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.

Repetitive transcranial magnetic stimulation (rTMS)

Evidence Summary

rTMS is an approved treatment for some psychiatric conditions. It may have cognitive benefits for individuals with MCI or AD, but more robust studies and optimal protocol(s) are needed.

Neuroprotective Benefit: Several meta-analyses suggest that rTMS could have a benefit for MCI and AD patients. However, the data is largely from small studies and there are conflicting results. The optimal protocol(s) are not yet established.

Aging and related health concerns: rTMS is approved for depression and smoking cessation. rTMS may have an impact on cardiovascular measurements and body weight, or utility for other indications such as pain. The clinical impact, if any, is not yet clear.

Safety: rTMS is associated with mild and transient adverse events including headache, skin or scalp discomfort or tingling, neck pain, fatigue, and dizziness. Serious adverse events are very rare, though can include seizure, particularly in at-risk populations.

Availability: rTMS is available for approved uses in specialized clinics; in clinical development for dementia.	**Dose**: The optimal protocol has not yet been worked out but likely involves multiple sessions and stimulating specific area(s) of the brain.
Half-life: N/A	**BBB**: Yes
Clinical trials: The largest meta-analysis of rTMS for cognitive impairment included 5,800 participants.	**Observational studies**: No observational studies assess rTMS and cognition or dementia. The largest observational study identified included 770 patients with depression.

What is it?

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique in which electricity passes through a coil, usually in the shape of a figure 8, to induce a magnetic field that focally stimulates an area of the brain under the skull. rTMS sessions may occur during a task (online) or in between tasks (offline). While the magnetic field is directed to one particular area of the brain, the effects are not necessarily restricted to that focal area as brain regions can affect others through their synaptic connections (Koch et al., 2024). 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 for at least some applications, such as for patients with AD (Ahmed et al., 2012). 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). rTMS has been FDA approved for treatment-resistant major depressive disorder, obsessive compulsive disorder, acute and prophylactic treatment of migraines, and for smoking cessation when other therapies have failed. It should be noted that the approval involves the overall technology, including the specific device and protocol (Cohen et al., 2022; Mann & Malhi, 2023). rTMS is being explored for use in a variety of other conditions, including for MCI and AD, among other dementias.

rTMS encompasses many different protocols, which can vary in frequency of stimulation pulses, duration of individual session, number of sessions, total duration of treatment, and total number of received pulses. Many of these points of protocol can be interrelated but not necessarily equivalent. For instance, intermittent theta burst stimulation (iTBS) involves a 3-pulse burst of 50 Hz stimulation every 200 milliseconds for less than 3 minutes, whereas a conventional 10 Hz rTMS session often lasts for 20 to 30 minutes; iTBS could therefore substantially reduce frequency and duration of treatment sessions, if proven to be as or more efficacious than conventional rTMS protocols (Aghamoosa et al., 2024). The brain region that is directly targeted by the stimulation also can impact the results. It may not just be a question of whether rTMS has efficacy for a particular condition, but also which specific protocol(s) are most ideal. The best protocol(s) for a given condition is an area of active debate and research. For this report, the acronym rTMS will be used to encompass all protocols, but specifics of the protocol will be included where relevant.

There are other non-invasive brain stimulation techniques, including transcranial electrical stimulation (tES) approaches of transcranial direct current stimulation (tDCS) and transcranial alternative current stimulation (tACS). This report will focus on rTMS.

Neuroprotective Benefit: Several meta-analyses suggest that rTMS could have a benefit for MCI and AD patients. However, the data is largely from small studies and there are conflicting results. The optimal protocol(s) are not yet established.

Types of evidence:

- 30 systematic reviews and/or meta-analyses
- 4 RCTs
- 2 open label studies
- 1 review
- Numerous preclinical studies

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

No studies have examined whether rTMS can reduce incidence of dementia diagnosis. There are several systematic reviews and meta-analyses that have assessed the potential efficacy of rTMS in patients with

MCI; many have found indications of benefit of rTMS, though there is conflicting evidence on the most beneficial protocol. Several of these meta-analyses included studies of both MCI and AD patients.

