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Treatment of late-life depression: A role of non-invasive brain stimulation techniques

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Abstract

Late-life depression (LLD) is a frequent complication of the ageing process, occurring in up to 5% of community-dwelling elderly and in a higher proportion of subjects with coexistent medical illnesses. Its presence has been consistently associated with cognitive impairment, greater disability and increased mortality. Approximately half of patients with LLD have evidence of subcortical ischaemic damage in prefrontal circuits revealed by MRI. This might constitute the biological substrate of the cardinal symptoms of depression and of executive dysfunction. An important proportion of patients with LLD do not achieve remission of their depressive symptoms in spite of adequate pharmacological and psychotherapeutic treatment. In addition, a group of LLD patients progress to further impairment and disability in the form of a dementing disorder. There is an imperative need to develop new treatment strategies for LLD. Non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are safe and efficacious interventions that might be used in combination with other therapeutic options to improve treatment outcomes. However, there are still questions regarding the optimal way in which rTMS and dTCS should be delivered as well as to the way in which we may identify the subjects who will benefit the most from these interventions.

Introduction

Late-life depression (LLD) occurs in up to 5% of community-dwelling elderly and its frequency is even higher in medical settings (Mulsant & Ganguli, 1999). We can expect that an increase in life expectancy will result in the increase of the number of individuals who will suffer the consequences of progressive cerebrovascular disease, of cumulative neurodegenerative changes, and who will face the limitations imposed by chronic medical illness. LLD aggravates these comorbid medical conditions and increases disability (Charney et al., 2003; Lebowitz et al., 1997). In addition, LLD is associated with cognitive impairment, affecting information processing speed, executive function, and working memory (Butters et al., 2000, 2004; Nebes et al., 2001, 2002).

It has been estimated that about half of LLD patients have MRI evidence of subcortical ischaemic damage affecting deep white matter pathways, thalamus and basal ganglia (Krishnan et al., 2004). These neuroimaging findings, suggestive of vascular changes particularly affecting neural circuits that connect the prefrontal cortex with subcortical

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structures involved in mood regulation, have been the basis for proposing a distinct subtype of LLD: vascular depression (VaD) (Alexopoulos et al., 1997; Krishnan et al., 1997).

Subcortical hyperintensities found in VaD correlate with psychomotor slowing (Hickie et al., 1995; Simpson et al., 1997, 2000), poor outcomes of depression (Hickie et al., 1995; Simpson et al., 1997, 2000) functional impairment (Steffens et al., 2002) and cognitive deficits (Lesser et al., 1996; Salloway et al., 1996; Simpson et al., 1997). Furthermore, investigators at Duke University have shown that deep white matter hyperintensities (WMH) are independently associated with mortality in depressed older patients (Levy et al., 2003).

Overall, LLD constitutes an extremely important clinical problem for which we have to develop therapeutic alternatives that would allow us to treat these patients in a safe and efficient way.

Treatment of late-life depression

Pharmacological treatment—There have been several meta-analyses examining the efficacy of antidepressants to treat LLD. Taylor et al. examined 18 placebo-controlled trials that involved 2,252 subjects. Overall, 71.5% of these trials observed significantly greater efficacy with antidepressants than placebo. However, most published studies examined small sample sizes and were not controlled for the presence of coexistent medical conditions, including cerebrovascular disease (Taylor & Doraiswamy, 2004).

Roose and Schatzberg (2005) analysed the available evidence on the efficacy of antidepressants for treatment of LLD. The clinical trials examined in this analysis did not select for patients with VaD, although many subjects would likely meet criteria for this diagnosis. Despite some discordant findings – two out of five methodologically rigorous studies did not find that antidepressants were more effective than placebo in this population (Roose et al., 2004; Schatzberg & Roose, 2006) – the authors concluded that antidepressants are effective in the treatment of LLD. However, they also pointed out that as many as 50% of patients do not achieve symptomatic remission.

Psychotherapy—There is evidence that psychotherapeutic interventions are effective in treating late-life depression, even in the group of patients with significant medical conditions (Andreescu & Reynolds, 2011).

Earlier meta-analyses have indicated a beneficial effect of different types of psychotherapy to treat depression in the elderly. For instance, Cuijpers et al. (2006) analysed the results of 25 controlled trials and reported a relatively large antidepressant effect (standardized mean effect size $d = 0.72$). However, many of these early studies have various methodological limitations and their findings are not easily generalizable. Overall, the efficacy of psychotherapy to treat late-life depressive disorders might have been overestimated (Payman, 2011).

