

Case Report

A Case Study: The Effect of Transcranial Magnetic Stimulation (TMS) on Stress Levels, Quality of Sleep, and the Autonomic Nervous System

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive procedure approved by the FDA in 2008 to improve symptoms of treatment-resistant depression. Magnetic pulses create an electric current within the brain which in turn activate the impacted neurons. Recent studies suggest that high-frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) assuages symptoms of depression and low-frequency stimulation to the right DLPFC aids in alleviating symptoms of depression and anxiety. This case study evaluated the differences in the effect of excitatory rTMS to the left and right DLPFC on stress levels, the autonomic nervous system, and sleep quality on healthy individuals through the use of salivary biomarkers, an autonomic nervous system monitor, and POMS2, a self-report mood assessment instrument (Profile of Mood States Second Edition). The results from this study suggest that excitatory left DLPFC treatment is more effective than right DLPFC and sham treatment in decreasing cortisol levels and increasing melatonin levels two days post-treatment. Subjects who received right DLPFC rTMS achieved an overall higher quality of sleep in comparison to the other two treatment groups, indicating a potential relaxing effect. Lastly, in terms of POMS2, the data from the placebo group showed the most promise, with decreased self-reported feelings of depression, anxiety, and fatigue. These results indicate a promising potential in the use of both left DLPFC and right DLPFC rTMS as a treatment for those suffering from stress and insufficient sleep respectively, fundamentally targeting the stress epidemic which is currently afflicting Japan.

Keywords: transcranial magnetic stimulation, DLPFC, stress, autonomic nervous system, POMS2

Introduction

Stress, especially in relation to work-life balance, has become an increasing health concern around the world, and Japan is no exception. In comparison to the rest of the world, work hours in Japan are much longer, and is one of the main contributors to the formation of the term “karoshi” in the 1980’s, which means death from overwork [1,2]. Currently, job-related stress remains high throughout Japan, reaching 65% throughout the years 2002 and 2007 [3].

In 2007, 58% of Japanese workers throughout Japan reported intense feelings of worry, anxiety, or stress in relation to their job [3]. These feelings of stress and anxiety have led to an astonishing incline of 6,000 suicides per year in 1997 to 9,000 in 1998 among employees [3]. In order to address this issue of mentally and physically debilitating stress throughout the nation in Japan, this case study looked at the effects of transcranial magnetic stimulation on stress levels, sleep quality, and autonomic nervous system activity.

Transcranial magnetic stimulation, or TMS, is a noninvasive procedure that was approved by the U.S. Food and Drug Administration (FDA) in 2008 as a treatment to alleviate symptoms of treatment-resistant depression [4] (FDA approval K061053). TMS was successfully reported for the first time in 1985 by Anthony Barker of the United Kingdom and his colleagues [5]. In this 1985 study, Barker and his colleagues applied TMS to the motor cortex and were able to produce twitching in a particular area of the hand, pioneering the way towards pain-free precise stimulation of the brain through magnetic stimulation [5].

The mechanisms that Barker and his colleagues used to develop TMS is founded upon the principle of electromagnetic induction proposed by Michael Faraday in 1831 [6,7]. Michael Faraday discovered that electrical currents can be converted into magnetic fields and magnetic fields can be converted back into electrical currents as well. This phenomenon became known as electromagnetic induction. Faraday found that through the process of electromagnetic induction, an electrical current which passes through one coil could induce a current in a nearby coil, which is essentially the basic mechanism on which TMS operates in order to achieve stimulation in the brain. In TMS, the brain acts as the second nearby coil in which a current is induced. By creating a rapidly changing magnetic field, the affected neurons become activated and essentially elicits neuronal activity [5,8]. Because of Faraday's discovery that electrical currents can be converted into magnetic fields and vice versa, upcoming scientists such as Barker et al., were able to apply this principle to eventually develop what is known as transcranial magnetic stimulation today.

Since Barker's groundbreaking experiment in 1985, TMS has become a widely utilized and researched procedure by neuropsychologists and researchers throughout the world. TMS has been investigated as a diagnostic and therapeutic tool for a myriad of diseases, such as Parkinson's disease and multiple sclerosis, as well as a device to improve memory. Although TMS has multiple promising areas of application, treatment for depression was the first major therapeutic goal set for TMS [9].