Hu et al., 2024 compared TMS to transcranial direct current stimulation (tDCS) and to control treatment in patients with MCI. The meta-analysis included 11 studies with a total of 406 patients. The authors found that there was a significant improvement in memory function in both approaches, and that rTMS may have a larger effect than tDCS (rTMS SMD=0.78; 95% CI 0.51 to 1.06; p<0.00001; I^2 = 0%; tDCS SMD=0.40; 95%CI: 0.10 to 0.71; p=0.008; I^2 = 33%). The researchers also compared single site rTMS to multiple site rTMS and found that while both had a significant association with improvements in assessments of memory, that multiple site rTMS had a greater benefit. Similarly, the researchers compared the efficacy based on the number of sessions; they found that while having 10 or fewer or more than 10 sessions were both associated with improvements in memory, that having more than 10 sessions and longer-term interventions were associated with greater improvements in memory function. Overall, they found that rTMS targeted to multiple sites with a frequency of 10 Hz over more than 10 sessions seemed to show the greatest effect. They also found that the benefits of rTMS were persistent for at least four to eight weeks after treatment cessation.

Like Hu et al., 2024, Zhang et al., 2021 also found that in a meta-analysis of 12 studies comprising 329 patients with MCI, rTMS treatment was significantly associated with improved cognitive function (SMD=0.83; 95% CI 0.44 to 1.22, p=0.0009) and memory function (SMD=0.73; 95% CI 0.48 to 0.97, p<0.00001) compared to sham treatment, and that rTMS stimulation of multiple sites and more than 10 sessions appeared to be more associated with improvements in cognition than either single site stimulation or fewer than 10 sessions.

Pagali et al., 2024 encompasses a systematic review of trials of rTMS in MCI, AD, AD-related dementias, and in patient populations with cognitive impairment but without neurodegenerative disease, as well as a meta-analysis of RCTs in MCI and AD populations. Their meta-analysis comprised 25 RCTs in patients with MCI and AD. Compared to sham stimulation, TMS significantly improved cognition in MCI and AD as measured by MMSE (SMD=0.80; 95% CI 0.26 to 1.33, p=0.003; n=24), MoCA (SMD=0.85; 95% CI 0.26 to 1.44, p=0.005, n=10) and ADAS-Cog (SMD=−0.96; 95% CI −1.32 to −0.60, p<0.001; n = 14). There was significant heterogeneity, perhaps in part because the study assessed results from studies of MCI and AD populations together.

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 used tDCS. Based on 13 studies (18 outcomes), cognitive function improved with a Cohen's effect size of d=0.42 (95% CI 0.09 to 0.74). 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).

Several other meta-analyses and/or systematic reviews report similar findings that rTMS treated MCI and/or AD patients have improved cognitive function compared to patients receiving sham treatment (Chou et al., 2020; Teselink et al., 2021). It should be noted that some of these studies performed subgroup analyses and found beneficial effects only in AD patients and not in MCI patients, but several meta-analyses in this report do find a benefit of rTMS in MCI patients. More work is needed to understand these discrepancies.

Other systematic reviews and/or meta-analyses have explored the efficacy of rTMS alone and/or in combination therapy. For instance, Yang et al., 2024 assessed combinations of non-invasive brain stimulation with cognitive training; in their 15 studies with 685 patients, including 6 studies of rTMS, they found that rTMS and cognitive training was particularly associated with improvements in global cognition for both MCI patients and patients with AD. However, an earlier network meta-analysis by Chu et al., 2021 reported that while there was a benefit of rTMS for general cognition compared to control treatment, especially in patients with AD, that cognitive training did not provide additional benefits. The systematic review and meta-analysis of rTMS in MCI and AD by Yan et al., 2023 also reported that rTMS was associated with an improvement in cognition in MCI and AD patients and no further benefit was seen in trials with rTMS and cognitive training.

Studies have also assessed the use of rTMS in other patient populations, such as those with vascular cognitive impairment (VCI) which can include post-stroke cognitive impairment; one systematic review and meta-analysis found that rTMS was associated with improved executive functioning compared to control treatment, particularly with higher frequency of 10 Hz, lower intensity, longer duration of treatment (more than 4 weeks), and combined therapy. They also found some evidence for benefit of iTBS over conventional rTMS (Wang et al., 2024).

The consistent association between rTMS and improvements in some element of cognition and memory suggests that there could be biological benefit. However, multiple studies suggest there may be stimulation protocols that are more beneficial than others, and the widely varying protocols and patient populations are barriers to full understanding of the best way to utilize rTMS for cognitive function. Some systematic reviews and meta-analyses seek to overcome some of these obstacles, such as that by Miller et al., 2023 that included only rTMS protocols that targeted the dorsolateral prefrontal cortex (DLPFC) in patients with age-related neurodegenerative diseases. While they found a significant improvement in cognitive function in rTMS treated patients compared to patients who received control treatment, they stated that their results should be taken with caution due to the small number of studies and heterogeneity between studies. Other studies, such as a systematic review and meta-analysis of different non-invasive brain stimulation methods and protocols in 19 RCTs of 599 patients found that rTMS stimulating the bilateral dorsolateral prefrontal cortex had the strongest improvement on cognitive function in MCI patients, but also stated that the small number of studies prevented more robust conclusions and called for more robust studies to more fully explore the best protocol for any given patient population (Liu et al., 2024). Studies in AD populations described in the 'Human research to suggest benefits to patients with dementia' section below have reported positive results from stimulating other brain regions such as the precuneus; future studies may also indicate that those protocols have utility in MCI populations.

