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Neuromodulation in Geriatric Depression: The Role of TMS and tDCS

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Abstract

Neurocognitive disorders and dementia are expected to increase along with the increasing numbers of the aging population. It is known that depression occurring in old age, also known as Geriatric Depression (GD), is linked with cognitive disorders in the elderly and that old individuals with anxiety and depression often receive multiple therapies. Consequently, they are at increased risk of falls, cognitive impairment, and delirium. Neuromodulation therapies seem to prevent these risks. Few studies have focused on neuromodulation therapies such as Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) in GD and on the neurophysiological mechanisms underlying both cognitive and mood aspects of this disease. This work investigates the role of TMS and tDCS, also in combination with or in comparison with other therapeutic strategies, in improving cognitive and mood aspects of affective disorders in the elderly. It was found that TMS and tDCs could be promising therapeutic strategies for depression in old age, even though further research is required to better understand the neurobiological basis of GD and, consequently, the rationale of TMS and tDCS employment in this disease.

Keywords: Elderly; Mood; Cognition; Polypharmacy; Brain stimulation.

Introduction

Major Depressive Disorder (MDD) is a relevant problem in the elderly, with a prevalence of 31.74% [1]. Some risk factors for GD are female gender, stressful events (such as bereavement and retirement), and medical illnesses [2,3]. Moreover, depression in the elderly is characterized by different aspects compared to other age groups, with symptoms such as widespread aches and somatizations, decreased appetite, asthenia, and irritability that often prevail during the affective episode [4,5]. In addition, cognitive symptoms [6] and particularly difficulties in various executive functions, such as planning, abstraction and organization [7-11] are also present.

The treatment of choice for geriatric unipolar depression is antidepressants with a therapeutic response like adult depression and remission rates that stabilize at 60-70% after more than three antidepressant treatments; therefore, approximately 30% of patients are resistant to pharmacological interventions [12].

Neuromodulation is a therapeutic strategy that aims at modulating relevant brain networks and offers the opportunity to directly interact with brain functioning in a non-invasive, safe, and painless way with good time resolution and relatively high spatial precision. TMS is a brain stimulation technique that employs a brief, intense pulse of electric current delivered to a coil placed on the subject's head. This coil creates a magnetic field through electromagnetic induction that, in turn, can induce an electrical field sufficient to depolarize superficial axons and activate neural networks in the cortex [13,14]. A particular form of TMS, that employs repeated application of such bursts in modified "Theta Burst" paradigms (TBS), may produce robust, self-limited physiological effects on human cortex and has been implicated in Long-Term Depression (LTD) and Long-Term Potentiation (LTP) processes in human cortex [15]. Similarly, repetitive Transcranial Magnetic Stimulation (rTMS) refers to the application of recurring TMS pulses to a specific brain region [16]. A typical treatment generally consists of 5 days per week between 4 and 6 weeks, with scalp discomfort and a transient headache being the main-reported side effects [17]. Finally,

Deep Transcranial Magnetic Stimulation (DTMS) is a specific form of TMS aimed at stimulating deeper neuronal regions, such as reward-related pathways. Consequently, since the electric field progressively decreases based on tissue depth, the H-Coil has been developed to directly stimulate these regions and overcome these limits [18].

tDCS is a non-invasive, safe, and tolerable brain stimulation technique without serious adverse events. It is based on the injection of an electric current of low intensity (<2 mA) that is delivered to the brain through electrodes placed over the scalp. After having passed through the skin, subcutaneous tissue, and cerebrospinal fluid and reached the gray matter, this current can induce excitatory or inhibitory effects on neural excitability [19], as well as on the modulation of cerebral flood flow, metabolism, and brain-derived neurotrophic factors [17].

When analyzing neuromodulation's employment in GD and in other mood disorders, we should first consider that it is a generally safe therapy [20-22]. In fact, it is known that older people, often receiving polypharmacy, are at increased risk of falls, cognitive impairment, and delirium, which seem to be prevented by TMS [23].

In the present work, we analyzed existing literature on TMS and tDCS employment in geriatric depression. We confined our investigation to studies involving these two brain stimulation techniques, excluding those addressing other therapeutic approaches beyond TMS and tDCS or addressing other conditions than GD. In addition, only articles written in English were included. We conducted our research from May to June 2023, revealing encouraging results regarding the security, acceptability, and efficacy of TMS and tDCS in GD.

TMS and tDCS in geriatric depression

TMS in geriatric depression

Three studies examined the utility of TMS to uncover new insights into the mechanisms underlying GD [24-26].

