# Cognitive Remediation Combined with Transcranial Magnetic Stimulation in Alzheimer's Disease

Lukas Schilberg[1], Anna-Katharine Brem[1], Catarina Freitas[1], Natasha Atkinson[1], Erica Seligson[1], Edward Gold[1], Ilya Vidrin[1], Alvaro Pascual-Leone[1]
[1]Berenson–Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center
Harvard Medical School, Boston, USA

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia. Histopathologically AD is characterized by amyloid plaques, fibrillary tangles, and cortical atrophy. Growing evidence suggests that aberrant plasticity as an early pathophysiologic process. Existing AD treatments show limited benefit and have side effects. We are evaluating a novel, non-pharmacological intervention merging transcranial magnetic stimulation (TMS) with computer based cognitive remediation (CR) in mild-moderate AD. TMS can be used to modulate brain plasticity and it may enhance the effects of cognitive intervention methods when administered in combination.

## Methods

### Patients

| N= 12, 6 Control, 6 Treatment | Treatment | Control |
|---|---|---|
| Age | 70.33 ± 2.07 | 69.83 ± 10.82 |
| Male/female | 2/4 | 4/2 |
| MMSE | 21 ± 2.97 | 21.67 ± 3.01 |
| Medicated | 6/6 | 6/6 |

**Main Inclusion Criteria :**
- Mild to Moderate AD patients
- Age 55-85 years
- MMSE 18-24

**Main Exclusion Criteria:**
- Brain related illness/injury
- Epilepsy
- Unstable medical condition

### Treatment

- The NICE system (NeuroAD™, Neuronix Ltd., Israel) interleaves cognitive training and rTMS (**Fig. 1**). Cognitive training is matched to the six regions targeted (right and left dorsolateral prefrontal cortex, right and left inferior parietal cortex, Broca, Wernicke) (**Fig.2**). Treatment course consisted in a 6 week course of 5 daily sessions per week.
- Sham treatment: combination of sham cognitive training and sham rTMS for a period of 6 weeks.
- Before and after the 6-week training, brain plasticity was assessed by applying single pulses (120% RMT) before and after intermittent theta burst stimulation (iTBS; 80% AMT) over the left hemisphere (**Fig. 3**).
  - Brain plasticity of M1 was assessed with TMS-EMG measures of the first dorsal interosseus muscle (FDI).

**Fig. 1** Study Protocol

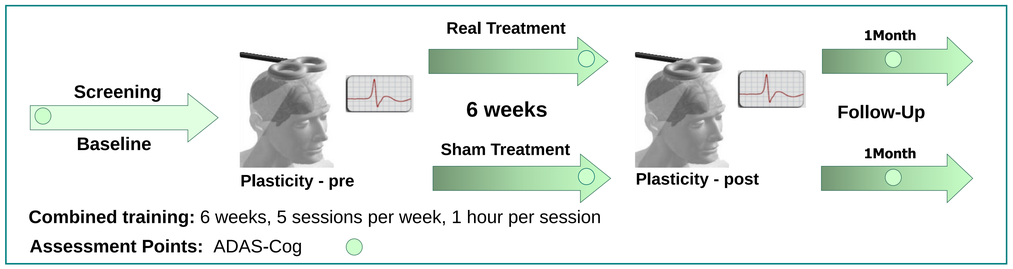
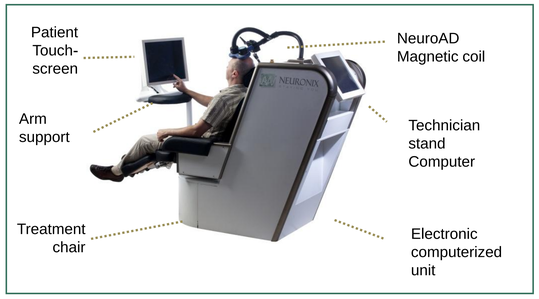



**Fig. 2** NeuroAD System



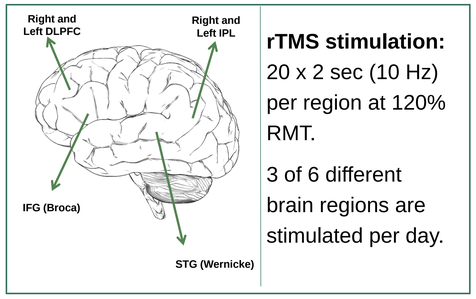
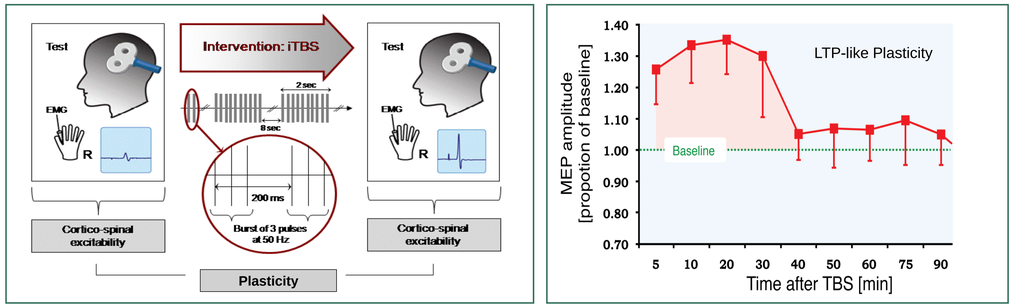




