Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Transcranial Magnetic Stimulation (TMS)

Evidence Summary

Evidence suggests that repetitive TMS (rTMS) may modestly improve cognition in elderly or those with cognitive decline, but the evidence is conflicting, and the optimal protocol is not established.

Neuroprotective Benefit: Most studies suggest a small clinical benefit to patients after rTMS; however, long-term benefits are more controversial, and an optimal protocol is not established.

Aging and related health concerns: There is some evidence for some modifications to cardiovascular risk factors, but the data is inconsistent, and it is not clear that this will translate to clinical outcomes.

Safety: rTMS is generally safe, but mild side effects are common. Severe side effects are rare.

Availability: Possibly off-label in select clinics	**Dose:** Usually 10-20 Hz over the DLPFC or using the NeuroAD protocol (6 regions w/cognitive training – see below)	**Chemical formula:** N/A
Half life: N/A	**BBB:** N/A	
Clinical trials: 1 phase 3; 14 small clinical studies	**Observational studies:** 0	

What is it?

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique in which electricity passes through a coil (usually in a figure 8 formation) to induce a magnetic field that focally stimulates an area of the brain under the skull. Studies have reported promising results in a number of neurological and psychiatric conditions including depression, acute mania, bipolar disorders, panic, hallucinations, obsessions/compulsions, schizophrenia, post-traumatic stress disorder, drug craving, Parkinson's disease, dystonia, epilepsy, rehabilitation after stroke, and pain syndromes (Rossi et al, 2009). It has FDA approval for treatment-resistant depression and migraines (single pulse TMS) (Cirillo et al, 2017).

rTMS has a stronger and more focal effect on the underlying brain tissue than transcranial direct current stimulation (tDCS). On the other hand, tDCS devices are portable, cheaper, quieter, and sessions are shorter (Alzforum). High frequency rTMS (HF-rTMS 5-20 Hz) induces a net-cortical excitatory effect while low-frequency rTMS (LF-rTMS < 1Hz) induces a net-cortical inhibitory effect (Tatti et al, 2016) HF-rTMS is used in the majority of clinical studies and is more effective than LF-rTMS (Ahmed et al, 2012). This report will focus on HF-rTMS, unless stated otherwise.

rTMS improved cognitive function in many small clinical trials in elderly individuals and Alzheimer's patients. However, investigators have used many different protocols and outcomes. Therefore, the most effective protocol is not established. Two rTMS coil placements are most common – the dorsolateral prefrontal cortex (L/R DLPFC) or in six brain regions (L/R DLPFC, L/R parietal somatosensory cortex (L/R PSC), Broca's area and Wernicke's area – the NeuroAD protocol from Neuronix). The NeuroAD protocol is generally accompanied by a cognitive training paradigm which adapts to the patient's skill. This therapy was developed and is marketed by Neuronix (NeuroAD is only approved in the EU and Israel).

Most protocols consist of daily 5-20 Hz stimulations within a 20-60 minute treatment window over 2-6 weeks. For instance, in one stimulation protocol, rTMS was applied over the left DLPFC. Subjects

received 10Hz pulses, each train lasting 5 seconds with 25 seconds in between, for 2,000 pulses (20 minutes) over two weeks. Cognition was measured at baseline, after the 2 week stimulation period, and one month later (Drummond Marra et al, 2015). rTMS sessions may occur during a task (online) or in between tasks (offline).

Neuroprotective Benefit: Most studies suggest a small clinical benefit to patients after rTMS; however, long-term benefits are more controversial, and the optimal protocol is not established.

Types of evidence:

- 1 meta-analysis of rTMS and tDCS based on 24 studies for healthy elderly and Alzheimer's patients
- 3 small clinical studies in healthy elderly
- 11 small clinical studies in MCI or Alzheimer's patients
- 1 phase 3 study in patients with mild Alzheimer's disease (not published)
- Numerous preclinical studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

No studies have examined whether rTMS can prevent dementia. Few studies report effects in healthy elderly. This report will not consider young individuals unless directly compared to elderly because of the uncertainty that beneficial effects in youth will translate to middle age or elderly individuals. Non-invasive brain stimulation in young adults leads to conflicting results on cognition (Tremblay et al, 2014; Horvath et al, 2015). Healthy young adults are more cognitively intact and face a potential ceiling effect in cognitive tasks. In addition, there are age-related changes in cognitive processing that makes interpretation of studies in young adults difficult to make for middle-age or elderly individuals.

