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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Transcranial Magnetic Stimulation (TMS) in the Elderly

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Abstract

Purpose of Review This article aims to review select applications of Transcranial Magnetic Stimulation (TMS) that have significant relevance in geriatric psychiatry.

Recent Findings Small study sizes and parameter variability limit the generalizability of many TMS studies in geriatric patients. Additionally, geriatric patients have unique characteristics that can moderate the efficacy of TMS. Nonetheless, several promising experimental applications in addition to the FDA-approved indication for major depression have emerged. Cognitive impairment, neuropathic pain, and smoking cessation are experimental applications with special significance to the elderly. Cognitive impairment has been researched the most in this population and evidence thus far suggests that TMS has potential therapeutic benefit. There is also evidence to suggest benefit from TMS for neuropathic pain and smoking cessation in working age adults. TMS is consistently reported as a safe and well-tolerated treatment modality with no adverse cognitive side effects.

Summary TMS is a safe treatment modality that can be effective for certain applications in the elderly. Additional research that specifically includes older subjects is needed to replicate findings and to optimize treatment protocols for this population.

Keywords Transcranial magnetic stimulation · Geriatric · Safety · Efficacy · Depression · Cognitive · Pain · Smoking cessation

Introduction

Repeated daily prefrontal Transcranial Magnetic Stimulation (rTMS) for 4–6 weeks for treating depression was first proposed as a treatment in 1994, and was FDA approved 14 years later in 2008 [1–3]. Almost a decade later, the field is still rapidly developing and changing. There are now five different TMS devices that have been cleared by the FDA for treating depression, and there is much interest in new pulse frequencies, delivery patterns, methods of determining where to place the coil, maintenance studies, and how to manipulate the patient's brain state with TMS [4••, 5•].

Specifically, with respect to its use as a treatment in the elderly, TMS offers unique advantages. Because the electrical stimulation is focal and not systemic, TMS has relatively few side effects, no deleterious cognitive effects, and no drug-drug interactions which are problems often found with other treatments in the elderly. There is much enthusiasm for the use of rTMS in the elderly and there have been several important studies in the last 3 years which are highlighted below.

Special Considerations of TMS in Geriatric Psychiatry

Safety

Age brings with it changes in physiological function that can impact the management of psychiatric symptoms in the elderly. Decreased creatinine clearance, increased glucose intolerance, impaired thirst mechanism, impaired renal sensitivity to antidiuretic hormone, decreased cardiac output, and decreased cardiac reserve all contribute to making geriatric patients more susceptible to psychotropic medications side effects, which can limit dose titrations and medication effectiveness [3]. Elderly patients are also more likely to be exposed to polypharmacy with its associated increased risk of falls, cognitive impairment, and delirium [6]. Cognitive impairment itself can predispose these

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patients to adverse effects and paradoxical reactions to pharmacotherapies that are otherwise well tolerated in the younger cognitively intact cohorts. rTMS offers a non-pharmacologic treatment modality with a favorable safety profile. Studies have consistently shown that rTMS is well tolerated by patients with only mild adverse effects, the most common being headaches, muscle twitches, and pain at the stimulation site [3, 7]. A Cochrane review in 2014 [8] found that adverse events after real rTMS were no more common than after sham rTMS. The only absolute contraindication to medical use of rTMS is the presence of implants or ferromagnetic devices in or near the head. Seizures are the most serious adverse event from rTMS but these have been unusual, with a reported estimated risk at less than 1 in 10,000 [9] and usually involved neurologically compromised patients or treatment parameters outside recommended standards [10, 11].

Treatment-emergent mania is another serious adverse event that has been reported with rTMS in patients with unipolar and bipolar depression. However, a review by Xia and colleagues of studies published from 1966 to 2006 did not find a statistically significant difference between the rates of treatment-emergent mania in the active versus the sham rTMS groups [12]. In a more recent review, Liu et al. [13] found reports of hypomania in 4 out of 56 older adults with bipolar depression treated with rTMS with comparable patterns of response as younger patients with equivalent illness severity. The most significant attribute of the safety profile of rTMS is the lack of reported cognitive adverse effects. Notably, rTMS has been safely used in patients with comorbid affective symptoms and neurological disorders including cognitive impairments with no reported cognitive adverse effects [14].