A recent study reported that interpersonal therapy (IPT) was not more efficacious than depression care management (DCM) as an adjunct to escitalopram in achieving remission of depression in older subjects (Reynolds et al., 2010). On the other hand, problem solving therapy (PST) was effective to decrease the severity of depressive symptoms as well as to reduce disability among cognitively impaired subjects (Alexopoulos et al., 2011). In this study, however, response and remission rates were relatively low (56.7% and 45.6% at 12 weeks of treatment).

Factors influencing treatment response in LLD—The presence of sub-cortical ischaemic changes and executive dysfunction characterize a significant number of patients

with LLD. This fact has been construed into the concept of vascular depression (Alexopoulos et al., 1997; Krishnan et al., 1997). Previous studies of VaD indicate that this form of depression may be more difficult to treat over time. For instance, Alexopoulos et al. have reported that, when compared with other older depressed patients, individuals with VaD have slower recovery, only partial response to treatment with antidepressants, executive deficits and a more chronic course (Alexopoulos et al., 1997; Hickie et al., 1995; Lesser et al., 1996). Furthermore, in a longitudinal MRI study, depressed elders who did not achieve or sustain remission had a significantly greater increase in WMH volume over time than the group that did achieve and sustain remission (Taylor et al., 2003). On the other hand, Salloway et al. (2002) reported that among 39 elderly depressed patients treated with sertraline and 111 depressed patients treated with citalopram, there was no relationship between treatment response and severity of WMH. In addition, a more recent study of very old depressed patients did not find a significant correlation between quantitative measures of white matter lesions and response to antidepressant treatment with citalopram (Sneed, Roose et al., 2007).

We can hypothesize, however, that the location of ischaemic damage plays a more important role than the total burden of lesions in the clinical response to different antidepressants. For example, among 13 older depressed patients receiving citalopram, having decreased fractional anisotropy of ventral frontal white matter tracts was associated with a lower rate of remission (Alexopoulos et al., 2002). Furthermore, it has been reported that structural changes of limbic networks revealed by diffusion tensor imaging (DTI) might be associated with poor treatment response (Alexopoulos et al., 2008; Shimony et al., 2009).

Recently, Sheline et al. studied predictors of antidepressant response among 217 subjects enrolled in a 12-week prospective trial examining the efficacy of sertraline to treat late-life depression. The investigators concluded that baseline neuropsychological function and white matter integrity predicted change of the severity of depressive symptoms over the 12-week trial course. These variables were strongly correlated with the number and severity of vascular risk factors (Sheline et al., 2010).

In summary, a significant proportion of patients with LLD will have a limited response to antidepressants and psychotherapeutic interventions. Although it is not absolutely certain that the presence of sub-cortical ischaemic damage is a significant contributor to treatment resistance, it is extremely important to develop therapeutic alternatives to increase response and remission rates among patients with different forms of LLD.

Brain stimulation—During the past few years there has been interest and experimentation with the potential antidepressant effect of brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). The fact that they are non-invasive procedures that can be administered in outpatient settings with few complications makes them a valuable alternative to treat frail elderly subjects with evidence of brain damage.

Repetitive transcranial magnetic stimulation—Firstly, we will examine the current evidence on the magnitude and clinical relevance of the antidepressant effect of rTMS. Secondly, we will examine the efficacy of rTMS to treat LLD and, particularly, VaD.

Loo and Mitchell (2005) recently reviewed seven meta-analyses of sham-controlled rTMS studies in major depression. The heterogeneity of the study groups, of the stimulation protocol, and of the methodology employed to administer rTMS, limits the significance of these studies. However, only one meta-analysis concluded that significant evidence for the efficacy of rTMS was lacking (Couturier, 2005). On the other hand, five studies found clear

evidence of efficacy. Although there is consensus that rTMS has statistically significant antidepressant effects, a more important question is whether these effects are clinically relevant. The meta-analyses above reported, on average, an effect size of Cohen's D of about 0.65, which is a moderate effect, in the same range as the effects of antidepressant medications.