Meta-analyses

Hsu et al (2015) conducted a systematic review/meta-analysis of noninvasive brain stimulation (both rTMS and tDCS) in elderly patients in studies that measured cognitive function, had >10 participants, reported outcome measures quantitatively, and were sham controlled. Most of the studies in healthy older adults used tDCS. Based on 13 studies (18 outcomes), cognitive function improved after brain stimulation with a Cohen's effect size of d=0.42 (95%CI 0.09-0.74). Studies specific for rTMS showed cognitive improvement in older adults. Cognitive outcomes in offline studies (not during a cognitive task) significantly improved (d=0.92) while cognitive outcomes in online (during a cognitive task)

studies did not (d=0.23, n.s.). Studies with multiple sessions were better than studies with a single session (d=0.89 vs d=0.44).

Individual Studies from Hsu et al (2015)
Offline stimulation (multiple rTMS session)
Kim et al (2012) reported that after five daily sessions of 10Hz rTMS over the left DLPFC in healthy elderly (n=16), reaction time for responses in the Stroop test improved in the rTMS group (~100ms). There were no changes in accuracy, but this could be due to a ceiling effect.

Koch et al (2018) reported in a cross-over trial that 2 weeks of 20 Hz rTMS over the precuneus in clinically confirmed prodromal Alzheimer's patients (n=14) improved performance on the delayed-recall Rey Audio Visual Learning Task (RAVLT). There were no improvements on the MMSE, RAVLT (immediate recall), frontal assessment battery, or digit symbol substitution test.

Off-line stimulation (single rTMS sessions)
Sole-Padulles et al (2006) reported that in elderly subjects with memory complaints without dementia (n=40), a single 5-minute (10 Hz) session over the prefrontal cortex between two face-naming tasks slightly improved associative memory. This was accompanied by increased fMRI activity in the right middle frontal gyrus, right medial frontal lobe, right/middle inferior frontal gyrus, and middle/superior occipital gyrus.

Online stimulation (single rTMS session)
Cotelli et al (2010) reported improvements in reaction time (~150ms), but not accuracy, in an action naming task in healthy elderly (n=13) when rTMS was applied to the left and right DLPFC. The lack of improvements in accuracy could be due to a ceiling effect.

Human research to suggest benefits to patients with dementia:
In the Hsu et al (2015) systematic review/meta-analysis of noninvasive brain stimulation (both rTMS and tDCS) in Alzheimer's patients of trials that measured cognitive function, had >10 participants, reported outcome measures quantitatively, and were sham controlled, about half used rTMS. Based on 11 studies (20 outcomes, 200 patients), cognitive function improved with a Cohen's effect size of d=1.35 (95%CI 0.86-1.84). Cognitive outcomes with offline studies significantly improved (d=1.04) as did cognitive outcomes with online studies (d=1.79). Studies with multiple sessions were similar to studies with a single session (d=1.20 vs d=1.49).

Another meta-analysis of seven (partially overlapping) RCTs in MCI or dementia patients with MMSE or ADAS-cog scores reported that rTMS moderately improved cognition (Hedges' g = 0.48; 95%CI 0.12-0.84) (Cheng et al, 2017). Subgroup analyses were less conclusive due to the small number of studies in each subgroup:

- Patients taking cognitive enhancing drugs (e.g. AChEi): g=0.66; 95%CI -0.21-1.53 (n.s.)
- Patients not taking cognitive enhancing drugs: g=0.44; 95%CI 0.08-0.8
- rTMS targeting a single brain region (mainly the DLPFC): g=0.39; 95%CI 0.05-0.73
- rTMS targeting multiple brain regions (w/cognitive training): g=0.94; 95%CI -0.09-1.97 (n.s.)

In general, rTMS moderately improves cognition in Alzheimer's patients. However, studies tend to recruit few patients (10-40) and have different protocols, making interpretation of the results difficult.

Individual studies

An effective therapy for Alzheimer's patients would preferably have long-term effects. A few studies have measured this.

