

Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls

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Abstract

As the global population gets older, depression in the elderly is emerging as an important health issue. A major challenge in treating geriatric depression is the lack of robust efficacy for many treatments that are of significant benefit to depressed working age adults. Repetitive transcranial magnetic stimulation (rTMS) is a novel physical treatment approach used mostly in working age adults with depression. Many TMS trials and clinics continue to exclude the elderly from treatment citing lack of evidence in this age group. In this review, we appraise the evidence regarding the safety and efficacy of rTMS in the elderly. A consistent observation supporting a high degree of tolerability and safety among the elderly patients emerged across the Randomised Controlled Trials and the uncontrolled trials. Further, there is no reliable evidence negating the utility of rTMS in the elderly with depression. We also identified several factors other than age that moderate the observed variations in the efficacy of rTMS in the elderly. These factors include but not limited to: (1) brain atrophy; (2) intensity and number of pulses (dose-response relationship); and (3) clinical profile of patients. On the basis of the current evidence, the practice of excluding elderly patients from TMS clinics and trials cannot be supported.

Key words: Transcranial magnetic stimulation; Depression; Geriatric; Treatment resistance; Treatment resistant depression; Repetitive transcranial magnetic stimulation; Neuromodulation

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Core tip: Depression in the elderly (geriatric depression)

is an emerging global concern. A major challenge in treating geriatric depression is the lack of robust efficacy for many treatments that are of significant benefit to depressed working age adults. An emerging intervention that shows promise in refractory depression is repetitive transcranial magnetic stimulation (rTMS). To date, most of the evidence for TMS in depression pertains to working age adults. We review the evidence regarding the safety and efficacy of rTMS in geriatric depression. In addition, we also review the literature on possible moderators of differential efficacy of rTMS in geriatric depression.

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INTRODUCTION

With an aging global population, depression in the elderly is emerging as a serious public health concern. At present it is estimated that nearly 8%-16% of the elderly (aged > 65) living in the community suffer from clinically significant depressive symptoms^[1], a harbinger of significant morbidity and early mortality^[2]. Older age of a depressed patient is a significant predictor of an unfavourable course with an increased risk of relapse^[3], reduced likelihood of treatment response^[4,5] and diminished chance of functional recovery^[6]. Furthermore, the emergence of treatment resistant depression (TRD) is common among the elderly, with an estimated rate of between 26 and 41 per 100 person-years^[7].

An important challenge in optimally treating geriatric depression is the reduced utility of conventional antidepressant treatments. Randomised Controlled Trials (RCTs) of antidepressants reveal a smaller size of treatment effect among the elderly compared to the younger age groups. The number needed to treat (NNT) for antidepressant vs placebo use for an acute response goes up steadily with age with estimated numbers of 6 in those aged < 55 years; 8 in those aged 55-65 years; and 14 in those aged > 65 years^[5]. This difference may be related to the differences in the pathophysiology and phenomenology of depression among older people.

Whilst depression is mostly a disorder of young adults (peak age of onset in 20 s, with a trend towards more younger age of onset in younger cohorts), late-onset depression (after age 50) has a higher probability of medical comorbidity. There are 2 groups of individuals among those with geriatric depression: one with an early onset (< 50 years) recurrent depression and other in whom depression occurs after the age of 50 for the first time (late-onset). Compared

to elderly patients with early-onset depression, patients with late-onset major depression often have greater vascular risk factors^[8], show greater executive dysfunction^[9], more psychomotor retardation, less agitation and guilt, and more disability^[10]. These factors in general predict poorer response to antidepressants^[10]. Furthermore, even among the elderly depressed with early-onset depression, the prevalence of treatment resistance is substantial^[7], and the risk of relapse despite successful treatment is particularly high^[3], highlighting the critical need to focus on alternative treatments that have fewer propensities to affect cognitive faculties and physical frailty while reducing the persistence of symptom burden.

Transcranial magnetic stimulation (TMS) involves the use of magnetic field applied on the surface of scalp to modulate brain function in a non-invasive manner. Repetitive TMS (also called rTMS) is a promising intervention for depression with a treatment effect size as large as the effect size seen when using antidepressant medications for depression^[11-13]. Several treatment guidelines have endorsed the use of rTMS as a second-line intervention for treatment of depression in adults^[14]. In particular, rTMS is often seen as complementary to electroconvulsive therapy (ECT) due to the reported lack of cognitive side effects, which may be highly advantageous when treating depression in older people. Nevertheless, with some earlier reviews dismissing its effectiveness^[15], the place of rTMS in the treatment of depression in older people is unclear at present.

