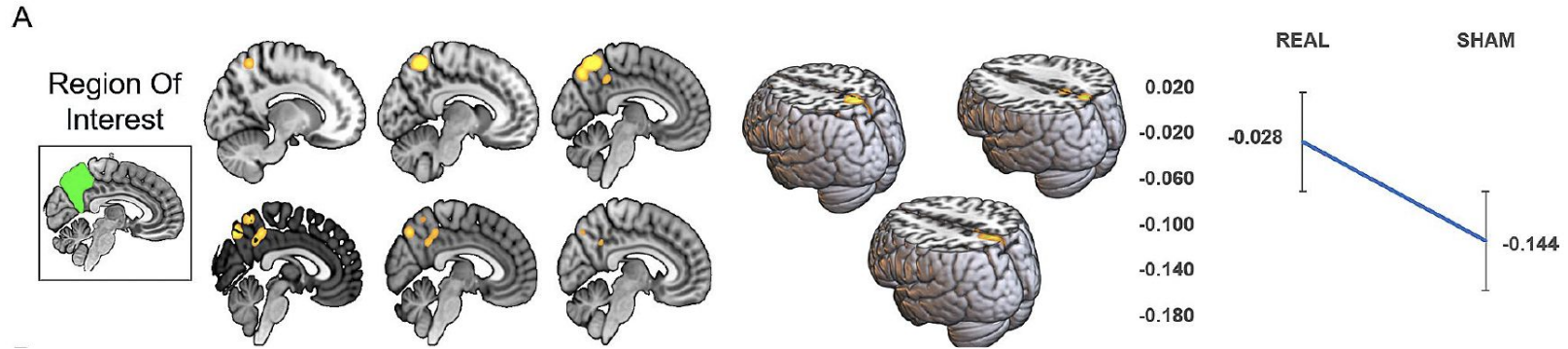
Carried out a 2-way ANOVA on
volumetric changes of the precuneus.



T1 weighted image of grey matter alteration in AD

Teipel et al. (2015)