Potential for TMS as a therapeutic treatment for depression was initially discovered in 1993 by a group of researchers in Austria who found that two patients suffering from severe depression experienced encouraging reactions after undergoing a course of repeated single-pulse TMS treatment before electroconvulsive therapy [9,10]. Since this discovery in 1993, recent studies suggest that high-frequency stimulation to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency stimulation to the right DLPFC aids in alleviating symptoms of depression and anxiety respectively and is a readily available and practiced procedure for treatment-resistant depression and general anxiety today [11-13].

Although practices and studies of diagnostic and therapeutic applications of TMS is increasing, the knowledge and implementation of TMS as a treatment for depression in Japan remains relatively low. This case study investigated the effects of TMS on stress levels, quality of sleep, and autonomic nervous system activity in order to determine TMS efficacy in targeting depression and depressive symptoms in a country enduring an ongoing epidemic of stress and stress-related depression and ultimately improve the quality of life of individuals throughout Japan.

Materials and Methods

Subject

In this study, 16 healthy individuals (male: n=7 female: n=9), with ages ranging from 24-57 years old, were randomly assigned to undergo one session of excitatory repetitive TMS treatment each to either the right DLPFC (n=7) or left DLPFC (n=5). Controls received a placebo treatment (n=4). Volunteers came from Juntendo Graduate Medical University as well as from Kobayashi Medical Clinic, Tokyo. Subjects had no history of mental health illness. This research was conducted with accordance and approval from the ethics committee of the Shinjuku Stress Clinic located in Shinjuku, Japan.

Experimental design

A general sample schedule was as follows: On day one, the subjects woke up in the morning and immediately put on the M-BIT 24-hour autonomic nervous system monitor before doing any other activities. The subjects ensured that the monitor is positioned on the left side of the chest where the pulse feels the strongest. After successfully putting on the monitor, the subjects turned on the monitor by quickly pressing the button found on the right side. Once M-BIT was turned on, a green light began to blink in a consistent rhythm. After the subjects put on the monitor successfully, the subjects took their first salivary sample of the day, before eating or brushing teeth, and placed the sample in the freezer immediately. The subjects deposited three more salivary samples throughout the day – one before lunch, one before dinner, and one before going to bed. At some point during the day, the subjects were required to fill out a POMS2 mood assessment questionnaire. After waking up the next morning, the subjects turn off the monitor before removing it. On the second day, the subject was not required to do anything. On day three (TMS treatment day), similar to day one, the subjects put on the M-BIT monitor in the morning but did not take a salivary sample. The subject undergoes a total of about seventeen-minutes of sham TMS treatment or excitatory rTMS to either the left or right DLPFC at Shinjuku Stress Clinic. Salivary samples were taken to the clinic directly before and after treatment. After waking up the next morning, the subjects were able to remove the monitor from day three and was finished for the day. On day five (the last day), the subjects repeated the same schedule as day one. This study lasted for about five days, with breaks on days two and four.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) utilizes electromagnetic induction in order to stimulate nerve cells within the brain. This study utilized excitatory repetitive TMS to either the left or right DLPFC. Each participant was subjected to an average of about 40% stimulation power. Some subjects received a lower frequency if any pain or discomfort was experienced. Each procedure of TMS was administered for a duration of about 17 minutes. TMS was administered at the Shinjuku Stress Clinic in Shinjuku, Tokyo by TMS certified professionals.

Salivary Cortisol and Melatonin Samples

Salivary samples were taken in order to measure levels of salivary cortisol and melatonin levels four times throughout the day (morning, afternoon, evening, and night) and directly before and after TMS treatment. All subjects were instructed to avoid food and caffeine one hour before depositing a salivary sample, in addition to before undergoing TMS treatment. Participants were required to deposit a sample of 1.0mL each time. Salivary samples were collected in a seated position using the Saliva Collection Aid (SCA, Salimetrics LLC). Samples were stored at -20°C until analysis. Cortisol and melatonin levels were measured using the ELISA kit.