More than 35 RCTs have been published reporting on the efficacy of rTMS when compared to sham stimulation^[16]. Most of these trials focus predominantly on working age adult samples. In recent times several meta-analytic syntheses of these trials have been published^[17,18]. The mean age of the samples included in these syntheses, when reported, range from 27 to 61 years^[19-26] (Table 1), indicating that very few cases of geriatric depression, if any, were included in the meta-analysed trials. Nevertheless, on the basis of sample mean values of 6 early RCTs (5 double-blind, one open-label), Fregni *et al.*^[27] concluded that older age is associated with poorer response to rTMS in depression. In line with this rTMS was considered to have no role in the management of geriatric depression^[15]. Several subsequent meta-analyses have failed to replicate this finding^[19,28,29]. Furthermore the inference based on Fregni *et al.*^[27]'s observation can be challenged on the basis of two important issues. Firstly, as highlighted earlier subjects with geriatric depression (age > 65) were not included in most individual trials. Secondly, moderator effects uncovered in meta-analytic studies are based on variances between sample means reported in studies, not variances between individuals who receive the treatment *per se*. Only by studying older subjects and estimating the influence of inter-individual age differences on the response, a firm inference regarding the effectiveness of rTMS in the

Table 1 Meta-analytic studies of the antidepressant efficacy of transcranial magnetic stimulation published on or after 2003

Ref.	No. of trials	Mean age	Effect size
Allan <i>et al</i> ^[29] 2011	25	Not presented	NNT = 5
Berlim <i>et al</i> ^[22] (bilateral) 2013	7	49.3 + 5.7	NNT = 6 (res); 7 (rem)
Berlim <i>et al</i> ^[47] (HF) 2013	29	47.6 + 7.1	NNT = 6 (res); 8 (rem)
Berlim <i>et al</i> ^[21] (LF) 2013	8	49.39 ± 7.0	NNT = 5 (res/rem)
Schutter ^[25] 2013 (add-on)	6	44.47 ± 7.55	NNT = 7
Couturier ^[91] 2005	6	Not presented	WMD = 1.1
Gaynes <i>et al</i> ^[76] 2014	18 (TRD)	Not presented	NNT = 9 (res); 5 (rem)
Gross <i>et al</i> ^[71] 2007	5	44.7 + 4.2	d = 0.76
Herrmann <i>et al</i> ^[28] 2006	33	49.14 (subgroups split at age 50)	d = 0.65
Lam <i>et al</i> ^[92] 2008	24	Not presented	NNT = 6
Lepping <i>et al</i> ^[16] 2014	22 (nTRD)	Not presented	d = 0.63 (nTRD)
	10 (TRD)		d = 0.74 (TRD)
Martin <i>et al</i> ^[20] 2003	14	41.8 - 60.9	d = 0.35
Schutter ^[25] 2009 (HF)	30	49.5 + 7.8	d = 0.39
Schutter ^[26] 2010 (LF)	9	50.0 + 6.3	d = 0.63
Slotema <i>et al</i> ^[13] 2010	40	Not presented	d = 0.55
Kedzior <i>et al</i> ^[19] 2014	14	27.0-53.0	d = 0.42

d: Cohen's d effect size; LF: Low frequency; TRD: Treatment resistant depression; nTRD: No treatment resistance; NNT: Number needed to treat; WMD: Weighted mean difference; res: Response; rem: Remission.

elderly can be made.

This review considers recent trials regarding the clinical utility of rTMS in depressed elderly patients. In particular we consider the: (1) evidence for efficacy and safety of rTMS in the elderly; (2) examine the moderators of efficacy; and (3) propose directions for clinical practice and future research.

LITERATURE SEARCH

Search strategy

This review is based on a literature search conducted primarily using the PubMed and Ovid databases in September 2014 with further searches including PsycINFO, CINAHL and Embase. Search terms used were "(Transcranial magnetic stimulation OR TMS OR rTMS OR brain stimulation) AND (geriatric OR elderly OR late life OR late onset OR age OR older) AND depress*." Articles in English published prior to the search date were included.

Eligibility criteria

RCTs evaluating the efficacy and safety of TMS (irrespective of pulse frequency) were included in this review. Due to paucity of research in this area we also included uncontrolled trials and retrospective reviews in the field. The primary outcome measure was chosen as a categorical response or a continuous change defined a priori in the individual trials on the basis of a standardised depression rating scale (*e.g.*, Hamilton Depression scale). In addition we also studied the adverse events reported in the trials. Only studies with a mean age of patient sample > 60 years were included. An exception to this rule was applied when subgroup analysis was performed with mean age > 60 for at least one subgroup.

