Abstract
Effects of cognitive training and rTMS in Alzheimer's Disease

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Introduction
Alzheimer's Disease (AD) is the leading cause of dementia with cognitive decline being one of the core symptoms. AD is characterized by changes in synaptic plasticity and brain structure, such as brain atrophy, accumulation of amyloid plaques, and fibrillary tangles. Current pharmacological treatments and cognitive training show limited benefits. Transcranial Magnetic Stimulation (TMS) has a modulatory impact on brain plasticity and may therefore enhance the effects of cognitive training if applied concomitantly. In this proof-of-principle study we are evaluating a new tool, which combines TMS with computerized cognitive training (NeuroAD^{TM}, Neuronix Ltd., Israel).

Methods
Patients with mild AD received either daily active or sham treatment during 6 weeks. Active treatment combined computerized cognitive training with rTMS (20 x 2 sec, 10 Hz per region per day at 120% RMT) in an interlaced fashion. Sham treatment consisted in sham cognitive training and sham stimulation. Each training session lasted 1 hour during which 3 of 6 different brain regions were stimulated: right or left DLPFC, right or left parietal cortex, Broca's area, or Wernicke's area. Cognitive functions trained were associated each with the treated brain sites. Before and after the training, brain plasticity of the motor cortex (M1) was assessed with TMS-EMG measures. Cognitive functions were assessed with the Alzheimer's Disease Assessment Scale (ADAS-Cog) including the Mini-Mental State Examination (MMSE), as well as the Clinical Global Impression of Change (CGIC), and Activities of Daily Living (ADAS-ADL).

Results
At training onset, active and resting motor thresholds in patients were similar to healthy controls, while baseline reactivity as well as maximum MEP change was significantly different. Treatment groups did not change significantly regarding M1 reactivity and plasticity after training.
Patients undergoing real treatment improved significantly in ADAS-Cog as compared to sham treatment within the first month after treatment (real: -6.59 ± 3.53; sham: 0.66 ± 2.91). The difference between the groups is therefore clinically meaningful. Non-significant improvements were observed in MMSE and CGIC, while groups improved similarly in ADAS-ADL (Fig. 1).

Conclusions
The NeuroAD intervention seems to be a promising tool to enhance effects of cognitive training in AD patients.

Keywords:
Alzheimer's Disease, Cognitive Training, Transcranial Magnetic Stimulation, Brain Plasticity

Learning Objectives:
1) Investigation of the use of TMS in the enhancement of cognitive training effects in patients with Alzheimer's Disease.
2) Investigation of the impact of combined cognitive training and TMS on cortical plasticity.

Figure 1. Cognitive and behavioral outcome