M-BIT Monitor

M-BIT is 24-hour autonomic nervous system monitor created by the BITAS corporation located in Tokyo, Japan (<http://bitas.co.jp/eng/index.html>) in order to allow individuals to measure, manage, and check autonomic nervous system activity. BIT stands for bioinformation tracer. M-BIT allows for wireless, real-time analysis while also being able to store memory, giving it the capability to measure autonomic nervous system activity for long, continuous periods of time. There are three different types of biosensors within the monitor which allow for different types of

analysis. One sensor is an electrocardiogram, or ECG. The ECG measures mechanisms such as autonomic nervous system activity, respiration rate, heart rate, and pulse abnormality. The remaining two biosensors, a skin temperature sensor and 3-axes acceleration sensor, detects information about the subject such as posture, position, and energy consumption. All of the information collected by these biosensors are stored in a memory chip inside of M-BIT and analyzed by BITAS analysis software once transmitted into a PC. This study used M-BIT to determine quality of sleep by analyzing the amount of time slept, sleep onset time, the number of times eyes opened during sleep, stress during sleep, and autonomic nervous system activity throughout sleep. In addition, M-BIT information was used to determine the coefficient of variation of R-R interval variability (CVRR) or total power. Subjects were required to wear the monitor for 24-hours two days before treatment, on the day of treatment, and two days after treatment (Days one, three, and five).

POMS2

The Profile of Mood States Second Edition, or POMS2, was also utilized on the first and last day of this study (day one and day five). This 35-question self-report instrument assesses the mood states of individuals and allows for a quick evaluation of fluctuating feelings and enduring affect states. The areas measured and applied in this study are depression-dejection (DD), tension-anxiety (TA), and fatigue-inertia (FI). The smaller the value, the better the condition.

Results

Salivary cortisol and melatonin levels

An overall improvement in average cortisol levels was found in the left DLPFC treatment group two days after treatment. Two days before treatment, average cortisol levels in the morning and afternoon in the left DLPFC condition was at 0.83 pg/mL and 0.50 pg/mL respectively. Two days after treatment, average cortisol levels dropped to 0.44 pg/mL in the morning and 0.15 pg/mL in the afternoon. In addition, the left DLPFC condition group experienced an increase in average cortisol levels directly after left DLPFC treatment (0.13 to 0.31 pg/mL). Little to no change was found in average cortisol levels in the right DLPFC treatment group. In contrast, the placebo treatment group displayed a decrease in average cortisol levels directly after treatment (2.0 to 0.09 pg/mL) (Figure 1).

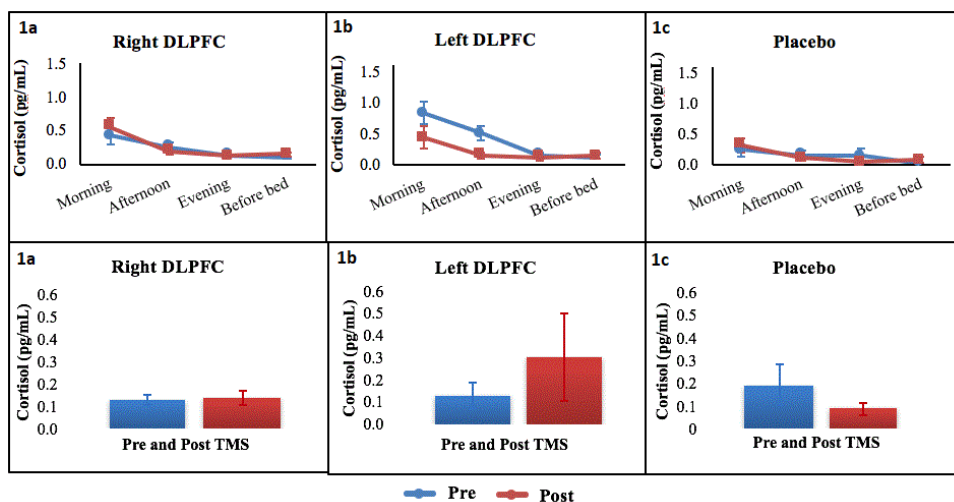


Figure 1: Effect on saliva Cortisol levels. (1a) Right DLPFC: Little to no change in average cortisol levels. **(1b)** Left DLPFC: Decrease in average cortisol levels in morning and afternoon two days post-treatment; Rise in cortisol levels right after TMS. **(1c)** Placebo: Decrease in average cortisol levels directly after TMS

