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Case Report

High-Frequency and Low-Intensity Patterned Transcranial Magnetic Stimulation over Left Dorsolateral Prefrontal Cortex as Treatment for Major Depressive Disorder: A Report of 3 Cases

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Current transcranial magnetic stimulation devices apply intense (near 1 tesla) repetitive magnetic pulses over a specific area of the skull at relatively lower frequencies (1-50 Hz). Nevertheless, different studies have shown that very small magnetic fields, at higher frequencies (50-1000 Hz.), produce therapeutic effects in major depressive disorder. We report the application of high-frequency and low-intensity patterned magnetic pulses over the left prefrontal dorsolateral cortex in three subjects diagnosed with clinical major depressive disorder. All three patients showed sharp changes in their self-reports as well as in the standardized clinical assessment. Hypothesized mechanisms of action of this new variant of magnetic stimulation are discussed.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has shown to be effective for the treatment of major depressive disorder (MDD), especially in subjects in which pharmacological treatment has failed to improve depressive symptoms [1]. Current rTMS devices apply intense (near 1 tesla) repetitive magnetic pulses over a specific area of the skull at relatively lower frequencies (1-50 Hz). These rapidly changing and intense magnetic pulses produce their biological activity by inducing an electric current inside the brain [2]. Nevertheless, the threshold for pulsed magnetic field effects on biological systems has been estimated to be at much lower intensities (1×10^{-7} teslas) [3] and different studies have shown that very small magnetic fields, at higher frequencies (50-1000 Hz), do produce measurable changes in brain's activity [4] and even therapeutic effects in some nervous system pathologies [5, 6]. Rohan et al. published a study where they applied low-intensity magnetic fields (around 2 militeslas) at 1000 Hz producing an antidepressant effect in patients with bipolar depression [5]. However, this same protocol was used in patients with MDD having mixed results [7, 8]. Another protocol using similar parameters, applied with 7 coils to the whole brain was also used for the treatment of MDD with good results [9].

In this paper, we report the application of high-frequency and low-intensity patterned magnetic pulses with a circular coil of 60 mm of diameter over the F3 coordinate of the 10-20 EEG system (left prefrontal dorsolateral cortex) in three subjects diagnosed with clinical MDD. The coil used in this protocol was selected over a figure 8 coil as the intensities used in the present study are not able to produce a motor threshold; without a motor threshold and in order to assure

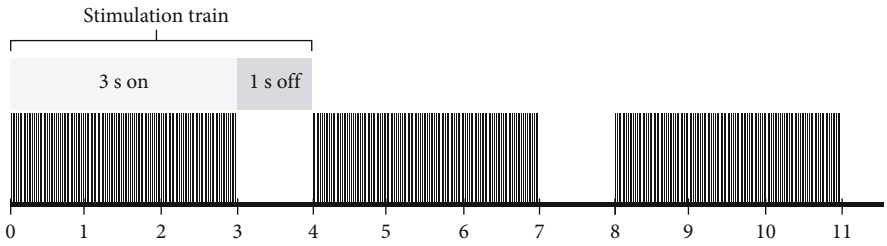

Figure 1: Stimulation pattern. The stimulation was divided in trains; each train consisted of a 3-second period of burst stimulation at 550-600 Hz and a 1-second period without stimulation. A total of 675 trains were applied during each session over the left prefrontal dorsolateral cortex.

that the prefrontal cortex was indeed stimulated, a circular coil with a larger area of stimulation was used.

The device used to apply the magnetic stimulation was designed and manufactured exclusively for this study by Actipulse Neuroscience (Boston, USA). The pulses were applied in trains: each train consisted of 3-second bursts of high-frequency pulses (550-600 Hz) alternated with 1 second without stimulation (see Figure 1 for more details about the stimulation pattern); a total of 675 trains (45 minutes of stimulation) were applied in each session. Each pulse had an approximate magnetic field intensity of 0.5 milliteslas. Sessions were applied to each patient once daily for 5 days each week, making a total of 15 sessions distributed in 3 weeks.