The evidence is less clear for use of rTMS in individuals without cognitive impairment. Non-invasive brain stimulation in young adults has led 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 extrapolate to middle-age or elderly individuals. Three systematic reviews and meta-analyses of trials in healthy populations all reported significant but small sized effects for certain cognitive domains (Patel et al., 2020; de Boer et al., 2021; Xu et al., 2024), and another systematic review and meta-analysis found a significant modulation of language performance in rTMS-treated healthy participants compared to participants who received control treatment (Qu et al., 2022). Like in patient populations, these analyses are hampered by the wide range of potential protocols and study design as well as by overall small study size.

Human research to suggest benefits to patients with dementia:

Many systematic reviews and meta-analyses have assessed whether rTMS may have benefit for patients with dementia. Most find some positive benefits of rTMS for patients but also cite issues of small sample sizes and varied protocols.

A systematic review and meta-analysis of rTMS and its optimal parameters for AD by Li et al., 2024 included 16 studies with 655 patients. They found that rTMS significantly enhanced global cognition (SMD=0.43; 95% CI 0.20 to 0.66, p=0.0002) and memory (SMD=0.37; 95% CI 0.09 to 0.65, p=0.009). When they looked at studies with follow-ups of at least 6 weeks, they found the following parameters to be associated with improved cognitive function: single or multi-site stimulation, higher frequency (20 Hz), stimulation time of 1 to 2 seconds, intervals of 20 to 30 seconds, at least 20,000 pulses in a session, and longer duration (3 or more weeks, or 20 or more sessions) (Li et al., 2024).

Chigareva et al., 2024 is a systematic review of 22 studies and meta-analysis of 14 RCTs assessing the efficacy of rTMS for cognitive function in AD. Their meta-analysis found that rTMS, was associated with significant cognitive improvement in AD patients with a moderate effect size, albeit with substantial heterogeneity (Hedges' g=0.580, 95% CI 0.268 to 0.892, p<0.001, I^2=59%). They found that protocols targeting the dorsolateral prefrontal cortex (DLPFC) were particularly associated with significant improvements in cognitive function.

A 2022 systematic review and meta-analysis of rTMS and tDCS in MCI and AD found that there was a significant cognitive benefit seen in the rTMS group compared to sham treatment with a medium effect size (pooled effect size=0.71; 95% CI 0.5 to 0.92; p<0.01). Their subgroup analyses found a similar benefit for both MCI and AD patients, without significant difference between the two groups (Šimko et al., 2022). Another 2022 systematic review and meta-analysis that included 16 total studies and 682 patients with AD who received either rTMS or shame rTMS found that patients who received rTMS has better immediate (SMD=2.07; 95% CI 0.37 to 3.77, I^2=97.8%, p<0.001) and long-term (SMD=5.04; 95% CI 2.25 to 7.84, I^2=97.8%, p<0.001) overall cognitive function than those who received sham rTMS. There was substantial heterogeneity in this study; meta-regression analyses indicated the heterogeneity may have stemmed from different in intensity of stimulation; high frequency rTMS (>1 Hz) was associated with better immediate and long-term overall cognitive function whereas low frequency (1 Hz or less) was not associated with benefit. The researchers did not see a benefit of rTMS on individual cognitive domains such as attention, executive functioning, or memory (Gu et al., 2022).

A network meta-analysis of individual patient data from RCTs looked at whether rTMS had benefits over pharmacological therapy for treatment of AD. The meta-analysis included 57 RCTs comprising a total of 15,548 patients receiving rTMS or monotherapy medication such as donepezil, memantine, rivastigmine, galantamine, or donanemab. They included trials with different control designs, including placebo, no intervention, sham TMS, or equivalent therapy. The network meta-analysis found that, when looking at rTMS and drug monotherapies individually, rTMS had the highest probability rank for improvement in cognitive function as assessed by MMSE and by ADAS-Cog, and the lowest probability for adverse events besides for the placebo group. None of these studies directly compared medication to rTMS which would be necessary to establish superiority, but they suggest a potential significant benefit of rTMS to patients (Wei et al., 2023).

