Theta Burst Stimulation in Adults with Symmetric and Asymmetric Visual Acuity

Ana Rita Tuna (✉ anaritatuna@gmail.com)

University of Beira Interior Faculty of Health Sciences: Universidade da Beira Interior Faculdade de Ciencias da Saude

<https://orcid.org/0000-0001-8490-4135>

Nuno Pinto Lc

University of Beira Interior: Universidade da Beira Interior

Andresa Fernandes

University of Beira Interior: Universidade da Beira Interior

Francisco Miguel Brardo

University of Beira Interior: Universidade da Beira Interior

Maria Vaz Pato

University of Beira Interior: Universidade da Beira Interior

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Abstract

Purpose: Theta Burst Stimulation can influence adult neuro-visual response in imbalanced visual pathways, possibly by influencing cortical excitability. Our objective was to compare suppressive imbalance (SI) and visual acuity (VA) after applying repetitive Transcranial Magnetic Stimulation (TMS) between groups of subjects with normal binocular vision, visual asymmetry and amblyopia.

Methods: Thirty – five volunteers between 19 and 51 years of age, were split into three groups: 6 volunteers with asymmetric VA (group A); 19 amblyopes (group B); and 10 subjects with normal binocular vision (group C). VA and SI of all groups were evaluated before and after a single session of continuous theta-burst stimulation (cTBS) or placebo stimulation over the right occipital cortex.

Results: In both groups A and B we found a significant VA improvement in the non-dominant eye after cTBS ($p=0.04$ and $p=0.01$, respectively). In SI evaluation, group A and group B also revealed a significant improvement after the cTBS session ($p=0.03$ and $p=0.01$, respectively).

Finally, in the group of volunteers with normal binocular vision and for placebo groups A and B, there were no significant differences in VA and SI after cTBS.

Conclusions: Amblyopic and visually asymmetric individuals improved VA and SI of the non-dominant eye after cTBS when compared to baseline and to placebo stimulation. These enhancements were not found in the group of volunteers with normal binocular vision. We can therefore reasonably assume that cTBS may interfere with the visual system of subjects that present some kind of asymmetry, possibly by improving neuronal imbalances.

1. Introduction

The binocular visual system can fuse two images that are seen separately by each eye, to promote a cyclopean view of the surrounding environment. Binocular vision allows human beings to have two different images of a scene, and to merge those two images into one, thereby allowing depth perception which is dependent on this binocular disparity.¹ Ocular dominance is also characteristic of binocular vision, which is defined as a tendency to rely on one eye for a given task, even though both eyes are working properly.[1, 2]

Different categories of ocular dominance exist, such as sighting, motor, and sensory dominance, and these are categorised by their applications. Sighting dominance consists of the tendency to use one eye over the other for specific tasks, like seeing through a telescope. Motor dominance is defined for the eye that does not lose fixation at the near point of convergence, with the extraocular muscles playing an important part in motor dominance.[1, 3] Sensory dominance can occur when one of the retinal images is brighter or clearer than the other, leading to a “rivalry” between eyes. [1, 3]

Amblyopia is clinically characterised by the presence of at least two lines of visual acuity difference between the eyes with the best-corrected visual acuity, in an eye without any apparent ocular abnormality.[4, 5] Amblyogenic factors can interfere with the normal development of the eye and may lead to amblyopia, as well as strabismus, anisometropia, and less commonly, visual deprivation. [4, 5] Amblyopia is commonly treated with occlusion or penalisation (atropine) of the non-amblyopic eye, to force the brain to use the amblyopic eye.[4, 5] Hess and Thompson conducted the first study where Transcranial magnetic stimulation (TMS) was applied to amblyopic subjects, and showed improvement in high spatial frequencies, using contrast sensitivity as a control parameter.[6]

In pediatric ages, a group of subjects with a difference of one line of visual acuity between the eyes needs follow-up, since there is a possibility of this condition progressing towards amblyopia. However, this condition is not generally followed up into adulthood. [7] There are no studies on this population with only one line of difference between both eyes of visual acuity in adulthood, namely using TMS.