2. Case 1

2.1. Patient Information. Case 1 was a male, 69 years old, with Latin American ethnicity and with a family history of diabetes mellitus and colon cancer. The patient has a history of aortic valve calcification due to which he had to have an aortic valve surgery 5 years prior to this evaluation. During the aortic valve surgery, the patient suffered a cardiorespiratory arrest and, as consequence, he developed chronic posthypoxic myoclonus affecting his head, trunk, and superior limbs. After discharge, depressive symptoms started and were mainly associated with a feeling of worthlessness due to motor function impairment. Four years ago, the patient attended a psychiatric evaluation for the first time, referring depressed mood nearly every day, anhedonia, alexithymia, social isolation, insomnia, and anxiety symptoms, for which he was prescribed sertraline and clonazepam at unknown doses showing mild response.

2.2. Clinical Findings. The patient was conscious and oriented. He presented postural and action tremor in the upper limbs with an accentuation on the left side of the body, while on the lower limbs, he presented bradykinesia. The patient also presented gait changes including reduced stride length and speed, reduced arm movement, and deviation to the right side. At the time of assessment and treatment, the patient was taking sertraline, primidone, acenocumarol, clonazepam, metoprolol, paracetamol, losartan, and atorvastatin.

2.3. Diagnostic Assessment. The patient was assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), 12 item General Health Questionnaire (GHQ-12), Mini-Mental State Examination (MMSE), and the Athens Insomnia Scale (AIS). Moderate depression was found through the MADRS and the BDI with a score of 24 and 26 points, respectively, while on the BAI, severe anxiety was found (score of 32 points), as well as the presence of insomnia (score of 9). Cognition was preserved, demonstrated through the application of the MMSE (score of 28 points).

2.4. Follow-Up and Outcomes. All tests were reassessed after 15 sessions of HFLI TMS, and an improvement in all measures was observed. On the other hand, both the MADRS (score of 10 points) and the BDI (score of 13 points) reduced their scores, indicating a change from moderate to mild depression, as well as the BAI, which indicated the presence of moderate anxiety (score of 23 points). Meanwhile, insomnia (AIS = 6) and cognition scores (MMSE = 30) were also improved, returning to normal values. In the self-report, the patient reported a clear improvement in mood, anxiety, and sleep disturbances.

3. Case 2

3.1. Patient Information. Case 2 was a female, 27 years old, with Latin American ethnicity and with a family history of cardiac disease, asthma, diabetes mellitus, and pulmonary emphysema. She was diagnosed with attention deficit and hyperactivity disorder 10 years prior to the evaluation; 9 years prior, a hygroma was found incidentally in an MRI scan performed for other reasons. She has a positive history of tobacco and drug use including cannabis, cocaine, LSD, methamphetamine, ecstasy, and hallucinogens. The onset of psychiatric symptoms was at age 12 with anhedonia, social isolation, apathy, emotional liability, and sleeping problems; at the age of 18, she had a suicide attempt and was institutionalized for a month. Trials with different medications (fluoxetine, sertraline, carbamazepine, valproate, and clonazepam) had a poor effect in remission of depressive symptoms and complete remission was never achieved.

3.2. Clinical Findings. The patient was conscious and oriented. She presents with anxiety-related tachycardia, as well as excessive sweat and paresthesia. At the time of assessment and treatment, the patient was taking a stable dose of venlafaxine for over 3 months.