**Fig. 3** Plasticity Visits




## Results

**Neuropsychological assessment (ADAS-Cog)**

- Within 1 month after the end of the active treatment period, patients improved on average by **6.48** points (± 3.68). AD patients in the sham group decreased on average by **0.66** (± 2.91) points (**Fig.4**).
- The difference between the two groups after the NICE-treatment is **7.14** points and is statistically significant (Mann-Whitney-U, ***p*=0.004**).
- The individual data shows that *all* subjects in the treatment group improve within the first month after the treatment.
- Within-group comparisons show a significant change for the treatment group (Willcoxon signed rank, ***p*=0.043**).

**Brain plasticity assessment**

- Neurophysiological measures show an increase in brain excitability and plasticity for the active treatment group (**Fig.5**). However, the changes do not reach significance.

**Fig. 4** Clinical response to treatment

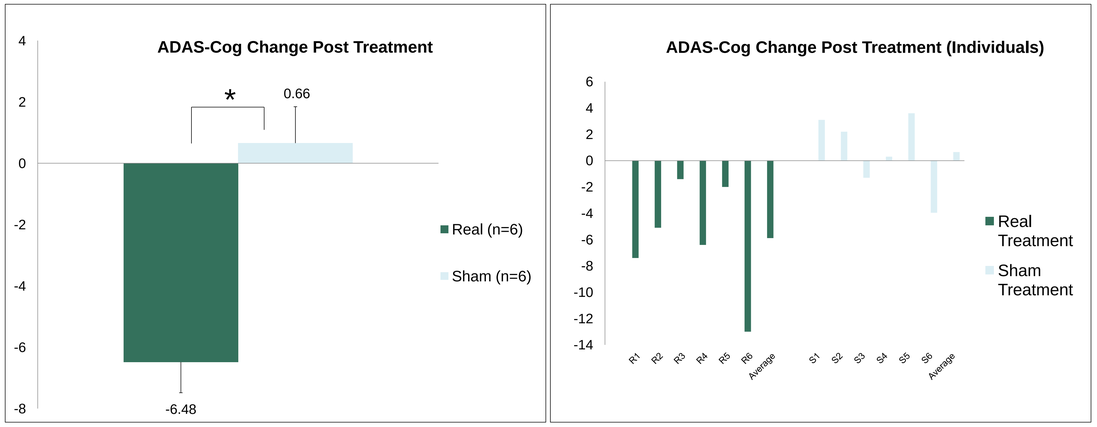
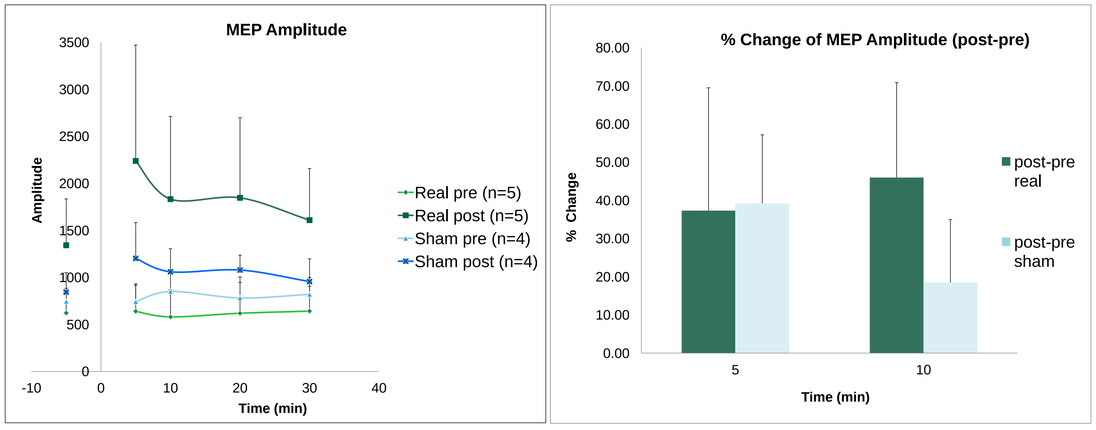



**Fig. 5** Excitability and plasticity measures from M1 (TMS-EMG)




## Conclusion

1. **Combined CR and rTMS with the NeuroAD seems to be a promising intervention to improve cognitive function in patients with AD.**
2. **Cognitive improvement is greater than that typically seen with medication.**
3. **Excitability and plasticity measures obtained from M1 increased after the NeuroAD intervention.**

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Contact: lschilbe@bidmc.harvard.edu