Study selection

One reviewer (PS) assessed articles identified as a result of the search and where necessary, in cases of uncertainty, a second reviewer (LP) also considered the articles. Studies were initially screened for relevance in the title and abstract. Duplicate articles were removed and the remaining full text articles were reviewed. The final papers chosen for inclusion were also hand searched to ensure relevant references were not missed.

In addition to the systematic review focussing on efficacy and safety in geriatric depression, we also appraised the wider literature to investigate the known moderators of treatment efficacy in geriatric depression. For this purpose, a broader search was conducted using the above search terms, but without restricting studies to a specific mean age of the samples.

RESULTS AND DISCUSSION

Evidence for efficacy in the elderly

We identified 4 RCTs that specifically included older subjects, resulting in mean sample age > 60 years (Table 2). Of these 2 trials reported no benefit from rTMS when compared to sham^[30,31] while 2 other trials (presented in a single manuscript) reported a substantial benefit^[32]. Both Manes *et al*^[30] and Mosimann *et al*^[31] used stimulation intensity that was fixed at or lower than the motor threshold. In contrast, Jorge *et al*^[32] employed a higher intensity. Jorge *et al*^[32] have also shown that the delivery of a higher dose (larger number of pulses - 18000 instead of 12000) is more beneficial in the older than in the younger age group of patients with treatment resistant vascular depression^[32].

Table 2 Randomised Controlled Trials investigating antidepressant effect of transcranial magnetic stimulation in older subjects (mean age of sample > 60)

Trial	Age range	TMS parameters	Sample size	Methodology	Results
Manes <i>et al</i> ^[30] 2001	60.7 ± 9.8	20 Hz; 80%MT; left DLPFC; 800 pulses/session; 5 sessions; no. of pulses = 4000	20 (sham = 10)	Double blind RCT with handle as sham in subjects with one antidepressant failure aged 50-70, withdrawn from antidepressants for 5 d	No sham <i>vs</i> active differences; in each group 30% responded. Non-responders had reduced frontal volume. No drop-outs due to adverse effects
Mosimann <i>et al</i> ^[31] 2004	62 + 12	20 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	24 (sham = 9)	Double blind RCT with tilted-sham in 40-90 years old subjects with TRD	No sham <i>vs</i> active differences
Jorge <i>et al</i> ^[32] 2008 (Trial 1)	62.9 (7.2)	10 Hz; 110%MT; MRI-based target localisation of left DLPFC; 1200 pulses/session; 10 sessions; no. of pulses = 12000	30 (sham = 15)	Double blind RCT with look-alike sham coil in subjects > 50 yr age with vascular depression and failed at least one antidepressant; all patients medication-free for at least 4 d before TMS	Age inversely correlated with response; frontal volume positively correlated with response. Active treatment: 33.3% responders; sham: 6.7% responders. No drop-outs due to adverse events
Jorge <i>et al</i> ^[32] 2008 (Trial 2)	64.3 (9.4)	10 Hz; 110%MT; MRI-based target localisation of left DLPFC; 1200 pulses/session; 15 sessions; no. of pulses = 18000	62 (sham = 29)	Double blind RCT with look-alike sham coil in subjects > 50 yr age with vascular depression and failed at least one antidepressant; all patients medication-free for at least 4 d before TMS	Active treatment: 39.4% responders; sham: 6.9% responders. Older subjects had better response for higher dose. No drop-outs due to adverse events

DLPFC: Dorsolateral Prefrontal Cortex; MT: Motor Threshold; RCT: Randomised Controlled Trial; TMS: Transcranial magnetic stimulation.

Several uncontrolled trials that focus on the efficacy of rTMS in older samples (age > 60) have been published. We identified 5 uncontrolled trials with mean sample age > 60 (Table 3), and 2 trials that specifically studied the subgroup effect for patients aged > 60^[33] or 65^[34]. Response rates (defined as proportion showing a 50% or greater drop in HDRS score) greatly varied, ranging from 18% to 58.5%. Notable variation was also observed for the rTMS dose parameters, with some studies using 100% or less of Motor Threshold (MT: the intensity of magnetic pulse required to elicit an observable thumb movement)^[34-36] and others using > 100% of MT^[33,37]. One study employed an intensity adjustment for predicted frontal atrophy by measuring the MRI-based distance between the coil and the cortical surface^[38]. Four studies explicitly studied the association between age and treatment response^[33,34,37,38]. While 2 studies found a reducing treatment effect with increasing age^[33,37], the other 2 studies failed to find a similar association^[34,38]. Taken together, there is no consistent evidence negating the utility of rTMS in the elderly. The heterogeneity among studies suggests that several clinical and treatment-related factors may moderate the therapeutic effect of rTMS in the elderly.