An average overall improvement in melatonin levels two days after treatment was found in the morning in both the left DLPFC treatment group and placebo group. In the left DLPFC treatment condition, melatonin levels raised

from 15.65 pg/mL in the morning two days before treatment to 26.9 pg/mL in the morning two days after treatment. Furthermore, in the left DLPFC treatment group, melatonin levels appear to have decreased right after undergoing TMS (16.76 to 5.10 pg/mL). In contrast, melatonin levels slightly increased directly after right DLPFC treatment (5.4 to 6.54pg/mL) and sham treatment as well (5.4 to 6.54 pg/mL) (Figure 2).

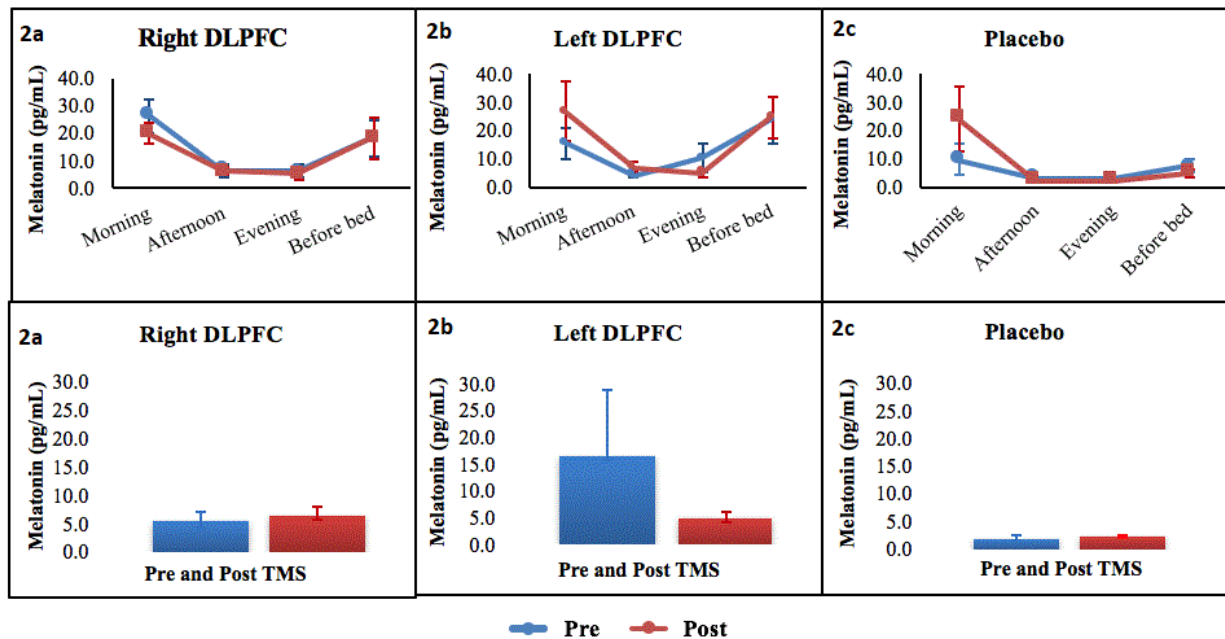


Figure 2: Effect of saliva melatonin levels. (2a) Right DLPFC: Slight increase in melatonin levels directly after TMS. **(2b)** Left DLPFC: Improvement in melatonin levels in the morning two days post-treatment; Decrease in average melatonin levels directly after TMS. **(2c)** Placebo Group: Improvement in average melatonin levels in the morning two days post-treatment; Slight increase in average melatonin levels directly after TMS

Sleep quality and autonomic nervous system activity

Autonomic nervous system activity measured by the M-BIT monitor revealed that the average amount of time slept on the day of treatment increased the most in the right DLPFC treatment group (328 minutes to 390 minutes). The left DLPFC group also experienced a slight increase in the average amount of time slept (328 minutes to 360 minutes). Although a decrease in the average amount of time slept on the day of treatment was found in the placebo group (401 minutes to 340 minutes), average time slept increased two days after treatment in comparison to two days before treatment (401 minutes to 441 minutes).