Lissemore et al. [24] studied 92 individuals (M=30, F=62, mean age=66,8±6,1 years) with Late-Life Depression (LLD), 41 healthy old people (M=18, F=23, mean age=69,0±8,3 years), 30 younger adults with depression (M=10, F=20, mean age=44,8±10,5 years), and 30 younger healthy adults (M=18, F=12, mean age=44,9±10,8 years) through single and paired pulse TMS to evaluate cortical inhibition and excitation. Old, depressed individuals who met criteria for MDD, single or recurrent and with early- or late-onset, as diagnosed by the structured clinical interview for the DSM-IV (SCID-IV) [27], were examined through the Montgomery-Asberg Depression Rating Scale (MADRS) for depression, and the Mini Mental State Examination (MMSE) for cognitive functions [28,29]. It was found that older individuals with and without depression and younger depressed adults had lower GABA cortical inhibition than younger Healthy Controls (HC). This confirms the idea that depression is a disease of accelerated aging and suggests that future research should look at diminished GABAergic neurotransmission in late life as a biological factor predisposing to depression.

The same authors analyzed the relationship between cortical plasticity and cognitive inhibition in Late-Life Depression (LLD) by measuring cortical inhibition/excitation in 51 individuals (M=21, F=30, mean age=66,6±5,9 years), and the potentiation of cortical activity following paired associative stimulation, linked with Long-Term Potentiation (LTP)-like cortical plasticity in 32 subjects (M=15, F=17, mean age=67,2±5,2 years). The correlation between these measures of cortical physiology and two indices of executive functioning such as the cognitive inhibition, assessed using the Delis-Kaplan Executive Function System Color-Word Interference ["Stroop"] test, and the cognitive flexibility, assessed using the Trail Making TesT [30], was evaluated. In addition, depressive symptoms were evaluated through cumulative illness rating scale for geriatrics [31] and anxiety via the brief symptom inventory, (anxiety subscale) [32]. It was found that elevated cortical plasticity is associated with diminished cognitive inhibition, which suggests the importance of strengthening synaptic connections to improve cognitive function. Meanwhile, the authors speculated that inappropriate responses in LLD could be induced by hyper-excitability of cortical circuits following repeated cortical activation, identifying LTP-like cortical plasticity as a neural mechanism that underlies an inhibitory control cognitive endophenotype of LLD [25]. Similarly, a work carried out in 48 depressed older adults and 34 age-matched controls examined motor cortical neuroplasticity using Paired Associative Stimulation (PAF) and TMS to induce motor-evoked potentials in the contralateral hand muscle before and after PAS. Depression was assessed through the SCID-IV and the MADRS, while the MMSE was used to analyze cognitive functions. Results showed that 68% of older adults with depression and 47.1% of HC had Long Term Potentiation PAS (PAS-LTP) successfully induced. Anyway, it was suggested that associative plasticity did not differ substantially between older adults with depression and age-matched HC [26].

To investigate TMS employment in GD in terms of tolerability, efficacy, and cognitive improvements, a work examined 25 participants (M=17, F=8, mean age=65±5,5 years) receiving active rTMS and 27 subjects (M=15, F=12, mean age=65, 4±5,5 years) who were administered sham rTMS. They were diagnosed with MDD via the SCID and assessed through the Hamilton Depression Rating Scale (HDRS-24) [33], the Antidepressant Treatment History Form (ATHF) [34], and the MMSE. It was found that the remission rate was significantly higher when employing an active rTMS rather than a sham one, while executive functions were not substantially changed, and no serious adverse events were reported. Only pain was an adverse effect highlighted more commonly in the active condition. The conclusion was that high-dose deep rTMS is a safe, well-tolerated, and efficacious option for the treatment of GD [35].

Levkovitz et al. [18] comparable conclusions were reached by [18], who examined 65 medically free depressed patients receiving DTMS over the left prefrontal cortex. Randomly, they were assigned to various treatment plans, each with its own level of stimulation and lateral distribution. Effects of DTMS on mood and anxiety were evaluated through the HDRS-24 and several secondary outcome measures, such as the Beck Depression Inventory-II (BDI-II) and the Hamilton Anxiety Rating scale (HAM-A), while the Cambridge Neuropsychologic Test Automated Battery (CANTAB) was used to assess cognitive functions. The results showed that HDRS, as well as several cognitive features, significantly improved when intense stimulation was applied compared to minimal stimulation, thereby bolstering the significance of sustained, intense stimulation in neuropsychiatric disorders.