Efficacy

Cortical atrophy, decreased functional hemispheric asymmetry, and increased white matter disease burden are examples of age-associated morphological and connectivity brain changes that can moderate the efficacy of TMS in the elderly by affecting the depth and spread of stimulation as described below.

The intensity of the magnetic field produced by the TMS coil decreases exponentially with the perpendicular distance from the coil [15]. Cortical atrophy increases this distance by increasing the distance between the skull where the coil is placed and the brain tissue, therefore decreasing the intensity of the stimulus (magnetic field) that actually reaches the brain. Manes et al. [16] reported in 2001 an inverse association between frontal cortex volume and antidepressant effect of rTMS in the elderly which has been subsequently confirmed [17]. This led researchers to ask whether there might be age-related prefrontal atrophy in depressed patients [18], and whether increasing the intensity of the stimulation to overcome this distance might make TMS an effective treatment in the elderly. This proved to be the case and the field now uses an intensity of stimulation (120%) that overcomes mild atrophy [19].

Studies of physiological and pathological aging suggest a reduction in functional asymmetry in the prefrontal cortex in the elderly compared to that in young participants [20–23]. In theory, this means that elderly patients could need different stimulation sites than younger patients to modulate the same functional circuitry. However, this has not been formally tested.

Increased white matter disease can also moderate the response of older patients to rTMS. Brodie et al. [24] reported a positive association between white matter volume underlying the rTMS coil and motor learning-related changes suggesting that the former could be used as a predictor for behavioral response to low-frequency rTMS. Similarly, Pennisi et al. [25, 26] reported an association between cortical hyperexcitability and white matter integrity in patients with cerebrovascular disease. These findings suggest that the increased white matter disease burden often seen in geriatric patients with cardiovascular risk factors can moderate the neuromodulatory effects of rTMS.

None of these findings negate the utility of rTMS in geriatric patients but instead highlight the need to develop and use age-appropriate dosimetry protocols for this population. Johnson et al. [27] confirmed that using a stimulus intensity of 120% of motor threshold addresses variations in frontal cortical atrophy in depressed patients up to age 65. Alternatively, deep rTMS (dTMS) (which was approved by the FDA in 2013 for treatment of depression) uses a device with an H-shaped coil design that can theoretically increase stimulation depth thereby potentially reaching deeper brain structures than does regular rTMS [28, 29]. Similar to stimulus intensity, the number of pulses has also been identified as a potential moderator of rTMS efficacy in the elderly [17]. Notably, Sabesan et al. [14] observed in their review of rTMS for geriatric depression that the majority of studies favoring the efficacy of rTMS in the elderly used higher number of pulses (which also means more days of treatment) than did studies that reported age-related reduction in efficacy.

Selected Applications of rTMS in Geriatric Psychiatry

TMS is being explored as a non-pharmacological and non-invasive neuromodulation modality for treating a wide range of neuropsychiatric disorders. We review the applications deemed most relevant to the geriatric psychiatry based on the prevalence of the symptoms being targeted and the quality of the evidence available. Table 1 outlines selected applications of rTMS reviewed in this article.

Table 1 Selected applications of Transcranial Magnetic Stimulation (TMS) in geriatric psychiatry

Application	FDA-approved indication?	Studies specifically including older patients?	Interpretation of data reviewed	Sample studies
Unipolar depression	Yes	Yes	Supports efficacy in geriatric patients	Jorge et al. [17], Lisanby et al. [30], Conelea et al. [31]
Cognitive impairment	No	Yes	Suggests potential therapeutic benefit for geriatric patients	Drumond et al. [32], Wu [33], Rabey [34]
Chronic pain	No	Yes (post-herpetic neuralgia)	Suggests potential therapeutic benefit for geriatric patients	Lefacheur [35], Ma [36]
Smoking cessation	No	No	Suggests potential therapeutic benefit for working age adults	Dinur-Klein [37]