We also need to emphasize that, during the past few years, rTMS trials have moved in the direction of administering longer duration protocols with higher intensities and greater total cumulative doses of magnetic pulses (Gershon et al., 2003; Grunhaus et al., 2003; Janicak et al., 2002). There has been consistent progress in the implementation of the technique and in the design of appropriate sham stimulation methods. In addition, small single site studies have given way to more powerful multicentre projects. For instance, the results of the first industrysponsored multicentre trial were recently available for analysis (O'Reardon et al., 2007). In a double blind, multisite study, 301 medication-free patients with major depression, who had not benefited from prior treatment, were randomized to active TMS (n = 155) or sham TMS (n = 146) conditions. The primary outcome was the symptom score change as assessed at week 4 with the Montgomery-Åsberg Depression Rating Scale (MADRS). Secondary outcomes included changes on the 17- and 24-item Hamilton Depression Rating Scale (HDRS), and response and remission rates with the MADRS and HDRS. Active TMS was significantly superior to sham TMS on the MADRS at week 4 (with a *post-hoc* correction for inequality in symptom severity between groups at baseline), as well as on the HDRS-17 and HDRS-24 scales at weeks 4 and 6. There were no significant differences in MADRS scores (the primary outcome measure) at 6 weeks. Response rates were significantly higher with active TMS on all three scales at weeks 4 and 6.

Remission rates were approximately two-fold higher with active TMS at week 6 on all scales. The effect size of the difference between HDRS-17 scores among the 301 subjects was 0.55 (i.e. in the moderate range). Furthermore, secondary analysis of the group of patients who were less treatment resistant (i.e. those patients who have failed only one adequate pharmacological trial) showed an effect size of 0.85, significantly greater than the one usually observed following treatment with usual antidepressants. Overall, patients with less resistant forms of depression and shorter duration of the current depressive episode had better treatment outcomes (Lisanby et al., 2009) In addition, rTMS was well tolerated, with a low drop-out rate for adverse events (4.5%) that were generally mild and limited to transient scalp discomfort or pain (O'Reardon et al., 2007).

Recently, George et al. (2010) reported the results of the first NIMH-funded prospective, randomized, sham-controlled, multicentre study on the antidepressant efficacy of rTMS. The trial had an adaptive design with 3 weeks of daily rTMS followed by up to 3 additional weeks of treatment among patients who showed a partial response. A total of 190 patients with major depression were included in the intention to treat sample. rTMS was delivered to the left prefrontal cortex at 10 Hz (120% motor threshold) using a figure-of-eight coil. Sham stimulation was carefully implemented with a similar shielded coil, and scalp electrodes that mimicked the somatic sensations associated with active stimulation. Thus, patients and staff were effectively blinded to the type of intervention they received. Intention-to-treat analysis revealed that patients receiving active rTMS were 4.2 times more likely to achieve remission than patients receiving sham. The number needed to treat was 12. Side effects were minimal and their frequency was not significantly different between the active and the sham groups. Furthermore, 86% of the patients receiving the active intervention completed the trial. Overall, these findings suggest that rTMS has a moderate but consistent antidepressant effect, particularly among subjects with less resistant forms of depressive disorder (George et al., 2010).

The age range for inclusion in these multicentre studies was 18 to 70 years. Age did not prove to be a significant predictor of treatment response in these two relatively large and well controlled studies. However, we need to keep in mind that the majority of participants were less than 55 years old. On the other hand, there is some evidence that older patients might be less responsive to rTMS (Figiel et al., 1998). As the intensity of the magnetic field delivered by a stimulating coil will exponentially decrease as a function of distance, the degree of prefrontal atrophy might affect response to rTMS among the elderly. However, proper adjustment of the intensity of the stimulation might overcome this deficit (Nahas et al., 2004).

Regarding rTMS efficacy among patients with LLD, two previous small controlled studies failed to show a significant effect of active rTMS (Manes et al., 2001; Mosimann et al., 2004). In the latter (Mosimann et al., 2004), high frequency left prefrontal rTMS was shown to have no specific effect on depression. In addition to the small sample size, this study had several methodological limitations such as the inclusion of several patients with bipolar disorder or early onset recurrent depressive disorder in the active but not the sham treatment group: an inadequate sham procedure, and a relatively low stimulation intensity (100% MT) for this age group. Furthermore, they used an empirical algorithm to localize the 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 17-item HDRS score in the responder group decreased from 24 ± 5.9 to 12.6 ± 5.5 while the six non-responders had pre-treatment 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 left dorsolateral prefrontal rTMS to treat depressive disorders associated with cerebrovascular disease (Jorge et al., 2008). Localization of the stimulation site in the prefrontal cortex was performed using quantitative MRI and image normalization to the Talairach coordinate system. The study consisted of two independent experiments.