Offline, long-term

Cotelli et al (2010) treated 10 moderate Alzheimer's patients with rTMS (20Hz – 25 minutes/day) (one group 4 weeks rTMS, one group 2 weeks sham/2 weeks rTMS) over the left DLPFC. At 2 weeks, the treatment group showed significant improvements over sham treatment in a sentence comprehension subtest of Battery for Analysis of Aphasic Deficits (SC-BADA), but not in 15 other cognitive outcomes (including MMSE – a cognitive test, instrumental activities of daily living – iADL, writing, naming, etc). At 12 weeks, both groups showed improvement in the same battery compared to baseline (not for the other 15 cognitive measures), but there was no difference between groups. A Bonferroni corrected post-hoc analysis showed that the improvement from baseline of the SC-BADA in the 4-week group was significant.

Ahmed et al (2012) treated 45 mild-to-moderate Alzheimer's patients with 5 daily rTMS sessions, or a sham stimulation, over the left then the right DLPFC (10 minutes/hemisphere). After treatment, patients treated with a 20Hz stimulation procedure showed significant improvements in MMSE, activities of daily living (IADL), and global depression scores (GDS) over sham-treated patients. MMSE improvements for the rTMS group were as follows: baseline – 18.4, after treatment – 21.4, three months follow up – 22.6. The sham group declined over time: baseline – 15.4, three months follow up – 14.4.

Alcala-Lozano et al (2017) compared rTMS for three weeks over the left DLPFC or the NeuroAD protocol (L/R DLPFC, L/R PSC, Broca, Wernicke – see below) without cognitive training in 19 patients (no sham treatment). Both groups showed similar improvements after week three and at week seven (no difference between groups). Improvements at week seven were ~6 points on the ADAS-cog and ~3 points on the MMSE.

Online stimulation

In Alzheimer's patients (n=15; 20 Hz stimulation; cross-over trial), Cotelli et al (2006) reported significant improvements in an action naming task when the left or right DLPFC was stimulated (45% correct vs. 30% correct for sham). However, there were no improvements for object naming tasks. In a follow up study using the same protocol (n=24), Cotelli et al (2008) reported significant improvements only in action naming tasks for mild-Alzheimer's patients but significant improvements in both action and object naming tasks for moderate-to-severe Alzheimer's patients.

In another cross-over study in Alzheimer's patients (n=10), Eliasova et al (2014) reported that 10 Hz stimulation over the right inferior frontal gyrus improved performance on the Trail Making Tests (TMT) A&B compared to baseline. A control stimulation procedure showed no benefit. No benefits were seen on the Stroop test or on a complex visual scene task.

NeuroAD Protocol

NeuroAD is a medical device approved in the EU and Israel and sold by an Israeli company, Neuronix. It is not yet available in the United States. rTMS stimulation (10Hz) is targeted to the left and right DLPFC, left and right parietal somatosensory cortices, left inferior frontal gyrus (Broca's area), and left superior temporal gyrus (Wernicke's area). During stimulation, participants undergo cognitive training that correlates to the regions being stimulated: syntax and grammar tasks (Broca's area); comprehension of lexical meaning and categorization tasks (Wernicke's area); action naming, object naming, and spatial memory tasks (L/R DLPFC); and spatial attention tasks (L/R PSC). The difficulty of the tasks is adjusted to the patient's performance.

In a 130 person phase 3 study in patients with mild-to-moderate Alzheimer's disease, patients receiving a six week treatment of NeuroAD maintained stable cognition six weeks after stimulation while placebo patients' cognition declined (presentation at 2017's Alzheimer's and Parkinson's Diseases Conference, Alzforum). However, patients in the stimulation group did not have cognitive improvement immediately after the stimulation period, which was the primary outcome of the trial.

In a randomized, double-blind study in 15 patients, Rabey et al (2013) reported that 1 hour/day of the NeuroAD protocol 5 days/week for 6 weeks significantly improved ADAS-cog scores compared to placebo by 3.76 points after the treatment period. This improvement was maintained 4.5 months after treatment (3.52 points). Another randomized, double-blind study in 26 Alzheimer patients reported that both the NeuroAD and sham groups improved after 6 weeks of treatment, though only the treatment group significantly improved from baseline (5.4 points for treatment vs. 2.9 points for sham – no significance between groups). In a subgroup analysis, improvements from baseline for ADAS-cog scores and MMSE scores were only seen in treated mild Alzheimer's patients, not in sham or moderate groups (Lee et al, 2016).