Moreover, Sabesan and colleagues performed a systematic review, including seven randomized controlled trials and seven uncontrolled trials. A large heterogeneity among studies, both in terms of the employed TMS dosage and the observed clini-

cal efficacy, was noted, thus highlighting the need for optimizing TMS dosage due to the unique clinical features of GD. After having defined TMS as a safe and effective therapy for GD, the authors identified some factors, other than age that could moderate TMS efficacy: brain atrophy, intensity, and number of pulses (dose-response relationship), and clinical profile of patients [36]. Besides, regarding the comorbidity between depressive symptoms and cognitive disorders, a recent case series investigated six drug-resistant subjects (M=5, F=1, age range=60-82 years), evaluated through DSM-5 criteria, MMSE and the Clical dementia rating scale, who underwent motor evoked potentials at baseline and after 3 weeks of 10 Hz rTMS on the left dorsolateral prefrontal cortex. They were assessed for serum nerve growth factor, vascular endothelial growth factor, brain-derived growth factor, insulin-like growth factor-1, and angiogenin as well as for psychocognitive functions at baseline and after 1,3, and 6 months. The authors concluded that, even though a mild improvement in mood was noted after rTMS at baseline, this could not be clearly attributed to high frequency rTMS [37].

Conelea et al. [38] when comparing TMS efficacy in elderly and in young individuals, a work by [38], analyzed 231 patients (156 of them <60 years and 75 with more than 60 years) with treatment-resistant depression. They were assessed through the DSM-V and underwent an acute course of outpatient TMS therapy at two outpatient clinics. No significant difference was noted between groups, and the change in depression severity was not considerably predicted by age.

Interestingly, it was reported that the TMS could be used as an indicator of the outcome of treatment in LLD. Lissemore and colleagues enrolled 76 outpatients (M=27, F=49, mean age=67±7 years) with LLD receiving venlafaxine who had been treated with single-pulse and paired-pulse TMS and analyzed the predictive performance of machine learning models that included or excluded TMS predictors. The response to venlafaxine was assessed through the MADRS. Venlafaxine response was successfully predicted by two single-pulse TMS, in terms of cortical excitability and its variability [39].

tDCs in geriatric depression

As for TMS, tDCS has been proposed for the treatment of cognitive and emotional aspects in the elderly. tDCS use in cognitive disorders is justified by its favorable action in stimulating motor network activity [40-42]. In older adults with and without cognitive impairment, factors that may predict better responses to tDCS are preserved brain structure, better baseline functional connectivity, genetic polymorphisms, and the use of concomitant medications [43]. Regarding the tDCS application for GD, different works focalized on its efficacy on cognitive problems. Szymkowocz et al. [44] found that tDCS together with Cognitive Training (CT) significantly improved depressive symptoms, as assessed through the BDI-II, in these individuals. More specifically, they suggested that the combination of bifrontal active tDCS with CT could be a valid tool to improve subthreshold depressive symptoms in older adults by targeting prefrontal neural circuitry and may promote neuroplasticity of the underlying neural network, with the final goal of preventing or reducing bad outcomes of older depression, such as cognitive dysfunction and lower brain volumes. In line with these findings, a work carried out in 20 older adults examined the effects of tDCS administered over the left dorsolateral prefrontal cortex on executive functions of geriatric inpatients with depression, assessed through the Geriatric Depression Scale (GDS), or anxiety, assessed through the Geriatric Anxiety Inventory (GAI). Participants were divided in two groups: the one receiving anodal (n=10, M=6, F=4, mean age=77,10±6,98), while the second (n=10, M=4, F=6,mean age=72,50±7,46) sham tDCs over the left dorsolateral prefrontal cortex. It was reported that tDCS increases inhibitory processing and cognitive flexibility in the anodal tDCS group, whereas no relevant changes in attention or working memory measurements were observed [45]. A similar work analyzed 33 participants with previous single or recurrent episodes of MDD, evaluated through the SCID-IV and MADRS. Between them, 18 (mean age=66,3±5,8 years, M=5, F=13) received active tDCS, while the remaining 15 were administered with sham (mean age=66,8±5,8 years, M=6, F=9) tDCS and all participants had their working memory and global cognition assessed, respectively, by a computerized N black task and a standard paper and pencil neuropsychological test battery. tDCS, despite being well tolerated in older individuals with remitted MMD, did not improve working memory or global cognition [46].

An interesting case study was carried out in a 92-year-old patient with major depression. The HDRS was used to assess depressive symptoms, the Beck Anxiety Inventory to investigate anxiety, and the Montreal Cognitive Assessment Scale for cognitive function. After 10 sessions of TMS, a reduction in HDRS score was noted, while no significant difference emerged for anxiety or cognitive functions [47].