TMS is a non-invasive brain technique that is able to modulate neuronal circuits. It involves the emission of magnetic fields, which pass through the scalp and induce changes in neuronal and synaptic activity. This technique has been approved by the United States Food and Drugs Administration to treat neurological disorders, such as depression.[6] Theta Burst Stimulation (TBS) is a specific type of TMS and the application of this protocol is described as having long after-effects (up to sixty minutes in the primary motor area), despite its shorter stimulation period when compared with traditional low-frequency repetitive TMS (rTMS).[8–10] The neuronal effects associated with the use of continuous TBS (cTBS) are probably related to a negative change in synaptic strength related to the phenomena of long-term potentiation (LTP) and long-term depression (LTD). [10–12]

In a previous study, we applied TMS to a group of amblyopic volunteers, and almost all of them showed improvement in their control parameters: visual acuity, suppressive imbalance, and stereoacuity [13].

The main goals of the current project were to quantify suppressive imbalance and visual acuity before and after applying TMS to subjects with amblyopia, to subjects with visual asymmetry and to subjects with normal binocular vision, to evaluate whether Transcranial Magnetic Stimulation can change these parameters in these different populations.

2. Methods

All volunteers were recruited in community-based screenings and were submitted to an optometric standard evaluation, as well as an eye health condition evaluation, where all ocular structures were checked. All refractive errors were corrected to achieve the best-corrected visual acuity.

Inclusion criteria were dependent on clinical characteristics. Group A: patients with a difference of visual acuity eye asymmetry of one line; Group B: patients with a difference of at least two lines of visual acuity between the eyes; Group C: volunteers with visual acuity of 0,0 logMAR in both eyes. All subjects had the capacity to give informed consent to participate in the study.

Exclusion criteria included: incapacity to give an informed consent; ocular structures with physical abnormalities; previous history of brain injury and/or head trauma; neurological and psychiatric diseases; seizures; pregnancy; alcoholism; history of drug intake and presence of metallic implants in the head or torso.[14]

2.1 Volunteer Characterization

Our group of volunteers consisted of 35 young adults – 27 female and eight male – with a mean age of 25.4 years (± 7.9). In these 35 subjects, 6 presented an asymmetry between their eyes of one line of Visual Acuity (Asymmetric), 19 presented at least two lines of difference of visual Acuity (Amblyopes), and 10 showed normal binocular vision. Of the 25 asymmetric volunteers, 12 had right-eye dominance, while the other 13 had left-eye dominance.

Subjects presenting a difference of one line of visual acuity between their eyes were placed in group A – all were submitted to cTBS and five of them were also submitted to placebo stimulation after the mandatory washout period. Subjects presenting a difference of at least two lines of visual acuity between the eyes – amblyopia – were placed in group B and split into two subgroups: 11 were exposed to active stimulation, while the other eight were part of the placebo group. Group A subjects did not have any apparent cause that could justify the visual acuity loss in one of the eyes. In addition, these individuals did not have any specific complaints or symptoms.

Volunteers with normal binocular vision were placed in group C and split into two sub-groups: 5 volunteers were exposed to active stimulation, while the other 5 formed the placebo group.

Subjects of groups A, B and C that were actively stimulated were exposed to one session of continuous Theta Burst Stimulation (cTBS).

All participants in the study gave their written informed consent in accordance with the Helsinki Declaration, and data protection legislation was followed, in terms of anonymity. The study was approved by the Ethics Committee of the University of Beira Interior (Study nr. CE-UBI-Pp-2019-009).