In experiment 1, subjects were randomized into two groups for active or sham stimulation, receiving 10 rTMS sessions in the left DLPC at a frequency of 10 Hz and an intensity of 110% of the motor threshold during a 6-s period, with a total of 20 trains separated by 1-min pauses. Treatment was administered during a 10-day period for a TCD of 12,000 pulses (i.e. TCD-12K group).

In experiment 2, subjects were randomized into two groups for active or sham treatment, receiving 15 rTMS sessions in the left prefrontal cortex at a frequency of 10 Hz and an intensity of 110% of the motor threshold during a 6-s period, with a total of 20 trains separated by 1-min pauses. Treatment was administered during a 10-day period with two sessions per day for 5 days to achieve a TCD of 18,000 pulses (i.e. TCD-18K group). 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 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 ($p = 0.5$). 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 (Jorge et al., 2008).

Age had a significant impact on the antidepressant response to rTMS. We used two-way analysis of variance to examine the percentage of decrease of HAMD-17scores among patients who received active rTMS and who were categorized along the following two grouping variables: first, the experimental group (i.e. experiment 1 versus experiment 2) and, second, age (i.e. 65 years or less, or more than 65 years). Analysis of the individual variables showed statistically significant effects for age (F1=7.3; P = 0.01) and for the interaction of age/experimental group (F1 = 6.8; P = 0.01). Further analysis of the latter significant interaction showed that it was due to the fact that older patients showed a significantly greater decrease of HAMD-17 scores to TCD-18K than to TCD-12K magnetic pulses (42.1% versus 16%; F1,44 = 7.33; P = 0.01). These findings suggest that increasing rTMS dose had a significantly greater impact on the antidepressant response of patients 65 years or older compared with those younger than 65 years. For active rTMS in the TCD-18K group, the response and remission rates for patients 65 years or older were 40% and 20%, respectively, compared with those observed for patients younger than 65 years, which were 38.9% and 33.3%, respectively.

We did not observe a significant correlation between distance from the stimulation site to the underlying cortex and the percentage of change in HAMD-17 scores. However, after including left and right frontal grey matter volumes, left and right frontal white matter volumes, volume of frontal deep WMH, and experimental group as predictors of response to active rTMS, a stepwise logistic regression model showed that greater left frontal grey matter volume (Wald $\chi^2 = 6.2$; P = 0.01) and right frontal grey matter volume (Wald $\chi^2 = 7.2$; P = 0.007) were associated with response to rTMS. This suggests that the structural indemnity of the prefrontal cortex (independently of the distance from the stimulation site) might be a predictor of a positive outcome.

It is also plausible that the severity of cerebrovascular disease and the presence of subcortical ischaemic damage may play a role in the type and extent of response to rTMS. Although we do not have measures of regional cerebral blood flow or cerebrovascular reactivity among our patients with VaD, we have quantified the volume of WMH and used this variable as a measure of subcortical ischaemic damage. The volume of the WMH, however, was not associated with the antidepressant response to rTMS. This phenomenon has been observed in other treatment studies as well. For instance, there was no significant correlation between quantitative measures of white matter lesions and response to antidepressant treatment with citalopram among very old depressed patients (Salloway et al., 2002).

We can hypothesize that, rather than the total burden of lesions, the location of ischaemic damage plays a significant role in the clinical response to different antidepressants. For instance, lesions of the white matter pathways connecting the left DLPC (i.e. the stimulation site) and the left anterior cingulate cortex might be selectively associated with poor response to rTMS.

We also examined whether the degree of memory or executive impairment assessed by subjects' performance in standard neuropsychological tests would identify a group of patients that were refractory to rTMS treatment. This was not substantiated by our data.

Safety—rTMS should not be indicated for treatment of depression in patients with a history of seizures or for those patients who have a cardiac pacemaker or intra-cardiac lines. In addition, there is practically no data on its safety among patients with dementia.

Furthermore, patients with evidence of ischaemic damage in the frontal cortex should not receive rTMS, in order to avoid chronic stimulation of a potential epileptogenic site. On the other hand, the presence of sub-cortical ischaemic lesions does not represent a contraindication for rTMS. In our studies there were no significant differences between the active and sham stimulation groups in the frequency of headaches or local discomfort at the stimulation site. In addition, headaches were mild and responded in all cases to low doses of common analgesics. Thus, there is consistent evidence that rTMS is a relatively safe procedure among the elderly.