Evidence for safety in the elderly

A consistent observation supporting a high degree of tolerability and safety among the elderly patients emerged across the RCTs and the uncontrolled trials. In most of the studied cohorts, there were no dropouts due to adverse effects. Only 2 studies reported loss of subjects due to adverse effects^[33,39]. Out of 102

patients of various ages reported by Pallanti *et al*^[33], dropouts occurred due to anxiety ($n = 4$), insomnia ($n = 5$), mood elevation ($n = 1$), discomfort of the scalp ($n = 5$), and hospitalization during treatment ($n = 4$). The 18.6% dropout rate reported in this study is unusually high, when compared to the overall 4.5% observed from other larger multisite studies^[40]. Pallanti *et al*^[33] did not study the influence of age on the dropouts. In the sample reported by Abraham *et al*^[39] one subject dropped out due to local discomfort. Jorge *et al*^[32] reported local discomfort in around 33% of the randomized sample. But no subjects discontinued treatment due to this effect, and the distribution of side effects was not significantly different between the sham and the active treatment groups^[32].

Efficacy of rTMS in comparison with ECT in the elderly

ECT has an important role in the clinical management of geriatric depression. A substantial proportion of all referrals received by ECT clinics fall into the age group > 65^[41]. ECT appears to be generally safe and highly efficacious in geriatric depression with response rates close to 70% reported in some studies^[42,43]. Interestingly, older age is associated with a more favourable response to ECT^[44,45]. In this context it is important to consider direct comparisons ECT and rTMS in treating geriatric depression.

We located 4 meta-analyses that synthesize the evidence from studies that compare rTMS and ECT (Table 4). The sample mean age of these studies span a range of 31.0 to 63.6 years^[46-49]. All 4 meta-analyses find that ECT is superior to rTMS in short-term when categorical response is considered,

Table 3 Uncontrolled studies exploring the effect of age on the antidepressant effect of transcranial magnetic stimulation by recruiting older subjects (mean age of sample > 60) or undertaking analyses in subgroups with mean age > 60

Trial	Age range	TMS parameters	Sample size	Methodology	Results
Figiel <i>et al</i> ^[37] 1998	60.0 (22-89)	10 Hz; 110%MT; left DLPFC; 500 pulses/session; 5 sessions; no. of pulses = 2500	50	Uncontrolled trial in patients > 18 yr attending a Mood Disorder Clinic (most referred for ECT)	Age associated with treatment response; < 65 (<i>n</i> = 28) responded better (56%) than > 65 group (<i>n</i> = 22; 23% response). Overall 42% responded after the 5 sessions
Nahas <i>et al</i> ^[38] 2004	61.2 (7.3)	5Hz; 103%-141%MT (distance adjusted); left DLPFC; 1600 pulses/session; 15 sessions; no. of pulses = 18000	18	Uncontrolled trial in patients 55-75 yr; not selected for TRD	No correlation between age and response; 27% responded; 22% remitted; No drop-outs due to adverse events
Fabre <i>et al</i> ^[35] 2004	67.9 (6.7)	10 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	11	Uncontrolled trial in patients age > 55 with vascular depression (first episode) and TRD but kept antidepressant free for 1 wk	5 out of 11 patients had clinically meaningful improvement in HDRS scores; response inversely related to frontal volume. No drop-outs due to adverse events
Abraham <i>et al</i> ^[39] 2007	66.8 (6.4)	10 Hz; 100%MT; left DLPFC; 1600 pulses/session; 10 sessions; no. of pulses = 16000	20	Uncontrolled trial in patients > 60 yr attending a specialist clinic - most referred for ECT	30% responded at the end of treatment; 1 dropout due to discomfort
Milev <i>et al</i> ^[78] 2009	69.0 (6.7)	Variable parameters: LF (1 Hz, 1200 pulses/session, <i>n</i> = 14), HF (10 Hz, 1600 pulses/session <i>n</i> = 31); both LF and HF (<i>n</i> = 4); 80%-110%MT; right or left DLPFC	49	Uncontrolled trial that includes patients with TRD referred to 2 specialist mood disorder clinics; all except 3 medicated	24.7% mean reduction in HDRS scores; 18% responders; 1 dropout due to discomfort out of 49. (Note: This sample includes <i>n</i> = 20 from Abraham 2007)
Pallanti <i>et al</i> ^[33] 2012	51.8 (14.1)	1 Hz; 110%MT; right DLPFC; 420 pulses/session; 15 sessions.; no. of pulses = 6300	102	Uncontrolled trial in consecutively enrolled nonpsychotic subjects in a TMS clinic with TRD	Age inversely related to response especially in patients > 60 yr; overall 56.9% responded. 62.1% of < 60 (<i>n</i> = 66) and 47.2% of > 60 (<i>n</i> = 36) responded at 3 wk. 18.6% drop-outs due to intolerance
Hizli Sayar <i>et al</i> ^[36] 2013	66.6 (5.8)	25 Hz; 100%MT; left DLPFC; 1000 pulses/session; 18 sessions; no. of pulses = 18000	70	Uncontrolled trial in patients > 60 yr with TRD	58.5% responded; 29.2% remitted; No drop-outs due to adverse events
Ciobanu <i>et al</i> ^[34] 2013	58.7 (14.0)	LF (1 Hz, 1200 pulses/session, <i>n</i> = 80), HF (10 Hz, 2000 pulses/session <i>n</i> = 13); 90%MT; right or left DLPFC; 15 sessions; no. of pulses = 18000	93	Uncontrolled trial in > 18 yr old subjects with TRD	Age not related to response; No difference between < 65 (<i>n</i> = 63; 53.3% responded) and > 65 age (<i>n</i> = 30; 46.7% responded) groups immediately and at 3 mo

