stimulation site that does not guarantee that they were actually stimulating the dorsolateral prefrontal cortex (DLPC) (Mosimann et al., 2004).

A small, open study has examined response to rTMS in treatment resistant VaD (Fabre et al., 2004). The results demonstrated that five of 11 patients were treatment responders with a drop in HDRS scores between 10 and 14 points. The mean HDRS score in the responder group decreased from 24 ± 5.9 to 12.6 ± 5.5 while the six nonresponders had pretreatment HDRS scores of 24.5 ± 7.2 versus post treatment 24.8 ± 5.9.

We have recently completed a NIH-sponsored project on the efficacy of rTMS to treat depressive disorders associated with cerebrovascular disease. We conducted two independent experiments comparing active left DLPC rTMS with sham stimulation. In the first one, we delivered a total cumulative dose (TCD) of 12,000 magnetic pulses while in the second one the TCD was increased to 18,000 magnetic pulses. To our knowledge, these are the first randomized controlled trials of the efficacy of rTMS to treat VaD and the largest trial in LLD.

In Experiment 1, the sham group showed a 13.6% decrease in HDRS-17 scores compared to a 33.1% decrease in the TCD-12K group (p = 0.04). Response rates were 6.7% in the sham group and 33.3% in the active group (p = 0.08) and remission rates were 6.7% in the sham and 13.3% in the active group (p = 0.50). In Experiment 2, the sham group showed a 17.5% decrease in HDRS-17 scores compared with a 42.4% decrease observed in the TCD-18K group (p = 0.0001). Response rates were 6.9% in the sham group and 39.4% in the active group (p = 0.003), and remission rates were 3.5% in the sham group and 27.3% in the active group (p = 0.01). The effect size of the difference between HDRS scores was 0.89 in this group of VaD patients.

Age had a significant impact on the antidepressant response to rTMS. Among older patients (65 years or more), active rTMS produced significantly greater reductions of HRSD-17 scores than sham stimulation only in the group of patients who received the higher rTMS dose (TCD-18K).

Greater antidepressant response to rTMS was significantly associated with higher frontal grey matter volumes. rTMS was safe, well tolerated, and not associated with cognitive deficits. We need to emphasize that a higher dose of left DLPC rTMS was associated with greater antidepressant efficacy. It is highly probable that we have not yet found an optimal TCD of rTMS to achieve maximal response and remission rates in this population.

In summary, there is consistent preliminary evidence suggesting that rTMS is a safe and effective antidepressant intervention among patients with VaD. However, future studies should examine several important issues. The first issue relates to the selection of those rTMS stimulation parameters associated with the higher response and remission rates that can be achieved by rTMS among this group of patients. A second issue is the need to determine whether VaD represents a subgroup of LLD that shows a greater response to rTMS or if, after optimization of the stimulation parameters, LLD patients without evidence of ischemic damage will show similar response to rTMS as VaD patients. Finally, if VaD proves to be more responsive to rTMS than other forms of LLD, we should investigate the underlying mechanism of this phenomenon.

Further studies should rely on a multicenter approach in order to enroll a larger sample of LLD patients that will allow more meaningful statistical inferences to be made. In addition, it is advisable to increase the dose of rTMS significantly, incorporate state of the art techniques to localize the stimulation site, adjust the rTMS dose to the degree of prefrontal atrophy, and optimize the sham stimulation condition.

Needless to say, LLD is a major health concern for which we still do not have optimal therapeutic options. rTMS constitutes a reasonable alternative considering both efficacy and safety issues. In our opinion, the available evidence clearly supports the need for further research in this field.

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Commentary
As we are all well aware, depression in older people remains one of the great challenges in our field. Prevalence of major depression in older people is usually cited as around 3%, but minor depressive symptoms are up to fivefold more common, may be as disabling as major depression and carry a poor prognosis. For example, Chuan et al. (2008) found that subsyndromal depression had similar adverse consequences on mental, physical and functional status as syndromal cases. In a 12 year follow-up, Andreescu et al. (2008) showed that minor depressive symptoms were associated with
future increases in symptoms, especially if subjects were female or had functional disability. Depressive symptoms were also more likely to persist over time in those with greater medical burden. Similarly, Lyness et al. (2009) showed that older people with minor and subsyndromal depression had a sevenfold risk of developing major depression over the subsequent year.