A 2025 systematic review and meta-analysis of non-pharmacological treatments to improve cognitive function in patients with AD looked at 68 studies of a total of 5,053 patients. They found that rTMS was one of three non-pharmacological strategies with the highest cumulative probability for improving overall cognitive function; the other two were tDCS and physical exercise (Dou et al., 2025).

Other systematic reviews and meta-analyses have also reported cognitive benefits to patients receiving rTMS compared to control, including Menardi et al., 2022, Huang et al., 2024, and Xiu et al., 2024, among others. Some systematic reviews have found a benefit of combination therapy of rTMS and cognitive training (Georgopoulou et al., 2024), though other systematic reviews and/or meta-analyses have reported contradictory findings as to the effects of rTMS and/or cognitive training; the discrepancies may be related, in part, to the small number of studies and small sample sizes in those studies.

Hsu et al., 2015 conducted a 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 to 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 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 to 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 to 1.53 (n.s.)
- Patients not taking cognitive enhancing drugs: g=0.44; 95% CI, 0.08 to 0.8
- rTMS targeting a single brain region (mainly the DLPFC): g=0.39; 95% CI, 0.05 to 0.73
- rTMS targeting multiple brain regions (w/cognitive training): g=0.94; 95% CI, -0.09 to 1.97 (n.s.)

Two individual RCTs to note are published in Koch et al., 2022 and then presented at Clinical Trials in Alzheimer's Disease (CTAD) 2024. Koch et al., 2022 details a 24-week trial in 50 patients with AD who were randomized to either sham treatment or personalized neuronavigated rTMS, with personalization based on patient MRI data and EEG to confirm treatment targeted the desired area. The trial began with an intensive, 2-week portion with one 20-minute session every weekday, followed by 22 weeks of once-weekly maintenance therapy. Compared to patients in the sham group, patients who received rTMS treatment had significantly better cognitive function as measured by CDR-SB at 24 weeks; the treatment group had stayed stable, whereas the sham group had declined over the course of 6 months. rTMS treatment was also associated with significantly better cognitive function at 6 months as measured by MMSE and ADAS-Cog and better daily function than sham treatment. In a substudy, the researchers found that patients who received rTMS had statistically significant positive effects on functional connectivity and gray matter volume (Mencarelli et al., 2024).

The researchers then extended the study to a total of 52 weeks; 31 of the original 50 patients continued into the second study and 17 new participants were recruited for a total of 48 participants. As presented at CTAD 2024, rTMS treated patients had significantly better CDR-SB scores than the sham treated patients at 52 weeks, which was the primary outcome. When they looked at secondary outcomes, rTMS also had significantly positive effects on cognition as measured by ADAS-Cog and MMSE, on daily functioning as measured by ADCS-ADL, and on neuropsychiatric symptoms as measured by NPI. rTMS treated patients appeared to have a 44% slowing of AD progression over the course of the 1-year study. When the researchers looked at disease progression based on CDR-SB scores, 37% of the rTMS group did not have any disease progression, whereas 17% of the sham group did not have any progression. Disease progression was delayed by 10.4 months over the course of the trial as measured by activities of daily living. For all outcomes, the treated group generally had no decline, whereas the sham treated group did decline. These overall results have not yet been published in a peer reviewed journal (Business Wire).

Other trials have also utilized personalized rTMS protocols. Menardi et al., 2022 performed a systematic review and meta-analysis to compare the effects of generalized compared to personalized targeting of rTMS in patients with AD. They also compared different protocol characteristics to identify whether particular protocol(s) were associated with cognitive outcomes. Overall, they did not find differences in outcomes between generalized or personalized approaches, though the researchers posited that this might be because the personalization approaches had not been thorough enough. They also did not find a difference in cognitive outcomes based on frequency of rTMS, in presence or absence of cognitive training, or in stimulating the left dorsolateral prefrontal cortex, or multiple sites. They did find the total number of pulses over the course of rTMS treatment to be associated with a larger effect size. It is worth noting that Koch et al., 2022 was published after the inclusion period used by Menardi et al., 2022, as were other personalized approaches such as that used in Jung et al., 2024. This latter study enrolled 30 patients with AD for a 4-week, sham controlled trial of personalized hippocampal network-targeted stimulation, and found that one month after the 4-week study, the rTMS treated group had significantly greater improvement in cognitive function as measured by ADAS-Cog and CDR-SB, as well as increased functional connectivity, compared to the sham-treated group.