The average amount of time taken to fall asleep after getting into bed decreased in all three conditions, with the largest decline evident in the left DLPFC treatment group (22 minutes to 8 minutes). The right DLPFC and sham treatment groups displayed a decrease from 17 minutes to 13 minutes and 7 minutes respectively.

An increase in the average number of times eyes opened during sleep was only found in the left DLPFC treatment group. The amount of times doubled from 5 to 10 times. In contrast, a continuous decline in the average amount of times eyes opened during sleep was found in both the sham and right DLPFC conditions. The sham group displayed a decrease of 10 to 7 times on the night of treatment, and eventually dropped to 5 times two days after treatment. Although there appears to have been only a slight to no change in the average amount of times eyes opened on the day of treatment in the right DLPFC treatment group (8 to 7 times), the amount of times gradually dropped by half two days post-treatment with values declining from 8 times to 4 times pre-and post-treatment respectively.

Based on BITAS analysis, quality of sleep was measured in terms of balance of autonomic nervous system activity, with perfect balance considered to be a value of 1.0. In other words, the closer to the value point 1.0, the better balance was considered in terms of autonomic nervous system activity. Improvement in quality of sleep on the day of treatment was seen the most in the right DLPFC treatment group, with numbers increasing from 0.7 to 0.89 on the day of treatment. A slight improvement in quality of sleep was also seen in the left DLPFC group (0.84 to 0.89). In contrast, the placebo group showed a decrease in quality of sleep with data declining from 0.85 to 0.77. Although a decrease was found on the day of treatment, an overall improvement was found two days post-treatment in the placebo group, with values rising from 0.84 pre-treatment to 0.91 post-treatment.

Stress during sleep, or sympathetic activity, was also measured through BITAS analysis. If sympathetic nervous system activity is too high during sleep, deep sleep is not able to be achieved, therefore causing stress during a time in which the body should be at rest. According to BITAS analysis, a value of 0.9 or less is considered to be an appropriate level of sympathetic nervous system activity during sleep. The lower the value, the more the body is considered to be at rest. Sympathetic activity increased slightly in all three conditions on the night of treatment (2.5 to 2.7, 1.1 to 1.7 and 0.8 to 0.9 – right, left, and sham treatment respectively). Although sympathetic nervous system activity increased on the night of treatment in all three groups, the right DLPFC condition displayed a decrease in sympathetic nervous system activity two days after the administration of TMS with values rescinding from 2.7 to 2.1.

The term CVRR stands for the coefficient of variation R-R intervals. CVRR is determined by dividing the standard deviation of RR intervals by the mean RR interval, and essentially represents “total power” or overall autonomic nervous system efficiency. CVRR values, although only slightly, increased the most in the placebo group on the day of treatment with values rising from 0.05 to 0.06. An even slighter increase in CVRR value was found in the right DLPFC condition and a minor decrease in CVRR was displayed in the left DLPFC group (0.06 to 0.05) (Figure 3).