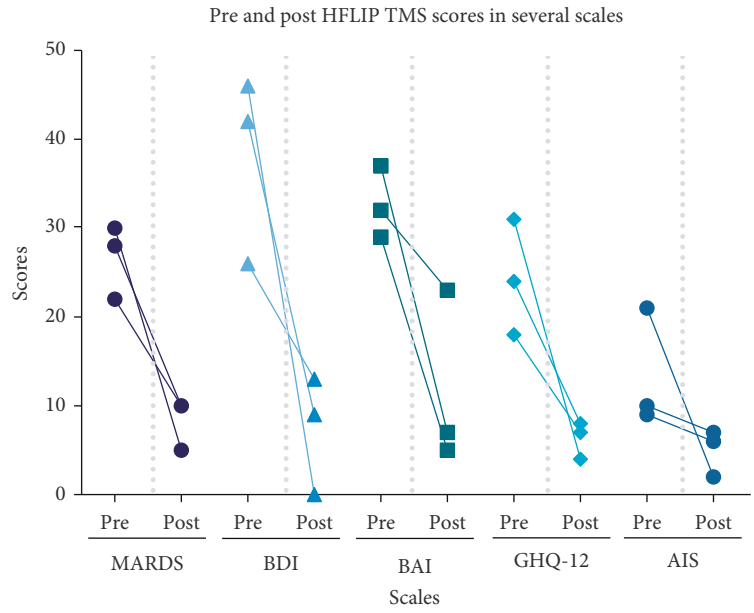

Figure 2: Pre- and post-HFLIP TMS scores in several scales. Several clinimetric scores were performed before and after HFLIP TMS: Montgomery–Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), 12 item General Health Questionnaire (GHQ-12), Mini-Mental State Examination (MMSE), and the Athens Insomnia Scale (AIS). All three subjects showed improvement in all measured scales.

3.3. Diagnostic Assessment. The patient was assessed with the same scales and inventories as the first case. On depression tests, the patient presented moderate depression through the MADRS (score of 30 points), while on the BDI, she presented severe depression (score of 46 points). On the other hand, severe anxiety was found (BAI score of 37 points), as well as the presence of insomnia (score of 21 points in AIS). Cognition was fully preserved, demonstrated through a flawless MMSE score (30 points).

3.4. Follow-Up and Outcomes. Tests were reassessed after 15 sessions of HFLI TMS, and an improvement in all measures was observed, reaching minimum levels. Both the MADRS (score of 5 points) and the BDI (score of 0 points) reduced their scores, indicating the absence or minimum presence of depressive symptoms. While the BAI indicated a minimum presence of anxiety (score of 7 points) and the AIS (score of 6 points) showed an absence of insomnia symptoms. Finally, the cognitive score was decreased by two points (MMSE = 28 points); however, it remained within normal values. The self-report of the patient corroborated the reported clinimetric changes; the patient reported minimum depressive, anxiety, and insomnia symptoms.

4. Case 3

4.1. Patient Information. Case was a 38-year-old Latin American female with a family history of cardiac disease, arterial hypertension, pulmonary, and testicular cancer. The patient was diagnosed 2 years prior to evaluation with borderline personality disorder and had positive tobacco and alcohol use, reaching inebriation at least once every 15 days. The patient presented depressive symptoms with labile mood for the first time at 18 years of age. At 21 years old, she was diagnosed with postpartum depression after symptoms of isolation, anhedonia, and emotional lability augmented. She had two suicide attempts at age 24 and 28, both of which were followed by the hospitalization of the patient. Since age 24, she had received several antidepressants intermittently (mainly fluoxetine and sertraline), with poor improvement of symptoms. Two months ago, depressive symptoms increased, and she started fluoxetine 40 mg daily by herself. Poor symptomatic response was achieved, and she continued with anhedonia, hopelessness, sleeping problems, irritability, and anxiety.

4.2. Clinical Findings. The patient was conscious and oriented. She complained of occasional tachycardia and lower limb paresthesia while being stressed, as well as acid reflux with every meal, leading to a diminishment in daily food intake; additionally, the patient appears to be sleepy and tired. At the time of assessment and treatment, the patient had suspended medication without physician supervision.

4.3. Diagnostic Assessment. The patient was assessed with the same scales and inventories as in previous cases. The MADRS showed moderate depression (score of 28 points), and the BDI indicated the presence of severe depression (score of 42 points). Meanwhile, the BAI indicated the presence of severe anxiety (score of 37 points), as well as the presence of insomnia (score of 10 in AIS). Finally, the MMSE indicated no impairment; however, the score is on a limit cut-off value (score of 24 points).

4.4. Follow-Up and Outcomes. Reassessment was performed after 15 sessions of HFLI TMS, showing an improvement in

all measures. The BDI (score of 9 points) demonstrated a reduction of depressive symptoms, reaching minimum levels of depression, while the MADRS (score of 10 points) score reduction reached mild depression levels. The BAI also indicated a minimum presence of anxiety (score of 5 points), and the AIS (score of 7 points) showed a minimum presence of insomnia symptoms. Finally, the cognitive score improved by five points (MMSE = 29 points), which could indicate that baseline evaluation could be influenced by concurrent MDD. The changes in the scales were corroborated by the self-report of the patient.