DLPFC: Dorsolateral Prefrontal Cortex; MT: Motor Threshold; RCT: Randomised Controlled Trial; ECT: Electroconvulsive therapy; TRD: Treatment resistant depression; TMS: Transcranial magnetic stimulation.

though Ren *et al*^[46] indicate that change in continuous Hamilton Depression Rating Scale (HAM-D) scores do not significantly differ between the two treatments. Furthermore, Berlim *et al*^[47] noted baseline differences favouring ECT (shorter duration and more severe illness). There is insufficient data to comment on medium or long-term efficacy^[46]. Interestingly, two of the three individual trials showing significant difference in favour of ECT^[50,51] included participants with higher mean age than the rest. When comparing ECT and rTMS, Janicak *et al*^[52] noted that older subjects required a higher number of rTMS sessions to experience a favourable treatment response when compared to younger subjects. Nevertheless, when considered as a moderator in the meta-analytic setting, mean sample age did not significantly predict the effect size of rTMS v ECT differences^[47]. An important predictor appears to be the presence of psychotic symptoms^[46,47]; in the presence of psychosis, ECT appears to be significantly superior to rTMS^[51].

But in samples with no psychosis, rTMS performs as well as ECT^[53]. Given that many patients with geriatric depression have psychotic symptoms, this may partly explain the superior efficacy of ECT in this setting, though more focused studies are required to provide conclusive support to this notion.

Rapidity of response is an important factor for which ECT is sought in the elderly. Difference in speed of response has not been studied directly in the 4 meta-analyses, but an important observation suggests that ECT may be superior to rTMS in terms of the rapidity of response. Xie *et al*^[48] observed that when rTMS treatment period was less than 4 wk, rTMS was significantly inferior to ECT. When the treatment period was increased to 4 wk, the difference between rTMS and ECT began to decrease, suggesting that ECT results in far more cases of early response than rTMS.

With respect to cognitive side effects in the relatively younger samples included in meta-analyses, ECT was associated with more impairment in several cognitive

Table 4 Summary of meta-analyses comparing transcranial magnetic stimulation and electroconvulsive therapy in depression

Meta-analysis	No. of studies/sample size	Mean age range	Summary of effect
Berlim <i>et al</i> ^[47] 2013	7/294	31.0-63.6	NNT = 6 favouring ECT for short-term response; at baseline, ECT samples had shorter illness duration and higher HAMD scores than rTMS samples. Age has no moderating effect on the differences
Ren <i>et al</i> ^[46] 2014	9/425	31.0-63.6	NNT = 7 for response; 6 for remission favouring ECT; No significant group difference when continuous change in HAMD scores is considered as outcome; In the absence of psychosis, rTMS as efficacious as ECT; Cognitive domains are better preserved after rTMS than ECT
Micallef-Trigona ^[49] 2014	9/384	34.0-63.6	Hedges'g = 1.28 for rTMS and 2.15 for ECT. rTMS produces a mean reduction of 9.3 points; ECT produces a mean reduction of 15.42 points on the HDRS
Xie <i>et al</i> ^[48] 2013	9/395	31.0-63.6	OR = 0.55 for response and 0.49 for remission in favour of ECT; rTMS is better tolerated than ECT (OR = 0.70); rTMS > 1200 stimuli/d is as efficacious as ECT

NNT: Number needed to treat; TMS: Transcranial magnetic stimulation; ECT: Electroconvulsive therapy; HAMD: Hamilton Depression Rating Scale.

domains^[46], though the dropout rates (acceptability) did not differ between the two interventions.

