Long-term follow-up of Alzheimer’s disease patients treated by repetitive transcranial magnetic stimulation combined with cognitive training

Jose M Rabey MD,1 Evgenia Dobrovinsky MD,1 Sergio Aichenbaum MD1, Ran Shorer PhD2, Ruth Peretz PhD2 and Michael Khaigrech MD2
1Department of Neurology, and 2Memory Clinic, Assaf Harofeh Medical Center, Zerifin, affiliated to Sackler School of Medicine, Tel Aviv University, Israel

INTRODUCTION
Transcranial magnetic stimulation (TMS) is a technique for noninvasive painless brain stimulation. It generates a small electric current in the brain that induces, if applied repetitively (rTMS), a modulation in brain cortical excitability. It was documented that rTMS may have beneficial effect on LTP (Long Term Potentiation) routes in the brain, responsible for memory and learning.

OBJECTIVES
To test the efficacy and long-term effects of the NICE system, which employs a unique combination of rTMS interlaced with cognitive training, for the treatment of Alzheimer’s disease (AD) patients.

METHODS

Patients
Inclusion Criteria (main):
- MCI to Moderate AD patients.
- DSM-IV criteria.
- Age 55-85 y
- MMSE 18-24
- Medicated at least 24h prior to the study, medication unchanged before or during the study.

Exclusion criteria:
- Epilepsy
- Unstable medical condition
- Pregnancy

Study Protocol

TMS
- Frequency of up to 20Hz.
- Varying magnetic field that lasts for about 200 to 400 microseconds.
- The magnetic field strength is approximately 1.5 to 1.75 Tesla.
- This results in current flow in neural tissue and in membrane depolarization.
- An intense calibration process is taken for each patient prior to treatment, a motor threshold, the TMS minimal energy required for activating a patient hand, is determined.
- TMS treatment intensity is determined to be in the range of 70% to 90% of the motor threshold intensity.

Treatment
Highly synchronized TMS and cognitive training to induce learning through LTP in AD patients

Cognitive Training
The paradigms for each brain area are as follows:
- Broca brain area - Syntax and grammar tasks
- Wernicke brain area - Comprehension of lexical meaning and categorization tasks
- Right dorsolateral prefrontal cortex (R-dPFC) and Left dorsolateral prefrontal cortex (L-dPFC) - Action naming, object naming and memory tasks
- Right parietal cortex (R-par) and left parietal cortex (L-par) - Spatial attention

The cognitive training tasks were developed with a scale of difficulty levels permitting each patient to advance through the levels at an individually appropriate pace.

RESULTS

Clinical response to treatment
- ADAS-Cog improvement of cognitive function -4.2 points after 6 weeks (p<0.01)
-4.0 points after 4.5 months (p<0.05)

- ADAS-Cog change after 3 months follow-up of 7 pilot patients -4.5 months with treatment and 4.5 without, 1 lost to follow-up was -2.79 from the baseline.

- No side effects were reported.

Significant cognitive function improvement

Compliance
Patient participation remained high throughout the entire study
Patient’s compliance to the treatment remained high throughout the study. Participation in 86.1% of the treatment sessions (28.8 in average, out of 30, in 6 weeks) was confirmed by signed CRF’s and computer files which recorded the cognitive training.

DISCUSSION
Scientific literature suggests that memory impairment results from reduced long term potentiation (LTP) mechanism. It is also known that TMS facilitates LTP mechanisms and learning is enhanced under such rTMS conditions. This may partially explain our results that memory and cognitive functions are improved following the combined treatment. Other possible mechanisms may involve increased cortical brain flow, increased release of neurotransmitters or activation of trophic factors.

CONCLUSIONS
We conclude that the treatment of cognitive functions by NICE™ system in AD patient may persist and may last beyond the treatment period.