Not all studies find benefit of rTMS. The largest RCT that tested rTMS in AD patients was published by Moussavi et al., 2024 and included 135 patients who received 2 or 4 weeks of active or sham rTMS treatment and then were assessed up to 6 months after treatment ended. The results indicated that there was significant cognitive improvement in both active treatment and sham treatment up until 6 months after treatment; they hypothesized that their sham treatment had some therapeutic effect. Whether this is unique to the protocol and set up of this specific group or a more widespread issue in the field is not yet known.

rTMS has also been explored for other conditions, such as vascular cognitive impairment (Wang et al., 2024), vascular dementia (Yi et al., 2024), Lewy body dementia (Guidi et al., 2023), Parkinson's disease (Li et al., 2022), and cognitive impairment after stroke (Liu et al., 2024), and some positive findings have been reported. More work is needed to further assess the potential efficacy and best protocol(s) for these neurodegenerative diseases.

In general, meta-analyses suggest that rTMS is statistically associated with improved cognition in Alzheimer's patients compared to control or sham group patients. However, studies tend to recruit few patients (10-40) and have different protocols, making interpretation of the results difficult. More robust studies that are larger and are designed to directly compare specifics aspects of the protocol are needed to

determine true efficacy and what protocol(s) may be most ideal. Several meta-analyses, for instance, find that targeting the dorsolateral prefrontal cortex is associated with more positive results, but the trial by Koch et al., 2022 targeted the precuneus in order to target the default mode network, and found significant, positive results. It may be too that many protocols can be beneficial to patients, or that specific protocols are most ideal for specific individuals. More trials with longer treatment and/or follow-up time are also needed.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

High frequency rTMS (5 to 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 is thought to modulate neuronal excitability by modification of membrane potentials. *In vitro* studies in hippocampal slice cultures suggest that high frequency magnetic 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).

Several neurotransmitter systems may be affected by rTMS. Preclinical animal and human studies suggest that rTMS affects the serotonergic system. Rat studies suggest that acute rTMS increases the expression of 5-HT1A receptors while chronic rTMS reduces the sensitivity of presynaptic 5HT receptors thus increasing serotonin level at the synaptic cleft (Cirillo et al., 2017). 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). rTMS may also affect GABA neurotransmission (Šimko et al., 2022). Studies in humans have also 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). It is possible that chronic rTMS is required to increase BDNF levels.

Together, the modulation of neuronal excitability, neurotransmitter system, and neurotrophic factors all impact synaptic plasticity and synaptic strength and mimic long-term potentiation/depression and thus

result in lasting changes in cortical excitability, which are thought to underlie the impacts of rTMS, including the long-term effects (Šimko et al., 2022; Koch et al., 2024). As it is thought that AD involves impaired cortical excitability and plasticity, rTMS may be able to restore some aspects of synaptic function. Other animal work suggests that rTMS may decrease pro-inflammatory cytokines such as IL-6 and TNF-α and decrease levels of Aβ and phosphorylated tau. rTMS may also increase the efficiency of brain clearance pathways such as through the glymphatic system (Koch et al., 2024).

APOE4 interactions:

It is not yet clear whether APOE status impacts response to rTMS.

There is some initial evidence that APOE status could potentially interact with rTMS treatment. A study of 20 adult participants over the age of 50 with subjective memory decline assessed the participants with fMRI while doing a cognitive task before and after rTMS treatment. At baseline, APOE4 carriers had different patterns of brain activation than the non-carriers, though there were no differences in cognition between the groups at baseline. After the rTMS treatment, the APOE4 carriers and non-carriers both had similar slight improvements in memory. However, after the rTMS treatment, the APOE4 carriers had brain activity patterns that were now much more similar to non-carriers, while the fMRI scans of non-carriers were relatively similar before and after rTMS. Whether this change in brain activity as measured by fMRI would lead to different cognitive impacts in different patient populations or over time is not known. If the results of this small study were representative, it would suggest a possibility that rTMS may have different effects based on APOE status (Peña-Gomez et al., 2012).

Aging and related health concerns: rTMS is approved for depression and smoking cessation. rTMS may have an impact on cardiovascular measurements and body weight, or utility for other indications such as pain. The clinical impact, if any, is not yet clear.

Types of evidence:

- 2 umbrella reviews of meta-analyses
- 6 meta-analyses and/or systematic reviews
- 1 RCT for blood lipid levels
- 1 observational study
- 2 reviews

rTMS is an FDA approved therapy for treatment-resistant major depressive disorder, obsessive compulsive disorder, acute and prophylactic treatment of migraines, and for smoking cessation when other therapies have failed (Cohen et al., 2022; Mann & Malhi, 2023). Managing mental health conditions and smoking cessation could have positive indirect impacts on age-related conditions.