Future studies—Non-invasive brain stimulation techniques, particularly rTMS, represent a fertile area of future research. There is a need to optimize rTMS protocols with respect to the frequency and intensity of the magnetic stimulation as well as the schedule in which it is delivered (e.g. clustering sessions to avoid daily visits to the hospital). Newer coil designs would allow producing focal stimulation of subcortical cerebral structures that might be associated with greater antidepressant efficacy. It is also plausible that stimulation of other cortical sites than the left prefrontal cortex would produce similar or greater effects on the neural systems regulating mood.

Combining rTMS with pharmacological interventions has the potential for a synergistic effect on the neuroplastic changes associated with the antidepressant response. In addition, rTMS might be combined with structured psychotherapy treatments to increase their therapeutic efficacy.

Finally, it is important to identify the group of depressed patients who will benefit the most from non-invasive brain stimulation. This includes analysis of demographic factors, psychopathological presentation (e.g. the severity of apathetic features) and neuropsychological profile. Neuroimaging biomarkers would also be a reasonable avenue of research as the structural and functional correlates of LLD and its subtypes are further delineated.

Transcranial direct current stimulation—Recently, tDCS has emerged as a potential non-invasive brain stimulation technique with potential antidepressant effects (Nitsche et al., 2008). Broadly, tDCS consists of delivering weak direct currents through the scalp that produce changes in the excitability of the underlying cerebral cortex. These changes depend on the polarity and intensity of the electrical stimulation.

tDCS is less focal than rTMS but it might produce similar neuroplastic effects. For instance, it has been shown that anodal stimulation of the motor cortex facilitates motor learning (Reis et al., 2009). This effect might be mediated by the activation of BDNF-TrKB pathways (Fritsch et al., 2010). It has also been reported that tDCS over the motor cortex modulates vasomotor reactivity assessed using transcranial Doppler (Vernieri et al., 2010). Furthermore, tDCS produces regional cerebral blood flow changes in areas of the brain that are distant but functionally related to the stimulated cortex (Zheng et al., 2011).

There is also some evidence that tDCS delivered to the dorsolateral prefrontal cortex might improve certain cognitive functions such as declarative (Javadi & Walsh, 2011) and working memory (Fregni et al., 2005; Mulquiney et al., 2011). In addition, a recent small study suggests that anodal stimulation of the left dorsolateral prefrontal cortex enhanced certain aspects of working memory in stroke patients (Jo et al., 2009). Interestingly, we have previously found comparable effects on patients' performance in executive tests in our early rTMS studies (Moser et al., 2002).

Clinical trials on the efficacy of tDCS as treatment of depression are scarce and involve small samples. Pascual-Leone and Fregni have pioneered the use of prefrontal tDCS to treat depressive disorders (Fregni et al., 2006; Nitsche et al., 2009) Fregni et al. (2006) conducted a proof of concept study among 10 major depressed patients who were randomized to receive five sessions of tDCS (1 mA for 20 min once daily) or sham stimulation. They observed a significant reduction of depressive symptoms (60 to 70%) in the group of patients receiving active stimulation compared with the group allocated to sham stimulation (Fregni et al., 2006). In a second pilot study, 40 patients with major depression who were not taking antidepressant medication were randomized to receive prefrontal (n = 21), occipital (n = 9) or sham stimulation (n = 10). The primary outcome measure was the severity of depressive symptoms assessed by the Hamilton Depression Rating Scale at baseline, immediately after, 15 days, and 30 days after stimulation. The authors concluded that prefrontal tDCS was associated with a significant reduction of depressive symptoms compared with sham or occipital tDCS. In addition, this significant difference was maintained at the 30 days follow-up assessment. In this study they duplicated the number of sessions (from 5 to 10) as well as the intensity of stimulation (from 1 to 2 mA) (Boggio et al., 2008). Recently, a case report suggested that tDCS might be also effective among patients with cerebrovascular disease (Bueno et al., 2011). The results of small trials are promising but they await appropriate replication. On the other hand, in a recent pilot trial, Loo et al. (2010) did not find a consistent antidepressant effect of tDCS.

Conclusions

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 ischaemic 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.

tDCS is another non-invasive brain stimulation technique that can be safely administered in elderly depressed patients including those with cerebrovascular disease and/or neurodegenerative changes. However, the evidence of its antidepressant efficacy is still scarce.

Brain stimulation protocols need to be further developed in order to optimize the efficacy of this intervention. There is also a need to increase our knowledge of the neurobiological substrate of the cognitive and behavioural changes produced by rTMS and tDCS. In addition, future clinical studies should rely on a multicentre approach in order to enrol a larger sample of LLD patients that will allow more meaningful statistical inferences to be made.

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