Moderators for efficacy in the elderly

Studies included in this review examined the role of several moderators on clinical response as described below.

Age: Age itself is not a consistent predictor of the antidepressant effects of rTMS as shown by conflicting evidence from adult samples^[29]. A large naturalistic study ($n = 307$) that included a broad age range (18 to 90) of patients receiving rTMS for depression concluded that age had no notable influence on the improvement in quality of life noted in patients^[54]. Furthermore the RCTs and uncontrolled trials reviewed here defy the notion that rTMS is ineffective in geriatric depression. Given the wide range of response rates reported among the elderly, it becomes important to understand the factors that may influence treatment response in this group. Some of the important factors that have been identified in this context are: (1) brain atrophy; (2) intensity and number of pulses (dose-response relationship); and (3) clinical profile of patients.

Brain atrophy: Manes *et al*^[30] first observed that the volume of frontal cortex was inversely related to the antidepressant response to rTMS in the elderly. This observation was later confirmed by Fabre *et al*^[35] and Jorge *et al*^[32]. In an atrophic brain, the distance between scalp and cortex (Scalp-Cortex Distance or SCD) increases. When applying rTMS the intensity of the magnetic field decays exponentially as we move from the scalp surface to the cortical surface^[55]. Herbsman *et al*^[56] have shown that nearly 60% of inter-individual variation in Motor Threshold can be explained by the distance between scalp and motor cortex alone (motor SCD). Using a simple linear model, Stokes *et al*^[57] estimated that for every 1 mm increase in motor cortex SCD, a 2.8% increase occurs in consistent with this observation, the degree of rTMS induced change in

frontal perfusion corresponds inversely with increasing frontal cortex SCD in depressed subjects^[58].

One may argue that as the intensity of stimuli used in the treatment of depression is generally based on an individual's MT, the effect of brain atrophy is already taken into account by adjusting the intensity applied to frontal cortex on the basis of MT. But in fact, with age, a disproportionately higher volume reduction occurs in the frontal cortex compared to motor cortex^[59]. As a result, the MT fails as a "benchmark" to calculate the intensity required for stimulating the frontal cortex. Several authors have proposed approaches to adjust the intensity of rTMS according to the measured SCD of the stimulated cortex^[38,55,60,61].

But the utility of employing a SCD-adjusted intensity is questioned by other authors. Firstly, the relationship between SCD and treatment response is not a consistent one. Unlike Fabre *et al*^[35], neither Kozel *et al*^[62] nor Jorge *et al*^[32] could find a relationship between frontal SCD and treatment response, though Jorge *et al*^[32] noted that the volume of prefrontal cortex mediated the beneficial effects of treatment. Secondly, while higher SCD is a proxy for age-related (or pathological) atrophic process, the biological effect of brain atrophy is better reflected by a measure of cortical thickness or surface area. Interestingly, lower motor cortical thickness in older adults appears to be associated with lower (not higher) resting MT^[63]. This indicates that brain atrophy could result in two contrasting changes 1. A reduction in the strength of the magnetic field that reaches the cortex upon the application of rTMS 2. An increase in the excitability of cortex, such that even smaller intensities are now sufficient to stimulate the brain. Taken together, there may not be any appreciable overall change in the MT with age. In fact, direct comparisons of the MT in the elderly and younger subjects have been so far inconclusive with some studies reporting age-related increase in MT, whereas others reporting no differences in MT between different age groups (reviewed by Rossini *et al*^[64]). Most studies examining the effect of

rTMS on cognition in dementia employ < 100% MT on DLPFC but still observed notable improvements in cognitive performance^[65]. It is likely that physiological effects of rTMS are induced despite notable cortical atrophy when stimulating frontal cortex in the elderly. On the basis of simulated models of brain atrophy that included both volume shrinkage and sulcal widening, Wagner *et al*^[66] argue that SCD based correction of pulse dose/intensity^[38,55,60,61] is an inaccurate oversimplification that fails to consider the geometrical changes and altered excitability of the shrunken brain.