Treatment Resistant Depression: BENEFIT

rTMS is an approved treatment for treatment-resistant depression (Mann & Mahli, 2023). Typically, rTMS sessions for depression use HF-rTMS and target the left dorsolateral prefrontal cortex. Some protocols include LF-rTMS application to the right dorsolateral prefrontal cortex in the same session, which is called bilateral rTMS. A 2021 umbrella review of meta-analyses of RCTs of rTMS in depression reported that compared to sham treatment, patients treated with HF-rTMS to the left dorsolateral prefrontal cortex had higher chance of response (OR=3.17; 95% CI 2.29 to 4.37) and remission (OR=2.67; 95% CI 1.79 to 4.00). The quality of evidence for both response and remission was high. Patients treated with bilateral rTMS were more likely to respond (OR=3.96; 95% CI 2.37 to 6.60) and have remission (OR=4.22; 95% CI 1.96 to 9.05) than those who received sham treatment, though the quality of evidence for bilateral rTMS was graded as moderate for remission and high for response (Razza et al., 2021).

Neuropathic Pain: POTENTIAL FOR BENEFIT

rTMS is thought to potentially reduce pain intensity for individuals with neuropathic pain. A narrative review indicated that use of HR-rTMS on the primary motor cortex reduced neuropathic pain, though the heterogeneity between studies and protocols is a challenge for the field (Tsai et al., 2023). Other systematic reviews and meta-analyses or umbrella reviews of meta-analyses have reported similar findings, that rTMS can reduce pain scores or pain intensity for patients but that the existing evidence was heterogenous and potentially subject to bias (Kontor et al., 2024; Duarte-Moreira et al., 2025). There are also conflicting findings. One group performed a systematic review and meta-analysis and reported that rTMS was associated with benefit for neuropathic pain (Che et al., 2021). They then performed an updated meta-analysis that included new, larger clinical trials, and their updated analysis did not support an effect of rTMS for neuropathic pain (Zhou et al., 2024). It should be noted that Che et al., 2021 and Zhou et al., 2024 both specifically looked at rTMS protocols targeting the dorsolateral prefrontal cortex, while Tsai et al., 2023, Kontor et al., 2024, and Duarte-Moreira et al., 2025 did not exclude rTMS studies based on target location. It should also be noted that the dorsolateral prefrontal

cortex is important for cognitive and executive function and thus is a common target for rTMS for other conditions, but it is not directly involved in pain pathways. Larger trials with more standardized protocols are required to assess whether rTMS has efficacy for neuropathic pain and if so, which protocol(s) provide significant benefit.

Cardiovascular disease: POTENTIAL IMPROVEMENT IN BIOMARKERS
Some studies have tested the effects of rTMS on outcomes related to cardiovascular functions. 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 (T4) 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 studies that used a sham stimulation, heart rate no longer significantly decreased. There was significant heterogeneity in all of the studies in the meta-analysis. Other meta-analyses found that rTMS was associated with decreased blood pressure and heart rate and improved heart rate variability (Lee et al., 2023) or that rTMS and other non-invasive brain stimulation approaches could modulate heart rate and heart rate variability (Schmaußer et al., 2022). As Schmaußer et al., 2022 notes, though, these studies are often small and underpowered, and the best stimulation protocol is still unclear. More research is needed to see whether rTMS has true efficacy for these conditions and how they impact other health conditions like overall cardiovascular health. rTMS is also being explored for obesity (Alhindi et al., 2023).

Safety: rTMS is associated with mild and transient adverse events including headache, skin or scalp discomfort or tingling, neck pain, fatigue, and dizziness. Serious adverse events are very rare, though can include seizure, particularly in at-risk populations.

Types of evidence:

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

- 5 meta-analyses or systematic reviews
- 1 professional resource
- 1 review

The International Federation of Clinical Neurophysiology promotes and supports a consensus conference that publishes safety and recommendations for rTMS use. These expert guidelines are regularly updated; as of the publication of this report, Rossi et al., 2021 is the most updated version as of January 2025.

The most severe potential safety issue with rTMS is seizure induction, although this is very rare. A literature review up through February 2020 found 41 reports of seizure; while the total number of patients who received rTMS is not known, it is thought to be in the many hundreds of thousands. A questionnaire sent to groups performing rTMS yielded responses from 174 groups who reported over 300,000 sessions and a total of 24 seizures, for a standardized risk of 7 in 100,000. As 19 of those 24 seizures occurred in subjects with elevated risks such as epilepsy, medications, or brain lesions, the risk appears to be different for those at higher risk of seizures than those who are not (Rossi et al., 2021).