Before and after changes in scales for the three subjects are presented in Figure 2.

5. Discussion

In this report, three patients with different history and clinical presentation of MDD were treated with high-frequency and low-intensity magnetic patterned pulses over the left dorsolateral prefrontal cortex and showed remarkable clinical improvement after 15 sessions of stimulation.

While each patient presented a different clinical background, all three patients showed sharp changes in their self-report and in the standardized clinical assessments. The mechanisms responsible for the observed clinical changes in these patients are almost certainly different from those produced by classical TMS devices. The pulse intensity applied by this device is several orders of magnitude lower than the one required to generate a motor evoked potential, so direct depolarization of neurons does not seem like a viable mechanism of the observed antidepressant effect [10]. Even if there is no direct depolarization of neurons, magnetic pulses at a low subthreshold intensity and relatively high frequency have demonstrated to change cortical excitability [11], modify brain metabolism [12], and change neurocognitive function in humans [13]. How does these kinds of magnetic fields modify the brain's activity is not completely understood, but animal and human evidence have shown an increase in plasticity [14], BDNF [15], and an anti-inflammatory effect [16], which, coincidentally, are normally affected in MDD [10].

Other studies using magnetic pulses have reported mixed results in the antidepressant effects of magnetic stimulation in a similar window of frequencies and intensities. Rohan et al. first published that the application of magnetic pulses at 1000 Hz and an intensity of no more than 2 milliteslas to the whole brain reduced depressive symptoms in patients with bipolar disorder and MDD compared to sham stimulation with just one session of stimulation [5]. Years after, a double-blind proof of concept clinical trial showed no difference between sham and real stimulation with this same stimulation protocol and device in improving depression scores in subjects with unipolar MDD, leading to the conclusion that more sessions of stimulation and longer exposure time could explain the lack of efficacy of this trial [7]. A new and more recent double-blind clinical trial using this same stimulation protocol showed improvement in mood scores in real stimulation compared with sham with three sessions of stimulation [8].

Taking into count those previous studies, we designed a stimulation protocol that acknowledged three main points from previously reported protocols.

Firstly, as classical rTMS devices, we decided to focus the stimulation just in one area of the brain instead of applying a diffuse and global magnetic field to the whole skull. Pathophysiologically, we considered it important to focus the magnetic stimulation on one area known to be affected in MDD such as the left prefrontal dorsolateral cortex [17]. Secondly, the pattern of stimulation seems to be very important in determining the effects of both classical [18] and low-intensity magnetic stimulation [19]. That is why we chose a novel pattern of stimulation that has been shown to modify the brain's activity in both animal models (unpublished data) and humans. This novel stimulation pattern has shown to improve mood and insomnia symptoms in healthy young people [20].

Lastly, while neuroplastic changes can occur after just one session of rTMS [18], lasting and clinically relevant changes typically occur after at least 10 sessions of classical rTMS devices [21]; we hypothesized that applying a similar number of sessions as classical rTMS stimulation could lead to a more pronounced and consistent antidepressant effect compared to other low-intensity protocols.

We advise to regard this report with caution, as only three cases without proper controls are described, so placebo effects could not be evaluated. Also, the size of the group and its heterogeneity could have influenced the results obtained in this work, as patients were very different amongst themselves.

To reach stronger conclusions about the effect of HFLIP TMS, the group size must be augmented, and their heterogeneity reduced by the application of strict selection criteria, rather than a sample selected by convenience. Moving forward, clinical trials using this new HFLIP TMS protocol should be performed with appropriate sham control to correctly assess the clinical efficacy, as well as to clarify if the placebo effect could play a role in the improvement seen on the patients or other effects this technique could generate in MDD subjects.

Data Availability

Anonymized data of the applied scores are available upon request.

Disclosure

The research was partly performed as part of the employment of two authors (VG and RA). The employer (Actipulse Neuroscience) was not involved in the manuscript writing, editing, approval, or decision to publish.

Conflicts of Interest

VG and RA are currently working in the research department of Actipulse Neuroscience. Dr. Albano has been a speaker for Actipulse Neuroscience educational events.