2.2 Monitoring Parameters

The monitoring methodology followed was similar to that of previous studies carried out by our group (Supplement 1).[13] Visual acuity and suppressive imbalance were used as monitoring parameters. [13]

Suppressive Imbalance values are given by the following equation:

$$\text{SuppressiveImbalance} = \frac{\text{NeutralDensityFilter(Righteye)} - \text{NeutralDensityFilter(Lefteye)}}{\text{NeutralDensityFilter(Righteye)} + \text{NeutralDensityFilter(Lefteye)}}$$

1

Suppressive Imbalance can vary between – 1 and 1, where 0 represents a lack of ocular dominance; and 1 (or -1) represents full suppression of one of the eyes. The closer the value is to 0, the less pronounced is any ocular dominance between the eyes. A negative value shows the dominance of the left eye, while a positive value shows the dominance of the right eye.[15] Suppressive Imbalance represents the relative depth of the non – dominant eye suppression against the dominant eye; in other words, it allows the determination of the strength of one eye over the other.[16] This technique was also used to determine the dominant eye of each volunteer. [15, 16]

2.3 Transcranial Magnetic Stimulation

Magnetic stimulation took place in the Neurophysiology Laboratory of the Faculty of Health Sciences – University of Beira Interior, using a MagVenture MagPro1G3 X100 5.0.1 with a butterfly coil MCF-B70, following standard safety recommendations.[14] Only one session of continuous Theta-Burst Stimulation was performed on each volunteer. Phosphene induction was used to determine the exact occipital point in which stimulation was performed, placing the butterfly coil directly over the cortical area most susceptible to inducing phosphenes. An individualised intensity was used, consisting of 100% of the minimum intensity needed to evoke phosphenes (phosphene threshold intensity – PTI).[17–19] The procedure was initiated by placing the coil in the mid-inion region with a lateral-medial orientation, starting with 50% of the maximum device output. Using a 1 cm right lateralisation (right hemisphere stimulation), vertical steps of 1 cm (up to 3 cm) were used until uni- or bilateral phosphenes were described by each volunteer. Continuous Theta Burst Stimulation intensities over 80% maximum device output were not used (but lower intensities could be used if the volunteer did not tolerate the high intensities). In case no phosphenes could be detected, this was also the maximum intensity used.[17, 18, 20, 21] Stimulation was performed following the standard protocol described by Huang et al., using 600 stimuli sessions, delivered continuously with bursts of 3 pulses at 200ms intervals (5Hz), during 40 seconds.[9, 10] Placebo stimulation was performed by changing the position of the coil according to the previously described methodology (Supplement 1). [13] Both the volunteers and the researcher that evaluated the final data were naïve to the type of stimulation used (cTBS or placebo).

2.3 Statistical Analysis

Since normality assumptions were not fulfilled for all results, we used a non-parametric test – Wilcoxon signed rank Test, to compare results before and after Transcranial Magnetic Stimulation. For comparison between the three groups, the Kruskal Wallis test was used. For the comparison of independent samples, we used the Mann Whitney U Test to compare two different groups. Statistics were performed using IBM SPSS Statistics 25.0. P values ≤ 0.05 were regarded as significant.

3. Results

At the initial evaluation of our volunteers, there were no significant differences among groups regarding age (*Kruskal-Wallis test* = 0.63; $p = 0.73$) or gender (*Kruskal-Wallis test* = 0.44, $p = 0.80$).

3.1 Group A – Asymmetries

3.1.1 – Visual Acuity

Group A (presenting a difference of one line of acuity between both eyes) was formed by 6 subjects (5 females and 1 male) with ages between 20–24 years (with a mean age of $22.5 (\pm 1.5)$). Three of them showed a dominance of their right eye (DO3, DO4, DO6), and the remainder had dominance of their left eye (DO1, DO2, DO5). Five of them (DO2, DO3, DO4, DO5, DO6) were also submitted to placebo stimulation after the washout period (placebo group A).

For 5 of the 6 volunteers actively stimulated, improvement was seen in visual acuity after the continuous Theta Burst Stimulation session (Fig. 1). Volunteer number DO3 showed no changes in visual acuity with continuous Theta Burst Stimulation. The data presented in graph 1 concerns volunteers' non-dominant eyes subjected to cTBS. The placebo group showed no relevant changes after the placebo stimulation. This data is presented in table 2.