Macro-Structural Results

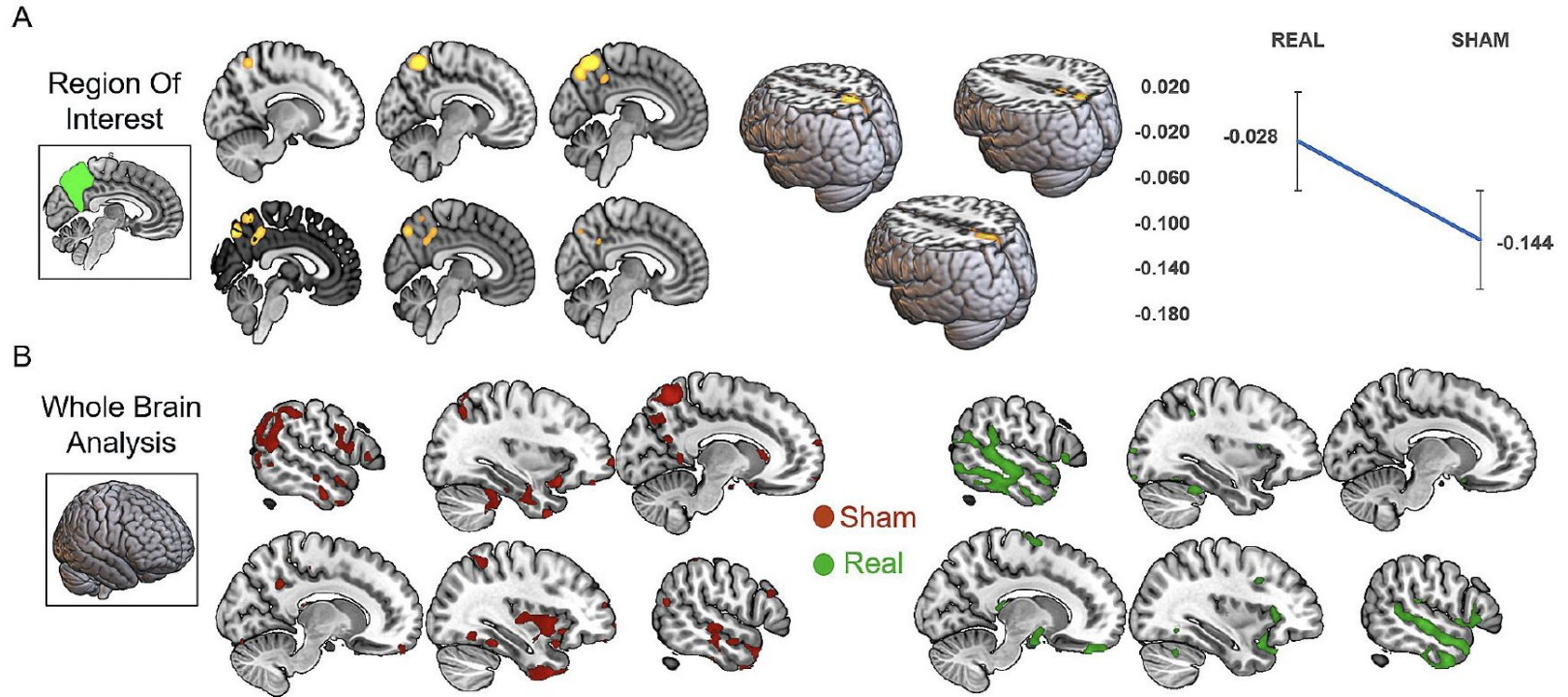


Macro-structural results.

Precuneus grey matter decrease
significantly higher for sham ($p < 0.001$)

Mencarelli et al. (2024)

Macro-Structural Results



Macro-structural results.

Mencarelli et al. (2024)

Analysis Methods (2)

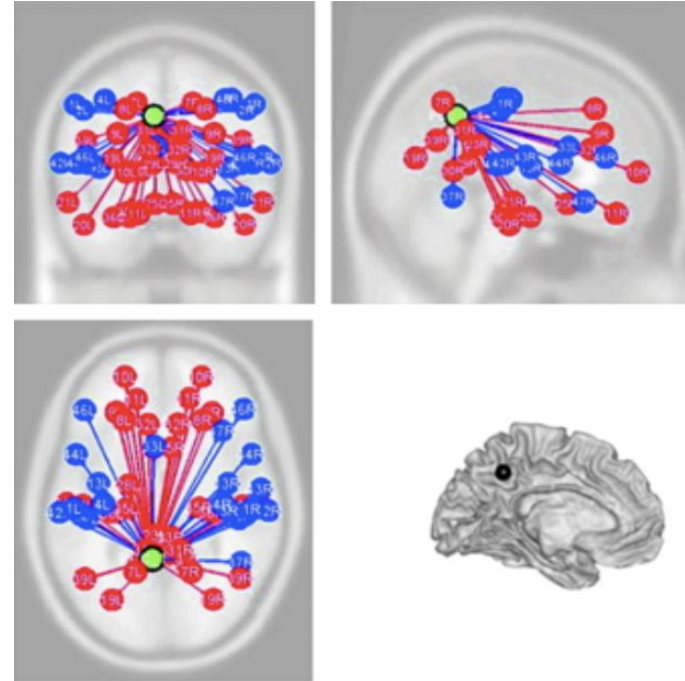
Macro-structural

- T1-Weighted MRI
- Voxel based morphometry
- Changes in Grey Matter ?

Functional

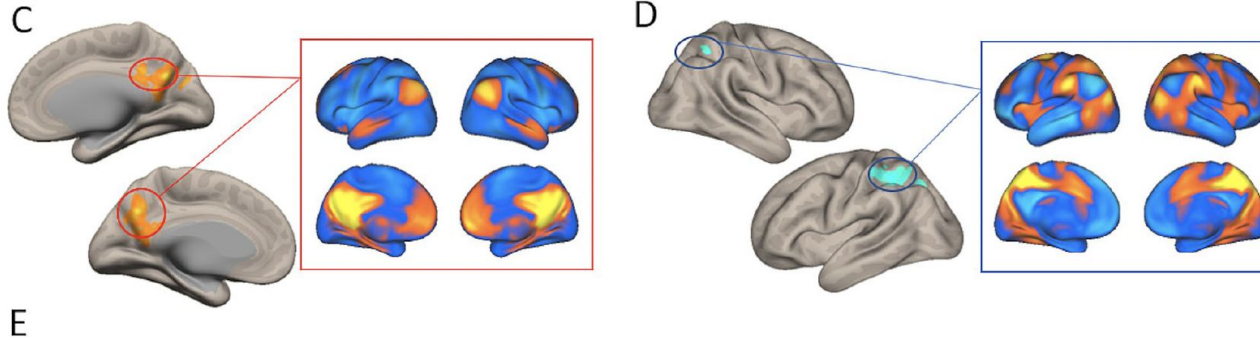
- BOLD timecourse (fMRI)
- Connectivity changes

Carried out a 2-way ANOVA
on seed (precuneus) to voxel
connectivity.