FDA-Approved Applications for rTMS

Currently, the only FDA-approved psychiatric indication for rTMS in the USA is the treatment of medication-resistant depression in adults. According to a review by Sabesan and colleagues [14], upward of 30 randomized controlled trials (RCTs) have been published reporting superiority of rTMS over sham for treatment of depression in adults. However, in this same review, the authors only identified four RCT studies that specifically included older subjects (mean sample ages > 60 years): two of them were negative studies and two were positive. The negative studies were conducted at substantially lower stimulation intensities than the positive ones and using different parameters than those now commonly accepted as therapeutic for treating depression: 10 Hz, 120% motor threshold stimulation over the left dorsolateral prefrontal cortex (DLPFC), 3000 pulses per session, and 5 sessions per week for at least 4 weeks [3, 38]. Using these parameters in a multisite, sham-controlled, RCT, Lisanby and colleagues [30] found that age was not a negative predictor of outcome and that patients aged 55 years and older and younger patients had a similar response to treatment. Similarly, Conelea and colleagues [31] reported no difference in response and remission rates after an acute course of rTMS between patients younger than 60 years and those over 60 years old in a naturalistic clinical setting that included patients on psychotropic pharmacotherapy. Qin et al. [39] reported that rTMS improved sleep quality and somatization and decreased suicidal ideation in a RCT conducted with elderly depressed patients. These findings support the mounting evidence suggesting that rTMS is an efficacious treatment for late life depression as long as the appropriate treatment parameters are used. In their study on treatment response trajectory, Gildengers et al. [40•] identified a subset of elderly patients with major depressive disorder who exhibit a slower response to pharmacotherapy. If the same holds true for rTMS, then some geriatric patients, particularly those with high medication resistance or longer disease courses, may need longer TMS treatments to achieve full therapeutic benefit [41]. Unfortunately, most insurance in the United States will not usually cover additional sessions beyond 6 weeks.

Concomitant use of psychotropic medications during rTMS treatment remains a focus of debate in the field. Some literature suggests that given the unclear benefit of rTMS as add-on to antidepressant pharmacotherapy and given the interference of different classes of drugs with cortical excitability, patients should undergo a tapered withdrawal or washout from psychotropic medications prior to rTMS treatment with reintroduction of pharmacotherapy upon treatment completion [1]. We find that in the clinical setting this approach may not be always practical and in fact most patients are kept on stable doses of antidepressant throughout their treatment unless their medication regimen includes drugs that lower seizure threshold (ex. stimulants, buproprion) [4••].

Non-FDA-Approved Applications with Level I Evidence

Cognitive Impairment

The potential role of TMS-induced neuromodulation on cognition is an active area of research with particular significance to geriatric patients given the incidence and prevalence of cognitive impairment in this age group. The details of the mechanism underlying this modulatory action remain to be elucidated but evidence thus far suggests that enhanced synaptic plasticity accounts at least partly for the effects of rTMS on the brain [42, 43]. In a systematic review of cognitive effects reported in studies published between 1999 and 2009, Guse and colleagues [44•] found evidence to suggest that rTMS can produce significant cognitive improvement in patients with cognitive impairment. Another review by Nardone and colleagues in 2014 [45••] reported that rTMS "shows considerable promise to reduce cognitive impairments, but results of the initial studies have to be considered as still preliminary at the present time." More recent studies have provided additional evidence to suggest that rTMS can be used to improve cognition, although small sample sizes and variability in the treatment protocols between studies continue to limit the generalizability of the data. Drumond [32]

conducted a randomized double-blinded sham-controlled trial of high-frequency rTMS in non-depressed elderly with mild cognitive impairment (MCI) and found a positive effect on everyday memory that was sustained at least 1 month after treatment. Wu explored the effect of rTMS on cognition and behavioral symptoms in patients with Alzheimer's disease (AD) in a randomized sham-controlled trial and found a significant improvement on both [33]. Bentwich et al. [46•] investigated whether the combination of cortical stimulation with rTMS and cognitive training would result in a synergistic effect on cognition. Their proof-of-concept study reports significant improvements in two of the scales used, the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) and the Clinical Global Impression of Change (CGIC), although there was no control group for comparison. In a successive randomized, double-blind, sham-controlled study, the authors [34] examined the efficacy of rTMS plus cognitive training in patients with probable mild to moderate AD. They report an improvement in the average scores for both the ADAS-cog and CGIC after 6 weeks and after 4.5 months of treatment in the group receiving real treatment compared with the sham group. The authors highlight that their results for those two parameters were superior to those reported for acetylcholinesterase inhibitors. The study did not screen for the presence of depression in either group, therefore improvements in mood symptoms could be at least partially confounding the observed improvements in cognitive function. This was an industry-sponsored study that provided part of the data supporting the safety and efficacy of a device that combines rTMS with cognitive training in patients with AD. The device has obtained CE Mark (certification that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area) and is applied clinically in Europe (Neuronix, Ltd.; neuroAD Therapy System).

