Repetitive Transcranial Magnetic Stimulation (rTMS) for Depression in Older Adults: Improving Depression and Stimulating Cognition

In Canada, as in all other Western countries, older adults are the fastest growing segment of the population. Depression is the most common, treatable, mental disorder in late life, making it a major public health concern: 2 to 4% of persons over the age of 65 suffer from major depression (Blazer 2003). LLD is also typically complicated by co-morbid medical illness and polypharmacy and it is associated with excess morbidity and mortality (both from suicide and co-morbid physical illness) (Ganguli et al. 2002). Current treatments for LLD provide modest efficacy. It is estimated that close to 40% of patients are resistant to antidepressants (Mulsant & Pollock, 1998; Whyte et al, 2004; Mulsant et al. 2006).

Further, the elderly are more likely to experience relapses and recurrences than younger adults (Reynolds et al., 2006; Tew et al. 2006; Mulsant et al. 2006). Augmentation strategies (e.g., addition of lithium or antipsychotics) are problematic insofar as the elderly have increased sensitivity to adverse effects (Dew et al., 2007) such as falls (Joo et al., 2002). Finally, although ECT is an effective treatment for LLD, this procedure requires general anesthesia and it is typically associated with cognitive side effects (Sackeim et al., 2007). Many patients are reluctant to engage in a trial due to stigma and the risk of cognitive side effects.

Cognitive impairments, particularly executive dysfunction, are prominent and disabling consequences of LLD (Kiosses et al., 2001). Several studies have reported that the presence of executive impairment in older adults with depression, predicts a poor response to antidepressants (Kalayam et al. 1999; Alexopoulos et al. 2000; Bogner et al, 2007). Also, successful treatment with antidepressants does not yield improvement in this cognitive domain (Nebes et al., 2003; Butters et al., 2000). In contrast, emerging data supports a potential beneficial effect of rTMS on executive dysfunction. In fact, a significant improvement in executive functioning was found in a group of depressed elderly subjects treated with rTMS (Moser et al., 2002). In addition, a recent, sham-controlled, rTMS study in older subjects demonstrated improvement in associative memory (Sole-Padulles et al. 2006). Moreover, there have been several studies in younger depressed adults that have also found improvement in domains of
executive functioning using rTMS (O’Connor et al. 2005; Martis et al., 2003; Boggio et al. 2005). Finally, the largest LLD study to date, showed improvement in executive functioning independent of mood changes in a group with both clinical and MRI defined vascular depression (Jorge et al. 2008). Taken together, these data suggest a compelling rationale to assess executive dysfunction in LLD and determine if rTMS treatment concomitantly improves executive functioning and resistant depressive symptoms.

Unfortunately there are only a few small studies evaluating rTMS for treatment resistant late-life depression (TRLLD). Moreover, these studies are limited in several important ways: suboptimal stimulation parameters (e.g., location of stimulus delivery, stimulation intensity), limited small sample sizes and insufficient treatment durations. For example, Manes et al. (2001) assessed high frequency left-sided (HFL) rTMS in 20 older depressed patients. However, the treatment duration was limited (i.e., 2 weeks or 10 treatments) and the stimulus intensity (80% motor threshold (MT)) was lower than what is necessary to achieve a therapeutic effect in an elderly population where the coil-to-cortex distance is typically increased. Mosimann et al. (2002) looked at the therapeutic effects of rTMS in relation to coil-cortex distance in a group of depressed elderly patients. They found that response to rTMS was related to the degree of prefrontal atrophy and recommended that stimulation intensity be adjusted to overcome this age-related effect. Despite this, Mosimann et al (2004) published a randomized sham-controlled study of rTMS in 24 elderly subjects, with a short treatment duration (10 sessions) and sub-optimal treatment intensity (100% MT). Not surprisingly, in these studies rTMS was not associated with positive outcomes. Nahas et al. (2004) used an open design in which they adjusted stimulus intensity based on coil-to-cortex distance and used MRI co-registration to target the dorsolateral prefrontal cortex (DLPFC), in 18 older subjects. The average intensity required was 114%; significantly higher than the intensity used in other treatment trials and they found a respectable 26% remission rate. Recently, Jorge et al. (2008) published the results of a relatively large placebo-controlled rTMS study in a mixed sample of patients with MRI-defined vascular depression and those with vascular risk factors. Though active rTMS lead to significantly better response and remission scores on the HAMD-17 compared to placebo, older patients
responded at a much higher rate in the group that received a higher number of pulses (18000 over 2 weeks). By comparison, more recent rTMS studies have used closer to 60,000 pulses (O’Reardon et al. 2007).

Although the evidence to date is limited, rTMS holds promise as an important treatment modality in this difficult to treat population. As part of my fellowship at the Centre for Addiction and Mental Health I am investigating an optimized rTMS protocol that accounts for possible moderators of rTMS effectiveness in older adults (i.e. accurate localization of the DLPFC using MRI co-registration, stimulation intensity that is adjusted for age-related prefrontal atrophy and increased stimulation duration and number of pulses). Additionally, I hope to further investigate the preliminary findings of improved executive functioning with rTMS with detailed neuropsychological testing. Hopefully, with refinement in treatment protocols currently being investigated in rTMS studies we will be able to improve outcomes for our patients with late-life depression.

Daniel M. Blumberger, MD, FRCPC
Brain Stimulation and Geriatric Psychiatry Fellow
Centre for Addiction and Mental Health
1001 Queen St. W. Admin Building Room #3008
Toronto, ON M6J 1H4
References