Seed to voxel connectivity using the precuneus
Whitfield-Gabrieli et al. (2012)

Functional Connectivity Results



Functional connectivity results.

Mencarelli et al. (2024)

Increased functional
connectivity with DMN

Decreased functional
connectivity with DAN
(superior parietal lobule)

Analysis Methods (3)

16

Julie

Mencarelli et al. (2024)

Macro-structural

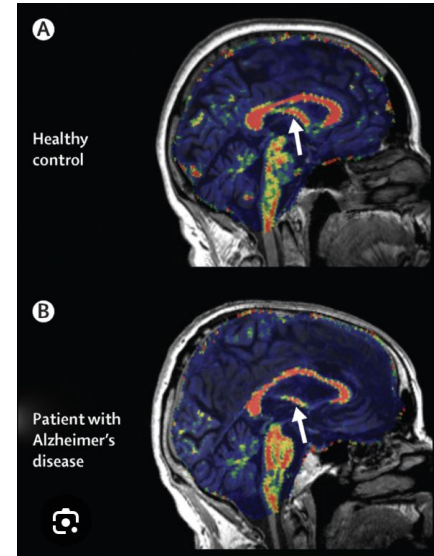
- T1-Weighted MRI
- Voxel based morphometry
- Changes in Grey Matter ?

Functional

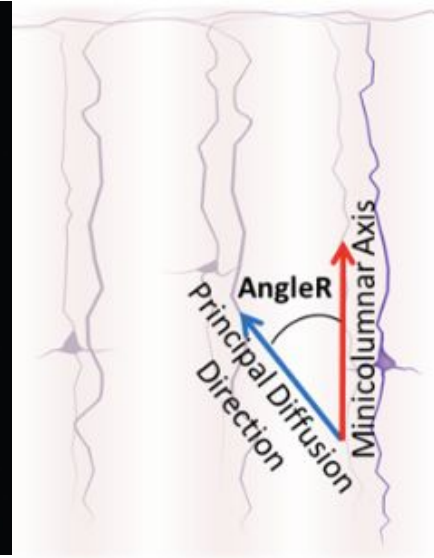
- BOLD timecourse (fMRI)
- Connectivity changes

Micro-structural

- Diffusion tensor imaging and AngleR
- Micro-structural grey matter changes



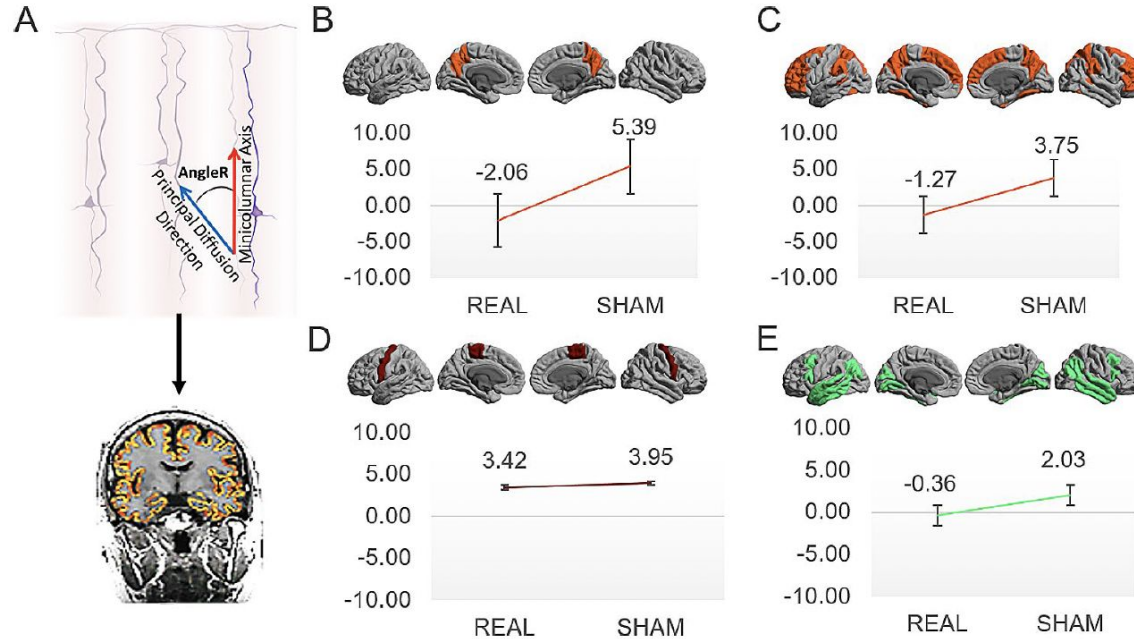
Diffusion V1



AngleR

GLMs to compare V1 and AngleR between groups.