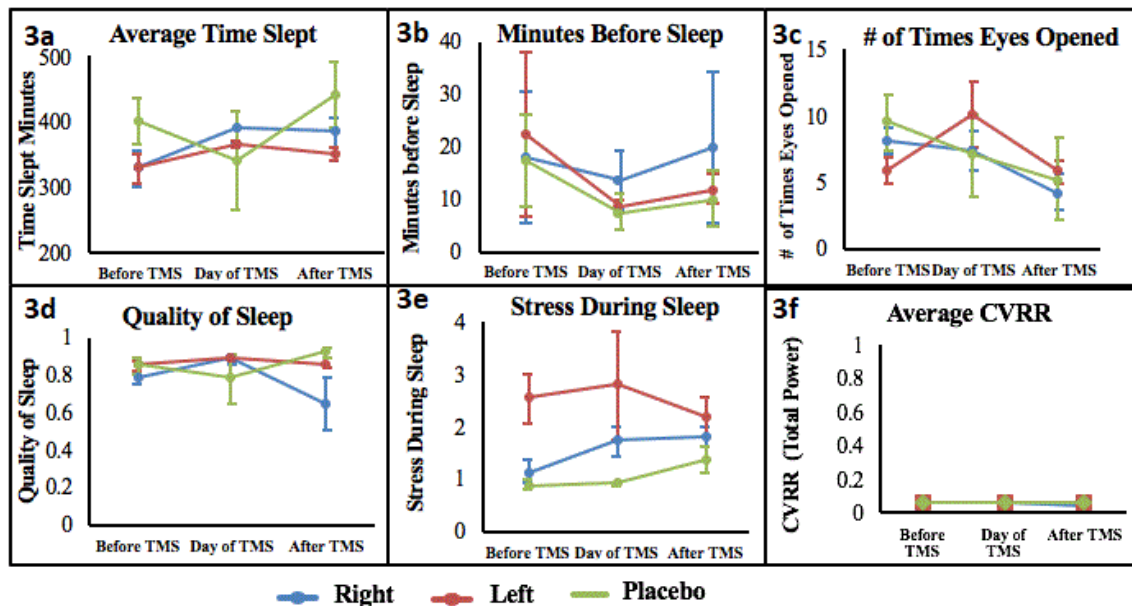


Figure 3: Effect on M-BIT sleep/ANS. (3a) Average Time Slept: Right DLPFC: largest increase in amount of time slept on night of treatment; Placebo: Increase in amount of time slept two days post-treatment. **(3b)** Minutes Before Sleep: Decreased in all three conditions; Left DLPFC: largest decline. **(3c)** Number of Times Eyes Opened: Left DLPFC: only condition that increased; Right. DLPFC: Amount of times dropped by half two days post-treatment. **(3d)** Quality of Sleep:

Right DLPFC: Most improvement on night of TMS; Placebo group: Decrease in quality on the night of TMS but improved two days post-treatment in comparison to pre-treatment. **(3e)** Stress (sympathetic nerve activity): Increased slightly in all three conditions on night of TMS; Right DLPFC: Decrease in stress two days post-treatment. **(3f)** CVRR (total power):