Two open-label studies (Rabey and Dobronevsky, 2016; Nguyen et al, 2017) reported benefits on ADAS-cog scores (~3 points in each) after 6 weeks treatment. However, at 6 months after stimulation scores had returned to baseline.

Although these pilot studies are promising, it still needs to be determined why there are differences in the maintenance of cognition between studies, what is the optimal patient population, and what the optimal treatment schedule and protocol would be.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
High frequency rTMS (5-20 Hz) is reported to increase cortical excitability while low frequency rTMS (<1 Hz) is reported to decrease cortical excitability. Preclinical and human studies suggest many possible downstream cellular effects of magnetic stimulation – however, different stimulation protocols may have different effects (Cirillo et al, 2017).

rTMS may initiate action potentials in neurons and modulate neuronal excitability by modification of membrane potentials. *In vitro* studies in hippocampal slice cultures suggest that high frequency magnetic stimulation alters the morphology of dendritic spines by increasing spine size. *In vivo*, rTMS can also alter glutamatergic signaling by modulating the expression of AMPA receptors and increase the expression of immediate early genes, such as c-Fos (Cirillo et al, 2017).

Serotonin – Preclinical animal and human studies suggest that rTMS affects the serotonergic system. Animal studies suggest that acute rTMS increases the expression of 5-HT_{1A} receptors while chronic rTMS reduces the sensitivity of presynaptic 5HT receptors thus increasing serotonin level at the synaptic cleft (Cirillo et al, 2017).

Dopamine – Mouse studies suggest that acute rTMS increases dopamine levels in the striatum and the hippocampus while chronic rTMS modulates expression of activity and monoamine transporters. Human rTMS-PET or SPECT studies show that stimulation of the DLPFC increases dopamine in the striatum (Cirillo et al, 2017).

Neurotrophic factors – Studies in humans have reported increased serum levels of BDNF in response to a 2-week stimulation of rTMS in depressed patients but no change with acute rTMS in healthy patients (Cirillo et al, 2017). Possibly chronic rTMS is required to increase BDNF levels.

Neuroendocrine system – rTMS over the DLPFC was reported to decrease cortisol levels in response to a stressor (Cirillo et al, 2017).

APOE4 interactions: None reported

Aging and related health concerns: There is some evidence for some modifications to cardiovascular risk factors, but the data is inconsistent and it is not clear that this will translate to clinical outcomes.

Types of evidence:

- 1 RCT for blood lipid levels
- 1 meta-analysis for heart rate, blood pressure, and heart rate variability outcomes

Ren et al (2017) reported that 2-week treatment of rTMS (10 Hz) over the right DLPFC decreased total cholesterol and triglycerides in elderly individuals (n=30) compared to sham. HDL-c and LDL-c non-significantly decreased. They speculate this is due to altered activity in the hypothalamo-pituitary-thyroid (HPT) axis as stimulation increased levels of thyroid-stimulating hormone (TSH) and thyroxine (T_4) levels.

In a meta-analysis of non-invasive brain stimulation (NIBS) studies looking at the response of heart rate, blood pressure, and heart rate variability, Makovac et al (2017) reported that heart rate and HRV significantly improved, while blood pressure did not (Hedge's g=0.17, 0.3, and 0.21 n.s., respectively). However, when comparing only studies that used a sham stimulation, heart rate no longer significantly decreased. There was significant heterogeneity in all the studies in the meta-analysis.

Safety: rTMS is generally safe, but mild side effects are common. Severe side effects are rare. Long-term effects are less clear.