Despite the limitation of distance adjustment approaches, a superior therapeutic response is noted when dose-adjusted intensity is employed in treating depression^[38,67], when compared to conventional doses delivered as a fixed proportion of MT. The intensity adjustment approaches employed by Nahas *et al*^[38] 2004 and Mosimann *et al*^[67] require an anatomical MRI to calculate the SCD. A more pragmatic solution was put forward by Johnson *et al*^[68], on the basis of a multisite RCT that studied 185 adults of age 22-69 years. The authors reported that most of the effect of frontal atrophy could be overcome by using an intensity that is 120% of MT^[68]. This resulted in distance-adjusted intensities that ranged from 93% to 156% of MT and was found to be both safe and efficacious in patients. So far, no studies in the elderly have evaluated the efficacy of 120% MT protocol, though most TMS clinics are now employing an intensity of 120% MT for left prefrontal stimulation working age adults with depression^[54,69].

Number of pulses delivered: In rTMS studies of depressed working age adults, a relationship between dose and response has been previously reported. A review by Gershon *et al*^[70] noted that rTMS studies delivering higher doses (pulses/day) for longer duration of treatment were more effective than shorter studies using lower doses. In this context, it is worth noting that over the years, the total number of pulses delivered in treatment of depression has increased in general^[11,19,71], partly explaining the increase in effect size of rTMS in depression over the years^[71].

An interesting observation emerges from the TMS trials (both RCTs and uncontrolled trials) in the depressed elderly reviewed here; almost all studies that conclude in favour of efficacy of rTMS in the elderly use a high number of pulses (18000^[32,34,36,38]) while most of the trials that found age-related reduction in efficacy employed smaller number of pulses (2500 to 6300^[30,33,37]). Jorge *et al*^[32] examined this issue closely by designing 2 experiments within a single trial. They noted that the elderly subjects with vascular depression who received 18000 stimuli in total responded more robustly than those who received only 12000 stimuli a day. While there are a number of other factors that could have influenced the heterogeneity of individual study results, the observation of lack of age-related reduction in efficacy when using higher doses (number of pulses) merits further consideration in

clinical practice.

Clinical profile: Apart from age, several other features differentiate geriatric depression from the depression seen in working-age adults. These include the higher prevalence of treatment resistance^[3,4], the excess of somatic/melancholic^[72] and psychotic features^[73], higher degree of cognitive impairment/dementia and medical comorbidity^[74,75] among the elderly. Evidence for the influence of these factors on rTMS treatment response in the elderly is considered below.

Treatment resistance: Meta-analytic evidence in depressed working age adults supports the use of rTMS in the treatment of refractory depression (no. of studies = 18 with at least 2 antidepressant failures; duration 1 to 6 wk; sample sizes 12 to 74; NNT = 5 for remission)^[76]. Some studies in depressed working age adults have observed a relationship between the degree of treatment-refractoriness and higher response rates for rTMS^[77], though other studies have observed a reversed relationship^[27,69]. Allan *et al*^[29] reviewed this issue and concluded that the presence of TRD in a sample does not influence its response to rTMS. In line with this, there is a lack of a predictable association in either direction among the studies considered in this review as well. Of the 12 rTMS trials (RCTs and uncontrolled studies) in the depressed elderly reviewed here, 5 include samples with at least 2 antidepressant failures while the rest include samples with minimum 1 antidepressant failure. Studies concluding in favour of rTMS in treating geriatric depression have included samples both with TRD (2 antidepressant failure)^[33,34,36,78] and 1 antidepressant failure^[32,38]. Taken together, the influence of the degree of treatment refractoriness on therapeutic response to rTMS in the elderly is still uncertain. No focused studies directly comparing subjects with TRD and without TRD in geriatric depression have been reported to date.

Psychosis: Several studies in working-age samples support the notion that ECT achieves a superior treatment response in psychotic than non-psychotic depression. In their meta-analysis comparing ECT and rTMS, Berlin *et al*^[47] reported that ECT was significantly superior to rTMS in primary studies where the samples had psychotic symptoms. Ren *et al*^[46] concluded that rTMS works as well as ECT in the absence of psychosis. The study that reported one of the highest response rates for rTMS in patients > age 60 (47.2% response after 3 wk) only included patients without psychotic symptoms^[33]. The mediating influence of psychosis on the antidepressant effect of rTMS in the elderly has not been directly investigated to date.

Melancholia: Melancholic features are more common among the elderly with depression. rTMS does have an alleviating effect on core melancholic features such as psychomotor retardation in working-age

adults^[79]. A reduction in melancholic features occurs irrespective of overall clinical response, suggesting a symptom-specific effect of rTMS on melancholia^[80]. In particular, psychomotor agitation, which is a common feature among the elderly, appears to respond to high-frequency rTMS^[81]. While some rTMS studies in working-age samples suggest that the presence of melancholic features itself indicate poorer overall response to rTMS^[82] other studies suggest the opposite^[83]. Among the elderly, the specific effect of melancholic features on rTMS treatment response has not been examined so far.