Despite its high prevalence, current treatments for depression in late life are arguably still very limited. The development of new and effective treatments for depression is especially challenging as, despite much knowledge about risk factors for depression, etiology remains essentially unknown and many of the established risk factors are not easy to modify, if they can be modified at all. The translation of treatments from younger adults to older adults cannot be automatically assumed, yet the evidence base supporting drug prescribing for affective disorders in old people is limited. For example, a recent survey of Old Age Psychiatrists found that although prescription rates for mood stabilizing drugs was high, over half of respondents indicated that lack of scientific evidence was a major concern when prescribing treatments for mood disorders in older people (Ephraim and Prettyman, 2009). Although antidepressants are effective in older people (Raskin et al., 2008), even novel dual acting agents such as duloxetine show non-response rates (as defined by greater than a 50% reduction in HDRS scores) as high as 60% at 8 weeks (Raskin et al., 2008). Better treatments are desperately needed, especially for those who do not respond to standard antidepressant treatments. Electroconvulsive therapy is widely accepted as an efficacious treatment for late life depression, although of course there are risks (albeit small) in older people because of the need for anesthesia. There is also a powerful anti-ECT lobby which undoubtedly has had an influence in the varied prescribing rates for ECT found both over time and between different countries. The search for a safe and effective alternative to ECT is therefore of great importance.

The top-cited paper under discussion (Manes et al., 2001) is a good example of a pioneering study in this regard and one that has had significant impact in the field. The authors applied rapid TMS (rTMS) (Jorge et al., 2008) to the left dorsal lateral cortex in depressed subjects finding no significant benefits (compared to sham treatment) at seven days’ follow-up. Intriguingly, they found that responders to treatment had significantly greater frontal lobe volume than nonresponders, suggesting that there may be an important interaction between structural brain abnormalities (which have been well identified in depression) and response to treatment, as others have previously shown (O’Brien et al., 1998; Almeida et al., 2003). As well as providing an excellent summary of the field and commentary in their reflection piece, Jorge and Robinson also describe two new studies of TMS of left dorsal atrophy frontal cortex compared with sham stimulation. Although full details, such as subject details and numbers of subjects, are described elsewhere (Jorge et al., 2008) the authors report benefits in terms of decreased HDRS scores (but not response rates or admission rates) in Experiment 1 and highly significant benefits of TMS in terms of reduced HDRS scores, response rates and remission rates in subjects with depression associated with cerebrovascular disease. Such a “vascular depression” has been categorized as a subtype of depression in older people which may have a specific clinical and cognitive profile and implications with regard to treatment. However, uncertainties about the relevance of vascular changes and how such people should be identified remains. As Almeida (2008) points out, vascular risk factors and cerebrovascular disease are so common in older people that if these alone are used to categorize subjects, almost anyone who develops depression after the age of 65 may be deemed to have a vascular depression. However, Jorge and colleagues are to be congratulated for undertaking one of the few therapeutic studies in the area, since it is only by further research in this area that the true significance of vascular factors and their implications for treatment can be determined. Their new studies directly result from their original pioneering TMS top-cited paper.

Intriguingly, in their recent studies, Jorge and colleagues have found that greater antidepressant response to rTMS is significantly associated with higher frontal grey matter volume. This finding is of interest as it totally replicates their earlier seminal study. Findings of their recent studies would also appear to support the use of rTMS in people with vascular depression. Of course, several questions remain. What is the appropriate clinical phenotype (assuming there is one) of VaD to select subjects for treatment? On what other characteristics should subjects be selected for treatment? Why is response greater in those with VaD as opposed to non-vascular cases, especially since structural brain changes like frontal atrophy (which are more common in those with VaD) actually appear to be associated with poorer response to rTMS? Will effects of rTMS persist in the longer term and how should rTMS be used in conjunction with other therapies for depression, whether pharmacological or psychological? What is the dose response for rTMS? The fact that these exciting findings raise a number of other important scientific questions is
a testament to the pioneering TMS work of Manes, Jorge, Robinson and colleagues. The authors are to be congratulated for following their earlier paper with larger, better designed, controlled studies and for tackling the subject of appropriate treatments for VaD. They conclude in their reflection that “the available evidence clearly supports the need of further research in this field”. I fully agree and, like others, I await the results of such research with great interest.

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