Types of evidence:

- 1 Consensus Statement from the International Workshop on "Present and Future of TMS: Safety and Ethical Guidelines"

The safety of long-term use (>5 weeks) of rTMS treatment is unknown. Using accepted guidelines (see Rossi et al, 2009), rTMS is generally safe with only minor side effects. In a meta-analysis on the safety of rTMS for depression, about 28% of patients experience headache and 39% experienced pain or discomfort during the procedure (compared to 16% and 15% for sham participants, respectively). The reason for the pain is unclear, though it is hypothesized that trigeminal nerve stimulation plays a role. Neck pain may occur because of the posture and head immobilization during the rTMS session. Most of the time the pain subsides after treatment. It should be noted that <2% of patients discontinue the procedure due to pain.
Mild, rare, and transient cognitive side-effects include excessive tiredness, concentration difficulties, and memory difficulties. Occasional burns have been reported.

The most severe potential safety issue with rTMS is seizure induction, although this is very rare. From 1998-2009, when TMS was administered within published safety guidelines (Rossi et al, 2009), only four seizures occurred (not sure how many people were treated, but over 1,000 rTMS papers [trials and reviews included] were published in this time).

TMS generates a loud acoustical artifact that can exceed 140dB, and hearing protection should be worn during the procedure.

Drug interactions:
The most potentially hazardous drug interaction with rTMS includes drugs that may lower the threshold for seizure including: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, amphetamines, cocain, ecstasy, phencyclidine, ketamine, GHB, alcohol, and theophylline (Rossi et al, 2009).

Drugs that are less hazardous, but should still be used with caution include: mianserin, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, reboxetine, venlafaxine, duloxetine, bupropion,

mirtazapine, fluphenazine, pimozide, haloperidol, olanzapine, quetiapine, aripiprazole, ziprasidone, risperidone, chloroquine, mefloquine, imipenem, penicillin, ampicillin, cephalosporins, metronidazole, isoniazid, levofloxacin, cyclosporin, chlorambucil, vincristine, methotrexate, cytosine arabinoside, BCNU, lithium, anticholinergics, antihistamines, sympathomimetics (Rossi et al, 2009).

Withdrawal from the following drugs are potentially hazardous due to increased seizure potential: alcohol, barbiturates, benzodiazepines, meprobamate, and chloral hydrate (Rossi et al, 2009).

TMS generates a strong magnetic field, thus could potentially displace magnetic implants in the head. Additionally, patients with cochlear implants should not receive TMS (Rossi et al, 2009).

Sources and dosing:
Most protocols stimulate the DLPFC or use the NeuroAD protocol (see above). Stimulation is usually for 20 minutes to 1 hour each day for 2-4 weeks. The optimal protocol is not established.

Stimulation for general cognition might be able to be done off-label in clinical around the country (although I am not sure of this).

Neuronix provides the NeuroAD protocol, but it is only approved in the EU and Israel.

Research underway:
Six trials are currently investigating rTMS in Alzheimer's disease.
Active Studies

- NCT03270137 – Comparison of 5 Hz stimulation over the left DLPFC compared to the six-region protocol (NeuroAD without cognitive training). In 22 patients will stimulate for four weeks and look at ADAS-cog scores post-treatment and four weeks later.
- NCT02190084 – 20 Alzheimer's patients with apathy will receive rTMS or sham treatment for 4 weeks. They will be tested for memory function, executive function, and apathy at the end of treatment, 4, 8, and 12 week later.
- NCT02908815 – 200 Alzheimer's patients will receive 20 Hz rTMS or sham treatment to the DLPFC for 2 or 4 weeks daily (5 days/week). ADAS-cog and a number of cognitive and functional tests will be measured at week 0, 3, 5, 13, 21, and 29.
- NCT02537496 – 36 Alzheimer's patients will receive 20 Hz rTMS or sham treatment to the DLPFC over 4 weeks. Performance on the N-back test, other cognitive tasks, and a number of EEG studies will be conducted at baseline, 7 days, 4 weeks, and 6 months.

Not yet recruiting

- NCT0331796 – 99 MCI patients will receive 10 Hz rTMS over the DLPFC for 20 sessions (1 or 2 per day). The California Verbal Learning Test-II and a number of other cognitive outcomes will be measured at baseline, 1 week, and after completing 20 sessions.

rTMS is being tested in a number of other neurological or psychiatric indications. There are over 400 trials ongoing.

Search terms:
Pubmed:
Transcranial magentic stimulation + alzheimer's, aging, elderly cognition, cardiovascular
Google:
Transcranial magnetic stimulation Alzheimer's