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The effectiveness of exogenous melatonin versus transcranial magnetic stimulation on the quality of sleep, memory and mood of young adult people

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The effectiveness of exogenous melatonin *versus* transcranial magnetic stimulation on the quality of sleep, memory and mood of young adult people

Abstract

Melatonin is a neurohormone that is secreted in the brain and which is associated with the sleep cycle, its clinical uses have been focused on sleep disorders, as well as on the improvement of cognitive performance and people's mood. Likewise, Transcranial Magnetic Stimulation (TMS) has been used in the same areas. The objective of this research was to analyze for two weeks, in young adults with an average age of 24 (the minimum age was 18 and the maximum was 32), which of the two treatments was more effective in inducing improvements in sleep quality, memory and mood. Four groups were formed, the placebo group (n=28), the sham group (n=28), the melatonin group (n=25) and the TMS group (n=16). All groups had a pre-test evaluation of sleep quality, memory, depression and anxiety. The experimental phase lasted 2 weeks and consisted of placebo exposure, sham stimulation, melatonin consumption (10 mg) and TMS (128 Hz). After this period, the post-test evaluation was carried out. The results showed that both treatments were equally effective in improving sleep quality, although TMS was more effective in improving memory and anxiety symptoms. It is inferred that both treatments are effective, although the question arises about their long-term use and the maintenance of the improvements.

Keywords: melatonin, TMS, depression, anxiety, sleep quality, memory

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Abbreviations: TMS, transcranial magnetic stimulation

Introduction

Melatonin (N-Methyl-5-Methoxytryptamine) is a neurohormone that is synthesized in the pineal gland as well as in other organs of the body and their functions are crucial to vertebrate's life since they include the regulation of circadian rhythms by facilitating sleep and being a free radical scavenger in the brain.[1–6] Moreover, the intake of exogenous melatonin has been associated with more complex functions such as being effective in improving the conditions of animals in depression/anxiety models as well as in patients with mood disorders.[7–10]

In addition to being effective in treating insomnia problems in older adults,[11] melatonin is also effective in improving cognitive functions such as memory.[12–15] Although it is not clearly known how exogenous melatonin promotes such improvement, both in humans and in laboratory animals, it has been found to promote the expression of antioxidant enzyme,[16] the increase in concentration of trophic factors[14] as well as increased neurogenesis in the hippocampus.[17]

On the other hand, it is also known that transcranial magnetic stimulation is effective in treating similar disorders in which melatonin has been effective.[18–20] That is the reason why the question arises of which of the two therapies is more effective in treating both sleep disorders and cognitive functioning. Thus, the objective of this investigation was to evaluate the independent effect of the administration of exogenous melatonin and transcranial magnetic stimulation on the quality of sleep, memory and mood in young adults.

Material and methods

Participants; 100 young people from the city of Ensenada, Baja California were asked to participate in the research, which was then submitted to the ethics committee of the School of Health Sciences of the Autonomous University of Baja California. Each participant was given an informed consent where he or she was aware of the objective of the investigation and was told that it could be distributed randomly in the different experimental conditions. The average age of the participants was 24, the percentage of women and men was 36% and 64%, respectively. Participants who were under psychopharmacological and/or psychological treatment were excluded from the study.

Materials/equipment

To evaluate the working memory, the computerized version of the memory span and digit span tests were applied using the PEBL platform. To measure the quality of sleep, a Pittsburgh sleep quality inventory was applied. Burns inventories were used to detect levels of depression and anxiety. The anxiety inventory has a score of 0 to 100 and the classification of minimum anxiety (0-4), limit (5-10), light (11-20), moderate (21-30), severe (41-50) and extreme (51-100). The inventory of depression has a score of 0 to 100 and is classified in the categories of non-deprecated (0-5), normal but unhappy (6-10), minimal depression (11-25), moderate depression (26-50), severe depression (51-75) and extreme depression (76-100).[21]

Melatonin: 10 mg sublingual melatonin tablets from the Eurovital nutraceuticals brand were used. Participants were asked to ingest the pill a few minutes before sleeping for two consecutive weeks.