Cognitive impairment: Patients with other comorbid psychiatric illnesses including dementia are often excluded from rTMS studies of depression. Geriatric depression is accompanied by a greater degree of cognitive impairment and a substantial number of patients, who are initially found to have depression with cognitive impairment, later develop dementia, suggesting that a subgroup of geriatric depression may indeed be a prodrome for dementia^[84]. After an episode of depression, the risk of dementia increases by nearly 87% over a period of 25 years^[85].

A number of studies indicate that rTMS may improve deficits and delay cognitive decline in Alzheimer's dementia^[86], with some studies suggesting a therapeutic effect that lasts for nearly 3 mo^[87]. Rutherford *et al.*^[88] suggest that some of the improvement in cognitive performance seen in patients with dementia after rTMS treatment can indeed be attributed to the antidepressant effect of rTMS. Furthermore, as concluded by Ren *et al.*^[46] in their meta-analysis comparing rTMS and ECT, rTMS appears to be superior to ECT in terms of cognitive side effects. Taken together, this suggests that contrary to the prevailing practice in most ECT clinics, there is no need to exclude elderly subjects with notable cognitive impairment from rTMS studies.

Medical comorbidities: To our knowledge, the moderating influence of medical comorbidities on the therapeutic response to rTMS has not been studied either in the working-age samples or the elderly. Most rTMS trials in working-age adults have excluded patients with significant medical illnesses; as a result the moderating effect of this variable has not been studied in the extant meta-analytic literature on the efficacy of rTMS. Among studies considering geriatric depression, some authors excluded patients with uncontrolled medical illnesses^[31,33,38,39,78] while others included subjects with medical comorbidities^[32,37]. rTMS has been investigated as a treatment modality in several neurological disorders that often present with comorbid depression in the elderly (*e.g.*, parkinsonism, stroke^[89]), and has been found to be safe.

Pitfalls

While the potential of rTMS in the treatment of depression is acknowledged widely, it has not entered the standard

stepped-care approach recommended for the treatment of depression in the elderly. An appraisal of the rTMS literature relevant to geriatric depression highlights several deficiencies and offers insight on the pitfalls of recommending routine use of rTMS in geriatric depression. Firstly, the practice of excluding older adults from rTMS trials has resulted in a dearth of good quality RCT data in this age group. The available evidence does not provide an unequivocal support for age related reduction in the antidepressant effect of rTMS. In contrary, it hints at several possible mechanisms for the inconsistently observed differential treatment response. Secondly, there is a scarcity of experimental studies investigating the variations in rTMS parameters to improve response rates in the elderly. Third, despite the numerous phenomenological and neurobiological differences between working-age adults and elderly with depression, moderators other than age have not been systematically studied in rTMS studies of geriatric depression.

Study limitations

We acknowledge that despite being broadly inclusive, several grey literature such as conference abstracts reporting on TMS efficacy for geriatric depression might have been missed. In addition, publications in languages other than English were not included in this search.

Direction for future research

Future studies are needed to replicate and confirm the hypotheses regarding the efficacy of higher number of pulses in the elderly. In addition, systematic exploration of the influence of various features (other than age) that differentiate geriatric depression from early-life depression is required to understand the moderating effect of these features.

Implications for clinical practice

Despite the limitations identified above, several clinical practice points emerge from this appraisal of rTMS focussed on older adults with depression. On the basis of the current evidence, the practice of excluding elderly patients from rTMS clinics and trials cannot be supported. Age-related reduction in antidepressant efficacy, even if present, is not specific to TMS^[90]. Adjusted dosing schedules that deliver higher intensity and pulses appear to improve the therapeutic response in the elderly, and these dose variations must be made available for the elderly depressed seeking treatment. In contrast to working-age adult samples where TMS is considered as an alternative "in line" with ECT, for elderly depressed patients, given the indications for a superior efficacy of ECT, rTMS could be offered either after an unsuccessful or poorly tolerated trial of ECT. In some carefully selected cases of non-psychotic depression, rTMS could be a potential alternative to ECT when rapidity of response is not crucial but

undesirable cognitive side effects to ECT are highly likely. While it is premature to recommend rTMS for regular use in geriatric depression, continued exclusion of this group of depressed patients from a well-tolerated and safe treatment option for resistant depression on the basis of their age appears to be clearly untenable.

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