Micro-Structural Results



Micro-structural results.

Lower AngleR for
PC-rTMS compare to
sham

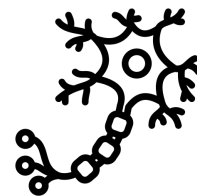
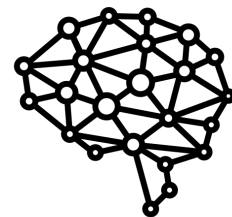


Less cortical
degeneration with
PC-rTMS

Mencarelli et al. (2024)

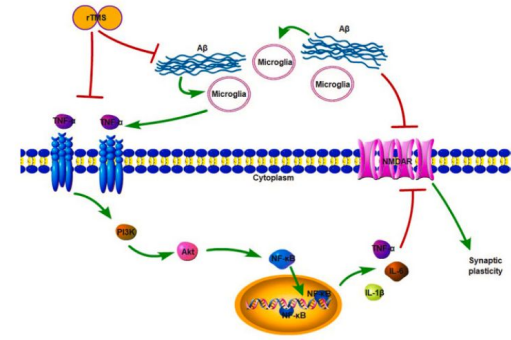
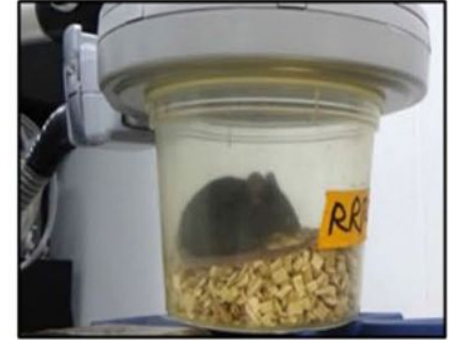
Discussion

- rTMS may be able to slow down atrophy in AD patients
 - GM volume preservation in PC-rTMS
 - spatially specific
- Connectivity improvements to DMN, reduced connectivity to the Dorsal Attention Network
 - PC for DMN modulation
- rTMS contributes to cortical microstructural preservation
 - Microstructural metrics as potential clinical trial outcomes



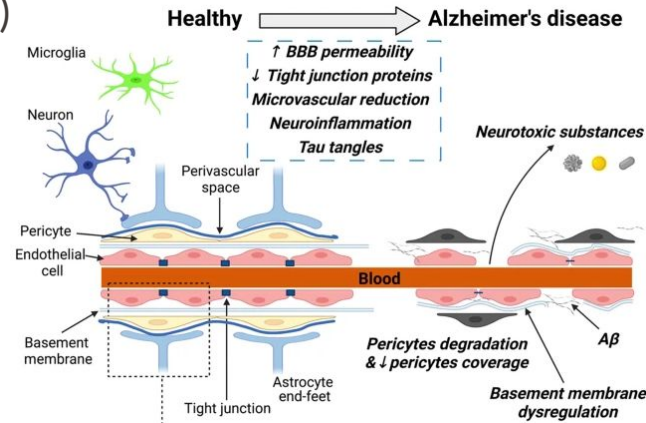
Animal Models

- Choung et al. (2021) showed that 20Hz-rTMS increases the expression of growth factors (BDNF) in mice
 - Counteracts AD synaptic loss and neurodegeneration
- rTMS reduces levels of $A\beta$ and microglia activation and decreases pro-inflammatory cytokines (Li et al.)



AD treatments

- TUS therapies that modulate BBB permeability to clear $A\beta$ are under development, rTMS could be capable of the same (Petrovskaya et al.)
- Other studies have shown long-lasting structural and functional reorganization following repeated NIBS, when coupled with cognitive training (Antonenko et al.)



Limitations

- Reduced sample size (8 per group)
- Unequal gender representation (6 females, 10 males)
- Cohort characteristics lacking
 - risk factors
 - ethnicities and family history
- TMS applied by hand
- Non longitudinal design
- Could not correlate the results with cognitive outcomes or clinical effects



Conclusion

- 1st pilot study to investigate the neurobiological alterations after multiple sessions of PC-rTMS in AD patients
- rTMS comes out as a possible auxiliary AD treatment to hinder atrophy progression, maintain connectivity and so hopefully delay cognitive symptoms
- Still lacking insights on cognitive and clinical impacts as well as long term effects of PC-rTMS

Supplementary Material

Cortical Diffusivity Analysis