Transcranial magnetic stimulation: The portable version of the Actipulse Home-depression device was used. The stimulation protocol consisted of placing the diadem to the participants for 30 minutes a day, from Monday to Friday for two weeks. The electromagnetic impulses generated by the main unit of the stimulator are square waves with an emission frequency of approximately 128 Hertz (Hz).

Procedure: the participants were randomly distributed to one of the following groups (it was a double-blind study); 1. Placebo group (n=28) (this group only received strawberry flavor pills and had psychometric tests); 2. Sham group (n=28) (this group wore the stimulation headband and it was placed without any current and the tests were performed) 3. Melatonin group (n=25) (this group received 10 mg melatonin tablets that were ingested a few minutes before sleeping for 2 weeks, the formerly mentioned tests were applied before and after the experiment) and 4. TMS (n=16) (this group received transcranial magnetic stimulation through a diadem 30 minutes a day for two weeks and the tests were also applied before and after the experiment). All groups had a pre-test evaluation of sleep quality, memory, depression and anxiety. The experimental phase lasted 2 weeks and consisted of placebo exposure, sham stimulation, melatonin consumption (10 mg) and TMS (128 Hz). After this period, the post-test evaluation was carried out.

Statistical analysis

The two-factor ANOVA was used where the dependent variables were quality of sleep, memory, depression and anxiety: the factors included in the analysis were "time" (that is, before and after the experimental intervention) and the "experimental condition" (that is, the group to which it belonged to). For multiple comparisons the data was analyzed using the Tukey test. The statistical program Graph Pad Pris 8 for Mac was used.

Results

In the applied quality of sleep scale, values close to 0 indicate quality of sleep while those close to 21 indicate poor quality of sleep. According to the cut-off point of the instrument, values above 5 indicate poor sleep quality. As can be seen in Figure 1, both in the placebo group and in the sham group the average quality of sleep exceeds the cut-off point and remained similar in the pre-test and post-test phase of the experiment. In the melatonin and TMS groups, an improvement in sleep quality was observed in both groups, with both of them approaching a 5. The two factor ANOVA showed that time, experimental condition as well as interaction of both groups were significant [F(3,80)=7,285, p<0.01]. The analysis of multiple comparisons confirmed that the melatonin and TMS groups showed the reported improvement in sleep quality.

Sleep Quality

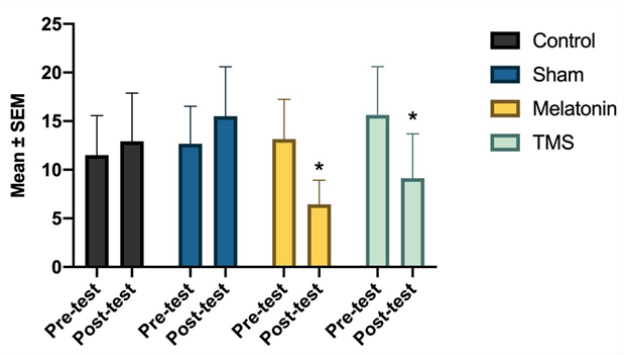

Figure 1 Shows the quality of sleep in the four groups before and after receiving the treatments; In the melatonin and TMS groups there was an improvement in sleep quality. The interaction between the "time" factor and "experimental condition" was significant in these groups [F (3, 80) = 7,285]. * Versus control, p <0.001

Regarding the execution of the memory tests, it can be seen in Figure 2 that in the memory span test the placebo, sham and melatonin groups had similar averages in the pre-test and post-test phases; however, the TMS group showed significant differences in the post-test phase [F(3,60)=6,92, p<0.01], which indicates an increase in the ability to remember images. In the digit span test, no significant differences were found due to the time factor, experimental condition or the interaction of both, however, an increase in the average of items remembered can be seen (see Figure 3). For example, the Melatonin group had an average of 5.5 and 6.5 of items in the pre-test and post-test evaluations, respectively; on the other hand, the TMS group had an average of 5.8 and 8 items before and after stimulation, respectively.