Using accepted guidelines (see Rossi et al., 2009 and Rossi et al., 2021), rTMS is generally safe with only minor side effects. A systematic review and meta-analysis of 406 patients with MCI who received rTMS or tDCS found that rTMS was associated with an increased risk of adverse events compared to control treatment (RR=3.18; 95% CI 1.29 to 7.83, p=0.01). These events included temporary headache, tingling sensation, dizziness, skin itching, skin redness, and fatigue. These were mild and transient, lessening or resolving on the scale of hours (Hu et al., 2024).

A 2024 paper included a systematic review of any clinical trial of rTMS that involved any type of cognitive impairment and cognitive function as an outcome as well as a meta-analysis of RCTs in patients with MCI and AD. The systematic review included 143 studies, and the meta-analysis included 25 RCTs. In the 143 overall studies, 2 studies reported 4 seizures as serious adverse events. One RCT included 3 seizures that occurred 6 to 12 months after TMS; 2 occurred in the sham stimulation group, and none were deemed related to rTMS. The four seizure events involved a participant experiencing motor movements during rTMS; this was determined to be a focal motor seizure and was resolved upon repositioning the rTMS coil. Only two other studies reported a serious adverse event of an acute myocardial infarction and urinary sepsis; neither was determined to be related to rTMS. Of the 143 total studies, 47 (33%) reported adverse events which typically included headache, local skin or scalp

discomfort, and fatigue; 40 studies (28%) reported no adverse events, and 52 (36%) did not report on adverse events. Only two patients were reported to have discontinued a study due to adverse events (Pagali et al., 2024).

A 2023 systematic review and meta-analysis of rTMS in patients with age-related neurodegenerative diseases included a total of 16 studies; 5 reported adverse events. Scalp pain, headache, discomfort over stimulation site, discomfort over eye, eyelid or facial twitching, and mild blurry vision or dizziness were all reported numerically more in the active rTMS group compared to the sham treatment group; the events were generally transient (Miller et al., 2023).

A 2021 meta-analysis of 12 studies of a total of 329 patients with MCI included adverse events from the 7 included studies that reported their adverse events findings. Of the 7 studies, one reported that a patient experienced a serious adverse event of severe pain after receiving two sessions of rTMS and then discontinued the study. All remaining adverse events were mild and included headache, dizziness, pain in the area of stimulation, neck pain, and a burning sensation on the scalp, all of which resolved quickly. The incidence of adverse events was higher in the rTMS group compared to the control treatment group, with 27 of 116 patients in the pooled rTMS group reporting an adverse event and 13 of 113 patients in the control group (RR=2.67; 95% CI 1.24 to 5.74, p=0.01, n=229) (Zhang et al., 2021).

A 2024 meta-analysis of 16 studies comprising 655 patients with AD found that patients receiving rTMS compared to sham had a significantly increased incidence of adverse events (SMD=2.29, 95% CI 1.23 to 4.27, p=0.009) and that approximately 20% of participants reported adverse events during rTMS treatment. These events included headache, scalp tingling, neck pain or stiffness, insomnia, and fatigue. Most of these adverse events were transient (Li et al., 2024).

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

Drug interactions:

Prior iterations of the rTMS safety guidelines suggested caution in concurrent use of rTMS and medications known to lower seizure threshold, as it was assumed that the combination might increase the risk of seizure (Rossi et al., 2009). A 2021 update reports that the available data do not currently indicate an increased risk of seizure when receiving rTMS and medication known to lower seizure

threshold. However, they continue to recommend vigilance for patients who are taking pro-convulsants, and they encourage continued documentation to further inform the field as to the extent of the risk of rTMS to patients receiving medications that lower seizure threshold. No specific drug interactions with rTMS have been identified, though the lack of systematic data of adverse events and specific medications means that the possibility cannot be ruled out (Rossi et al., 2021).

Rossi et al., 2009 included a list of drugs that are potential hazards for rTMS. This list was not repeated in Rossi et al., 2021.

As rTMS can affect hearing, patients who are at greater risk of noise-induced hearing loss, like those on ototoxic medications such as aminoglygoside antibiotics and platinum-based compounds should have careful conversations with their providers to determine whether rTMS is an appropriate choice for them (Rossi et al., 2021).

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, Rossi et al., 2021).

Research underway:

There are over 600 ongoing studies utilizing TMS that are registered on clinicaltrials.gov. Many of these studies are for different neurological or psychiatric indications. Of these, approximately 60 studies are investigating the use of TMS for cognitive function in healthy adults or adults with subjective cognitive decline, MCI, AD, or other related neurodegenerative diseases.