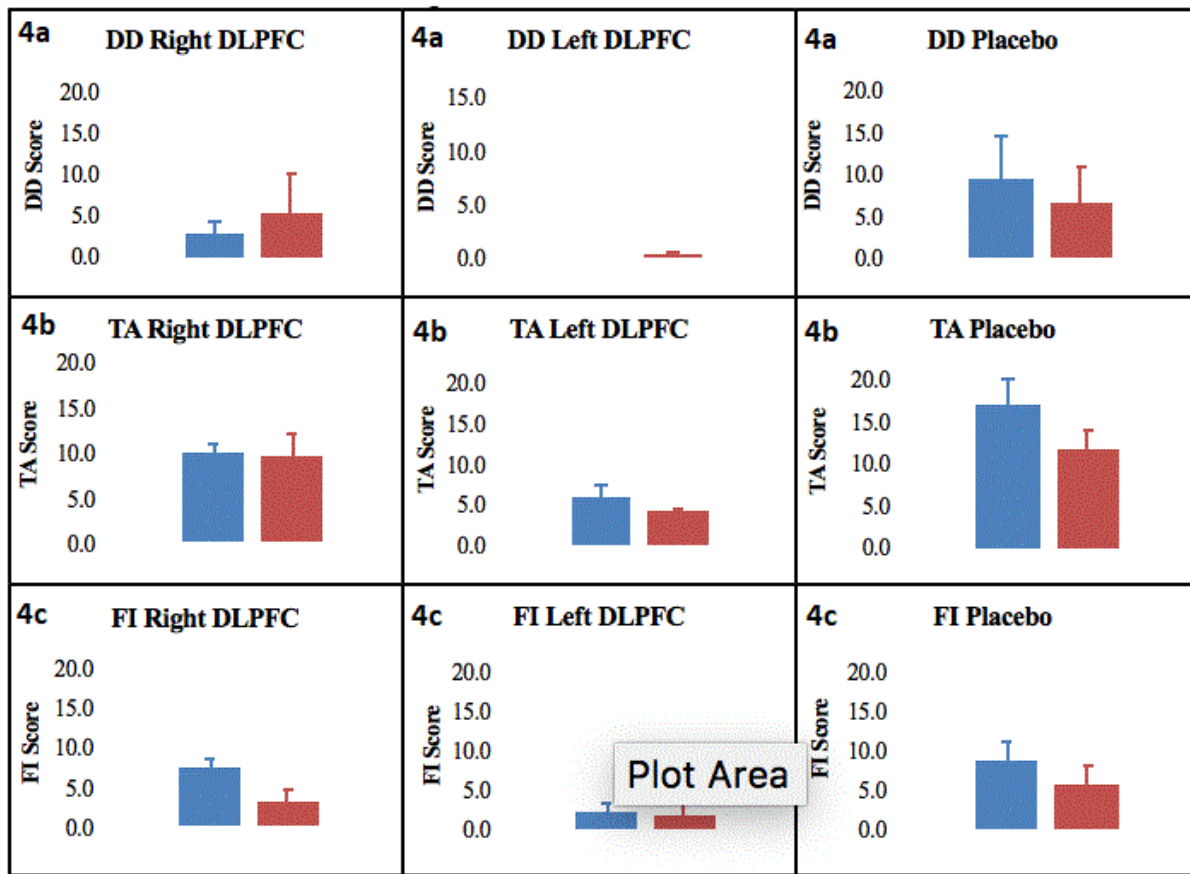
Placebo group: Slight increase on night of TMS; Left DLPFC: slight decrease on day of treatment

Profile of mood states edition 2 (POMS2)

The sham treatment group self-reported a decrease of depressive symptoms with numbers dropping from 9.5 to 6.75. In both the right and left DLPFC treatment conditions, a slight increase in self-assessed depressive symptoms were found (right: 2.86 to 5.43, left: 0 to 0.25).

All three conditions experienced a self-assessed decrease in tension and anxiety, with the placebo group displaying the most improvement (right: 9.86 to 9.57, left: 6.0 to 4.25, placebo: 16.75 to 11.75).

In the fatigue and inertia division, all three treatment conditions experienced a decrease in self-assessed symptoms of fatigue with the most improvement seen in the right DLPFC and sham treatment groups (right: 7.57 to 3.0; left: 2.0 to 1.75; 8.75 to 5.5) (Figure 4).



DD: Depression-Dejection, TA: Tension-Anxiety, Fi: Fatigue-Inertia

Pre Post

Figure 4: Effect on Mood States. (4a) Placebo: DD score decreased direct after TMS; Right and Left DLPFC: Increase in DD Score. **(4b)** TA score decreased in all three conditions; Placebo: Largest decrease in TA score. **(4c)** FI score declined in all three conditions; Right DLPFC and Placebo: Largest decline in FI score

Discussion

Due to the high frequency of stress and depressive symptoms throughout Japan, this study aimed to discover if TMS can be considered an efficient procedure to alleviate these treatment-resistant symptoms and essentially improve overall quality of life.

In terms of average salivary cortisol levels, the left DLPFC treatment group showed the most improvement, with cortisol levels dropping in the morning and afternoon two days post-treatment in comparison to two days before treatment. Stress levels increased right after undergoing TMS treatment, but this rise in cortisol could be attributed to nerves and stress of undergoing a new procedure. Some subjects in this group also commented feelings of pain and discomfort during this procedure, which could also be an underlying cause for the rise in cortisol levels directly after treatment. In contrast, the placebo group displayed a decline in average cortisol levels directly after TMS. This could be attributed to the fact that because it was a sham treatment, no pain was experienced, and therefore allowed subjects to mentally and physically relax during the procedure, causing a decline in cortisol levels. Because cortisol levels continued to decline and remained lower two days post-treatment in the left DLPFC TMS condition, left DLPFC excitatory rTMS may be considered a potential procedure to efficiently lower stress levels in individuals throughout the day. This is consistent with the current use of excitatory left DLPFC rTMS in individuals with treatment-resistant depression [10].