Memory span

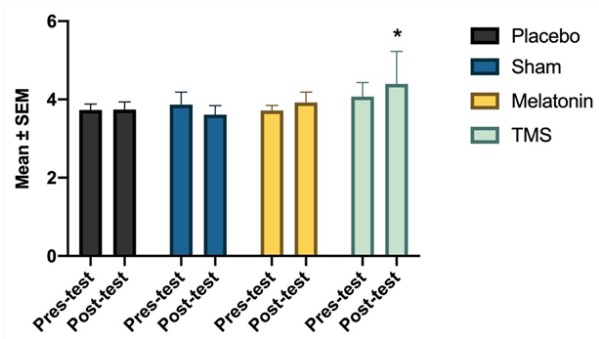

Figure 2 Shows the average of correct answers in the Mspan test in the four groups before and after receiving the treatment. While in the placebo, sham and melatonin groups there are no changes in the pre-test and post-test evaluations in the TMS group, the two-way ANOVA revealed a significant effect of the "experimental condition" factor [F (3, 60) = 6,922]. * Versus control, p <0.001

Digit Span

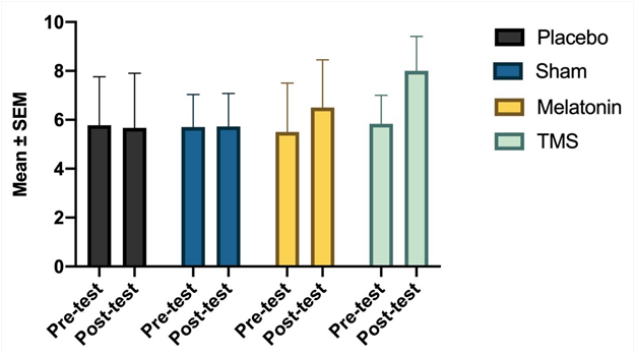

Figure 3 Shows the average number of correct answers obtained in the Dspan test in the four groups before and after receiving the treatments. Statistical analyzes did not reveal significant changes after treatments. However, it can be seen in the experimental groups a tendency to improve in the execution of said test. * Versus control, p <0.001

The average levels of depression found in the pre-test phase in the four groups were similar and according to the interpretation of the Burns depression inventory corresponded to the levels of moderate depression (Figure 4). In the post-test phase, this trend was maintained with the exception of the melatonin group, where there was a combined effect of the "time" factor and "experimental condition" to significantly reduce depression values [F(3,98)=3,103, p<0.01]. The average levels of depression in this group after melatonin treatment corresponded to those of minimal depression.

Anxiety in the placebo and sham groups was similar in the pre-test and post-test evaluations (Figure 5). According to the classification of the Burns anxiety inventory in both groups, it was detected that the average score corresponded to a moderate level of anxiety. In the case of the melatonin group, the pre-test evaluation showed moderate

anxiety and in the post-test evaluation the participants' scores corresponded to those of light anxiety. Statistical analysis showed that the experimental condition factor had a significant reduction in anxiety in the TMS group [F(3, 96)=4,23, p<0.01].

Depression

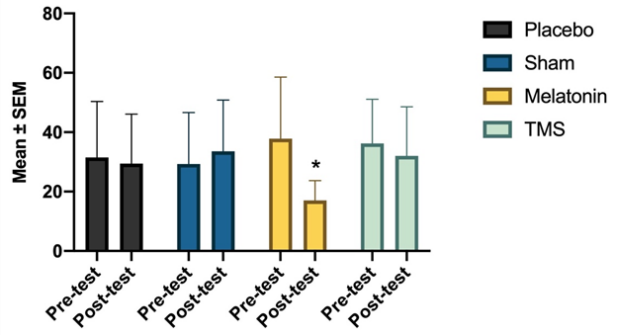

Figure 4 Depression levels in the melatonin group significantly decreased after the two week treatment [F (3, 98) = 3,103]. *Versus control, p <0.001

Anxiety

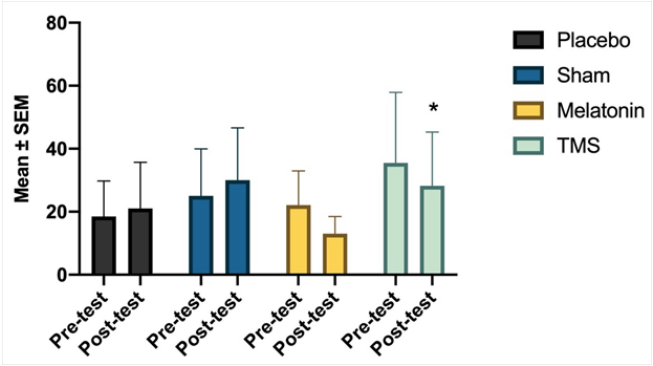

Figure 5 Shows the anxiety levels before and after the experimental phase. As can be seen, anxiety levels had a decrease in the TMS group; Statistical analyzes showed that the experimental condition factor had a significant effect on [F (3, 96) = 4,227]. *Versus control, p <0.001