Pain

Alternative treatment modalities for chronic pain have significant relevance to geriatric patients who are particularly susceptible to adverse and paradoxical reactions to first-line pain medications, especially if there is a comorbid cognitive impairment. Aging itself is associated with more degeneration-related physical pain and consequently an increased risk of exposure to narcotic medications. A 2011 Institute of Medicine report on pain [47] estimates the prevalence of chronic pain among older adults living outside institutions to be anywhere from 18 to 57%. The authors also reported that "elderly people are more vulnerable to severe or persistent pain and that the inability to tolerate severe pain increases with age." Given the frequent co-occurrence and association between pain and both affective and cognitive symptoms in the elderly, as well as the potential impact of opioid medications on mood and cognition, rTMS may offer a promising alternative for pain management in geriatric patients. In a 2014 Cochrane review, O'Connell et al. [8] found research studies providing proof-of-concept that rTMS can have a therapeutic role in the treatment of certain chronic pain syndromes but the authors warned about the data being insufficient to confirm specific indications and treatment protocols. A group of European experts commissioned to establish guidelines on the therapeutic application of rTMS concluded that "there is a sufficient body of evidence to accept with level A (definite efficacy) the analgesic effect of high-frequency (HF) rTMS of the primary motor cortex (M1) contralateral to the pain" [35]. Neuropathic pain appears to be one of the chronic pain syndromes that can benefit the most from rTMS [48]. Ma et al. [36] conducted a randomized sham-controlled trial to investigate the effect of high-frequency rTMS over the motor cortex in patients with post-herpetic neuralgia, which is a neuropathic pain condition prevalent among the elderly. The researchers found significant reductions in pain scale scores extending 3 months after treatment which led authors to conclude that "daily high frequency rTMS targeted over the painful region (face, hand, or foot) on M1 is tolerable and effective as an add-on to pharmacological treatment for pain relief in patients with post-herpetic neuralgia."

Smoking Cessation

The Centers for Disease Control and Prevention (CDC) estimate that approximately 8% of individuals 65 years and older in the USA were current cigarette smokers in 2013 [49]. Older smokers are more likely to have chronic diseases and have more severe nicotine addiction than younger smokers [50]. Older smokers are also at increased risk of experiencing smoking-related adverse health effects including cognitive decline, lung cancer, and COPD [51] and they can continue to benefit from smoking cessation regardless of age [52]. Cawkell and colleagues reported in their review: "There is a serious dearth of high-quality evidence for effective smoking cessation pharmacotherapy strategies targeted for the elderly population" [51]. TMS has emerged as a non-pharmacological experimental intervention with a safe adverse effect profile that could potentially be used for smoking cessation in older smokers. On the basis of its neuromodulatory potential, rTMS provides a tool that can possibly manipulate the reward-related brain circuitries involved in addiction. Studies suggest that high-frequency rTMS of the dorsolateral prefrontal cortex can reduce nicotine consumption and craving in working age adults [53–55]. More recently, Dinur and colleagues [37] conducted a randomized double-blinded, sham-controlled study to explore the effects of deep rTMS on smoking cessation. They found that high-frequency deep rTMS of the lateral prefrontal cortex and insula significantly reduced cigarette consumption and nicotine dependence with enduring smoking

cessation effects 6 months after treatment. Mean age for all experimental groups was between 48 and 51 years.

Conclusion

rTMS is being investigated for a wide range of medical applications with variable success. Study sizes and parameter variability limit the generalizability of many studies. Nonetheless, several promising applications in addition to major depression have emerged. Cognitive impairment, neuropathic pain, and smoking cessation are examples of rTMS applications with special significance to geriatric patients. Evidence suggests potential benefit for this population. Geriatric patients have unique characteristics that can moderate the efficacy of rTMS and therefore caution extrapolating results from studies conducted on non-geriatric cohorts is advisable. Additional research that specifically includes older subjects is needed in many areas to optimize treatment protocols for the elderly.

Compliance with Ethical Standards

Conflict of Interest Ilva G. Iriarte and Mark S. George declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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