Melatonin levels also improved in the left DLPFC condition in the morning two days post-treatment, which implies an improvement in sleep quality. If melatonin levels are high in the morning, it indicates that melatonin remained high during sleep, which is essential for a deep sleep. The placebo group also experienced this increase in melatonin levels in the morning two days post-treatment. This data suggests that left DLPFC TMS and sham TMS treatment may be effective in rising melatonin levels throughout the night, and essentially improving overall sleep quality.

Although the left DLPFC treatment group showed the most improvement in terms of salivary stress levels, the right DLPFC condition displayed the most influence in sleep quality. Average time of sleep increased the most in the right DLPFC condition as well as quality of sleep. In addition, the average number of times eyes opened during sleep decreased overall two days post-treatment as well as stress, or sympathetic activity, during sleep. This data indicates that excitatory right DLPFC rTMS may have a relaxing effect and can potentially be efficient in aiding individuals obtain longer and higher quality of sleep. This relaxation effect is also found in the results of many clinical TMS studies. For instance, Schutter et al, discovered that participants in a TMS study reported significance decrease in anxiety after right DLPFC treatment [11]. In addition, a more recent study by Cress et al in 2016, utilized the Beck Anxiety Scale to determine the efficacy of right DLPFC TMS on anxiety and concluded that it is a promising procedure for generalized anxiety disorder [12]. The results from this experiment are in accord with these studies suggesting that right DLPFC rTMS possesses a relaxing effect and may aid in achieving better quality of sleep.

In terms of self-reported feelings of depression, anxiety, and fatigue, the sham group displayed the most improvements. This improvement in self-reported mood states may be due to the fact that subjects did not endure any pain during the procedure. This result of amelioration in self-reported mood suggests that a placebo effect may also be important in terms of TMS and its potential application as a sham procedure should be further explored.

The data in this study suggests that excitatory left DLPFC rTMS is more effective than right DLPFC and sham treatment in decreasing cortisol levels and increasing melatonin levels two days post-treatment. This is in line with its current usage as treatment for depressive symptoms. Excitatory right DLPFC rTMS encompasses a potential relaxing effect, which allowed subjects in this study to achieve higher quality of sleep in general in comparison to the other two treatment groups. Lastly, in terms of POMS2, the data from the placebo group showed the most promise, with decreased self-reported feelings of depression, anxiety, and fatigue.

For future studies, a bigger sample group should be investigated per condition and each participant should undergo multiple, time-consistent treatments of TMS. Because each subject in this study experienced only one session of TMS, nerves and anxiety about undergoing a new treatment may have possibly skewed the results of this study. If each participant is able to receive numerous treatments of TMS, stress and anxiety of receiving a new treatment will eventually subside, allowing for evaluation of the effects of TMS on stress levels to become clearer. In addition, more than one treatment of TMS may be necessary for TMS to take effect. In other words, one session may not be sufficient to examine the full capabilities and biological effects of TMS on an individual. Because some subjects reported feelings of pain and discomfort during the TMS procedure, ways in which pain during TMS can be decreased should also be taken into consideration for future studies and application. In addition, participants diagnosed with treatment-resistant depression and/or chronic stress may provide a more appropriate sample. To our knowledge, the determination of the efficacy of TMS on stress through the use of biomarkers has not yet been explored. Therefore, continuation of this study aims to further explore the potential to utilize biomarkers to determine the effect of TMS on stress and depressive symptoms.

This study confirms the results of current TMS clinical studies that report beneficial effects of excitatory left DLPFC rTMS for treatment-resistant depression and excitatory right DLPFC rTMS for depression and anxiety. In this study, left DLPFC rTMS decreased salivary stress levels and right DLPFC rTMS improved overall quality of sleep. These results indicate a promising potential in the use of both left DLPFC and right DLPFC rTMS as a treatment for those suffering from stress and insufficient sleep respectively, fundamentally targeting the stress epidemic which is currently afflicting Japan.

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