Discussion

Sleep quality is a condition that was affected in all participants of this research. However, the melatonin treatment as well as the magnetic stimulation treatment was effective in improving the quality of sleep as reported by the participants. This data is consistent with reports where exogenous melatonin is useful and widely used to treat sleep disorders.[22] Thus, for example, there is evidence where relatively low doses of melatonin (1mg/day) administered for 5 weeks (of which 2 received placebo) were effective in reducing the difficulty of waking up, reducing sleep during school hours and increasing sleep time in adolescents whose ages ranged from 14 to 19.[23] Our data also agreed with studies where patients who were in a treatment against heroin addiction and who underwent a 10 Hz stimulation protocol for six weeks reported a significant improvement in sleep quality.[24] While melatonin was more effective in improving sleep quality, statistical analyzes did not show that one treatment was more effective than the other. These results could be explained because melatonin has the natural function of regulating sleep cycles, increasing the REM sleep cycle and decreasing sleep latency.[2] In the case of TMS, it has been shown that it induces the propagation of slow waves, similar to those of the deep sleep phase.[25]

Memory improvement can be clearly seen in the memory span test in the group that received TMS for two weeks. These results agree with reports where TMS in the motor cortex is able to improve the learning of motor sequences in 22 year olds.[26] Similarly, they agree with memory improvement in mice exposed to microgravity conditions (which causes cognitive damage); in that case, 15 Hz TMS was applied for 14 consecutive days.[27] In this investigation, memory improvement was associated with an increase in dendritic spine density of the dentate gyrus of the hippocampus, as well as an increase in the expression of postsynaptic proteins NR2A, NR2B, PSD95 (associated with memory formation) as well as an increase in BNDF/TrkB growth factors. On the other hand, although melatonin was not able to significantly improve performance in memory tests, although if there is a tendency to increase the average number of successes in both tests and it seems that the effects on this function are observed with more days of treatment, at least for two more weeks.[28]

The depression variable was the one that got benefited the most by the melatonin treatment. This is consistent with research in which mice that received the 10 mg/k intraperitoneal injection of melatonin and that had been pretreated with liposaccharides had a reduction in depressive symptoms induced by such drugs. This improvement was associated with the increase in glutathione antioxidant enzyme, increase in BNDF and decrease in TNF-a in the hippocampus.[29] On the other hand, these results are consistent with the fact that the administration of 10 mg/k melatonin in rats was able to reverse depressive symptoms induced by continuous stress. Neurochemical analyzes confirmed that this improvement was related to an increase in norepinephrine levels in the hippocampus.[30] Furthermore, our results agree with preclinical studies where melatonin has shown antidepressant properties. Although statistical analyzes did not show a reduction in depression levels in the TMS group if a tendency to decrease can be seen, which would be consistent with reports of the effectiveness of this treatment for depression.[31,32]

Anxiety showed high values in all the groups evaluated and decreased with experimental conditions. This data is consistent with reports where TMS was effective for the treatment of anxiety disorders.[2,3] It should be noted that the group that had higher levels of anxiety before the experiment was that of TMS and after that treatment the anxiety levels decreased significantly, so it is likely that TMS use has higher anxiolytic properties than that of melatonin's.

Conclusion

After two weeks of treatment, both melatonin and TMS were effective in improving the sleep quality of young adults. TMS was more effective than melatonin for relieving anxiety symptoms and for improving memory test scores. On the other hand, the melatonin treatment was more effective in reducing the symptoms of depression. However, there is still the question of knowing how the effectiveness of such treatments would be long-term (one or two months) and knowing if these effects are maintained after the end of the treatment.

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Conflicts of interest

The authors declare no conflict of interest.

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