Discussion

Our work showed that, firstly, TMS may help to clarify neurophysiological and biochemical mechanisms underlying GD, such as the hyper-excitability of cortical circuits following repeated cortical activation that may promote inappropriate responses in LLD [25] and a reduced GABAergic neurotransmission in the elderly [24]. In line with these findings, there is supportive evidence for the effectiveness of rTMS and of DTMS on the prefrontal cortex in treatment-resistant depression [48,49]. Furthermore, it is known that the antidepressant mechanism of action of TMS may require connectivity from the cortex proximal to the stimulation site to the striatum [50]. Two studies reported that TMS could be a well tolerate, effective, and promising therapy for late-life depression [35,18]. These data are analogous to previous findings by Cappon et al. [51], who considered TMS a valid option for GD, even though they highlighted the need for optimizing TMS dosage by recognizing the unique clinical feature of GD. Similarly, Blumberger et al. [17] pointed out that old, depressed individuals may be able to benefit from rTMS particularly if administered following daily schedules compared to the 5-day-a-week treatment schedule.

In addition, it has been reported that rTMS, administered to the DLPFC, is useful in improving memory function and executive performance [52]. Moreover, other beneficial effects of rTMS on cognitive performance or linguistic skills were reported in patients with frontotemporal dementia and primary progressive aphasia [53] as well as in Mild Cognitive Impairment (MCI), where it could modulate symptoms in MCI patients and prevent the progression to dementia [54]. Intriguingly, a study pointed out TMS utility in predicting clinical response to pharmacological treatments and, consequently, its potential role in clinical decisions [39].

We also provided evidence of a mild [37] or absent [38] effect of TMS in GD, while a work enhanced both positive and negative aspects of TMS in GD [36].

Besides, literature reports that rTMS has a beneficial effect

on GD, especially when administered with repeated pulses for different days, although evidence of its efficacy is not always so strong [36,55].

Interestingly, there is also growing interest in TBS application in GD, as revealed by a study protocol for a randomized, double-blind controlled trial that aimed at investigating the role of this treatment in major depressive disorders in the elderly via the employment of biomarkers such as the Brain-Derived Neurotrophic Factor (BDNF) [56].

About tDCS, we reported potentials good effects in reducing negative outcomes associated with older depression, such as cognitive dysfunction [45] and mood problems [47] whereas one work did not find significant improvements from tDCS in working and cognitive function [46]. In older people with functional limitations, tDCS has been proved to improve executive functions and dual tasking [57]. As for TMS, the growing interest in tDCS application in geriatric depression has recently emerged: Ingawa et al. [58], in fact, prepared a study protocol for the investigation of cognition, assessed through the Alzheimer Disease assessment Scale, depressive symptoms, measured by the GDS and quality of life, evaluated by the Medical Outcomes Study 36-item Short-Form Health Survey, in patients with neurocognitive disorders.

Renewed interest has recently emerged in discussing potential neuroimaging or electrophysiological biomarkers related to TMS response that could eventually lead to a personalization of the treatment with TMS or TBS [60]. TMS and tDCS have been proven to be useful alternatives to other brain stimulation techniques employed in GD, such as Electroconvulsive Therapy (ECT), which is sometimes associated with cognitive effects and does not always have a good public perception [17].

Overall, our data support other findings stating that TMS and tDCS may be advantageous in improving working memory, attention, and vigilance of older individuals [60] as well as in potentially improving cognition and depression in cognitive disorder [61].

Conclusion

Globally, despite the limited literature available, some interesting findings on the safety of TMS and tDCS in geriatric depression, as well as on their tolerability and efficacy, were highlighted. Nevertheless, evidence for a clear effect of TMS and tDCS in GD remains incomplete and heterogeneous. The dysregulation of GABA-ergic pathways together with an alteration in LTD mechanisms have been hypothesized at the basis of GD [24,25]. Intriguingly, these pathways could be targeted by TMS [26]. We may think that neuromodulation could be a valid tool that clinicians could use if there are too many side effects from common drugs. In addition, another good aspect of TMS and tDCS is that they do not require anesthesia, as in the case of ECT [20] and have lower costs if compared with pharmacological therapies and ECT [62]. Finally, encouraging findings were reported from the combination of TDCs with cognitive behavioral therapy, especially on subthreshold symptoms of GD. This could be a starting point for other combination strategies, such as pharmacotherapy together with TDCs; in this way, it may eventually be possible to reduce drug doses and, as a result, their side effects [44].

Further studies are needed to better clarify these promising effects of TMS and tDCS in modulating cognitive and affective disorders in older individuals and, consequently, shed new light on their potential employment as future therapeutic strategies for GD.

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