The studies in cognitively intact populations plan to enroll 30 to 150 patients. Some studies involve both cognitively intact and MCI populations. One is an open label design; most are randomized controlled trials, some with crossover designs and the rest with parallel allocations. Some are investigating the impacts of single sessions or single protocols, while others involve up to 20 sessions. The studies are generally focused on aspects of cognition, whether it is working memory (NCT05460468), memory (NCT03574207, NCT05556655), or gaze and gait changes (NCT05864313). One study is a combination approach of TMS and cognitive training (NCT06095063).

Instead of looking directly at cognition, one is assessing electrical patterns of activity in the brain after different types of TMS sessions (NCT06344559).Two of the studies are looking specifically at sleep and/or cognitive impairment that is co-morbid with insomnia (NCT06710652, NCT06687161); the latter is also a combination trial of both TMS and cognitive behavioral therapy.

Other studies are assessing the effects of TMS in other populations that do not have MCI, AD, or another neurodegenerative disease. NCT06316557 is an RCT exploring the use of TMS in patients with cognitive impairment after stroke. NCT06043765 is an RCT of cognitive strategy training and TMS in adult patients with glioma. NCT06658769, NCT06482749, NCT05668559, NCT05575583, and NCT06392919 all are assessing the effects of TMS on the cognitive function of post-operative patients.

Several studies are enrolling between approximately 25 and 165 patients with MCI. One is an open label trial; most are randomized controlled trials, some with crossover designs and the rest with parallel allocations. All of the trials involve multiple sessions over the course of days or, more commonly, weeks, ranging from 2 weeks up to 12 weeks.

Some studies look at outcomes of cognitive batteries or performance on multiple cognitive assessments (NCT05992831, NCT06608316) and some look at memory and/or cognition and memory (NCT04558164, NCT03962959). NCT03962959 also looks at APOE status and functional and structural connectivity. Two look at neuropsychological outcomes such as depression (NCT03665831) and apathy (NCT03590327). NCT05327257 is comparing TMS protocols in different brain regions and is looking at feasibility, while NCT04549155 is comparing different TMS approaches and looking at changes in memory and connectivity. Five of the studies are combination trials; NCT06470113, NCT05730296, and NCT06024473 are all assessing the effects of TMS and cognitive training, and look at changes in clinical global impression of change or cognition. NCT06467253 also involves cognitive stimulation and then additionally compares TMS to transcranial direct current stimulation (tDCS), while NCT04583215 is assessing the use of paired association stimulation, which involves both TMS and also peripheral nerve stimulation.

Some studies are enrolling patients with AD or other dementias. These studies aim to enroll between 20 and 200 individuals. One is an open label trial; the rest are randomized controlled trials, some with crossover designs and the rest with parallel allocations. The trials all involve multiple sessions, with durations ranging from a few days up to 8 weeks. Many trials have outcomes of assessments of cognition and/or memory, including NCT06669182, NCT06597942, NCT06524817, and NCT05468268.

NCT06538311 will enroll patients with conditions other than AD, including progressive aphasia and MCI, and look at change in memory and brain connectivity. NCT06385106 will look at cognition and sleep, whereas NCT05977088 will look at cognition and biomarkers, and NCT05389644 will look at changes in apathy behavior. Two are combination trials; NCT04866979 will assess the effects of different TMS protocols and/or cognitive training on memory and connectivity, and NCT06445894 will involve TMS and balance training, and look at the change in balance and cognition. NCT05138588 will assess the physiological effects of TMS in dementia with Lewy bodies (DLB).

Other studies are investigating the utility of TMS in other neurodegenerative diseases, such as Parkinson's disease (PD). Some are investigating cognitive impairment in the context of PD (NCT06399731, NCT06090682) or other conditions besides AD that impact cognition (NCT03217110), while others look more broadly at PD symptoms or complications (NCT06087926, NCT06639945, NCT06583278, NCT06570824, NCT06542991, NCT06415682, NCT06383247, NCT06365190, NCT06363071, NCT06350617, NCT06237868, NCT06009471, NCT06002581, NCT05537597, NCT05478057, NCT05198076). One study is assessing the use of TMS in amyotrophic lateral sclerosis (ALS) (NCT05983211) and another is assessing the use of TMS in progressive supranuclear palsy (PSP) (NCT04468932).

There are other studies that use TMS as a tool to measure some aspect of brain function; trials using TMS as a tool are not included in the above list.

Search terms:

Pubmed, Google: transcranial magnetic stimulation

- Alzheimer's, aging, elderly cognition, cardiovascular, weight, MCI, APOE

Websites visited for transcranial magnetic stimulation:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- Cafepharma

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