Mean visual acuity value for the non-dominant eye for this group, before continuous Theta Burst Stimulation, was $-0.02 \log\text{MAR} (\pm 0.07)$, and of $-0.1 \log\text{MAR} (\pm 0.09)$ after continuous Theta Burst Stimulation. Thus, we found significant differences between before and after stimulation (*Wilcoxon* = -2.02; $p = 0.04$) in group A actively stimulated volunteers.

Regarding placebo group A, there were no significant changes in visual acuity between before and after (*Wilcoxon* = -1.41; $p = 0.16$). Visual acuity results for placebo group A are presented in table 2 in order to a better understanding of data, due to the non-significant changes observed.

3.1.2 – Suppressive Imbalance

For Suppressive Imbalance, all volunteers from group A actively stimulated showed improvement after only one session of continuous Theta Burst Stimulation, which shown in Fig. 2, with the suppressive imbalance values closer to 0. The mean suppressive imbalance value before and after continuous Theta Burst Stimulation was $0.05 (\pm 0.08)$ and $0.02 (\pm 0.04)$, respectively. We found significant differences between before and after continuous Theta Burst Stimulation suppressive imbalance responses (*Wilcoxon* = -2.21; $p = 0.03$).

Concerning the placebo group A, there were no changes for suppressive imbalance for either the five volunteers after placebo stimulation (*Wilcoxon* < 0.0001, $p > 0.99$). Data are shown in table 3.

3.2 Group B – Amblyopes

3.2.1 – Visual Acuity

In this group, there were 19 volunteers (15 females and 4 male) with ages among 19–51 years, and a mean age of 28.0 (± 10.3) years. Nine of them showed right eye dominance, and the other ten showed left-eye dominance. They were split into two sub – groups: eight were submitted to a placebo stimulation (placebo group B) and eleven were submitted to an active stimulation.

There were clear visual acuity differences before and after continuous Theta Burst Stimulation in actively stimulated patients of group B (Fig. 3). Volunteer A9 showed no improvement, and volunteer A8 showed only slight improvement (these volunteers had in common the fact that they had never had amblyopia treatments before, and both were women). Mean visual acuity value before continuous Theta Burst Stimulation for the actively stimulated group was 0.34 logMAR (± 0.21), and 0.22 logMAR (± 0.17) after continuous Theta Burst Stimulation. Data presented in Fig. 3 shows volunteers' amblyopic eyes actively stimulated values.

Placebo group B showed no changes in visual acuity. Data is presented in table 4. Significant differences were seen in visual acuity between before and after continuous Theta Burst Stimulation (*Wilcoxon* = -2.82; $p = 0.01$), for the actively stimulated group. Contrariwise, no significant differences were found for visual acuity of the placebo group B, after placebo stimulation (*Wilcoxon* < 0.0001, $p > 0.99$).

Significant differences were found for visual acuity between the placebo group B when compared with the group B that was actively stimulated (Mann – Whitney = 4.50, $p > 0.00$).

3.2.2 – Suppressive Imbalance

For suppressive imbalance nine of the 11 volunteers in group B that were actively stimulated showed improvement in their suppressive imbalance, suggesting that, after continuous Theta Burst Stimulation, their eyes became more balanced. This can be observed in Fig. 4, with suppressive imbalance values coming closer to zero. Volunteers A13 and A14 did not show any apparent improvements in their suppressive imbalance; these volunteers had in common the fact that they showed the same level of asymmetry (exactly two lines of visual acuity difference between their eyes), the same amblyogenic factor (strabismus), and both had had occlusion as a child. Mean value of suppressive imbalance for the actively stimulated group before continuous Theta Burst Stimulation was 0.25 (± 0.17), which shifted to 0.12 (± 0.12) after continuous Theta Burst Stimulation, showing a significant difference between before and after continuous Theta Burst Stimulation (*Wilcoxon* = -2.67; $p = 0.01$).

For suppressive imbalance for placebo group B, no relevant changes were seen after placebo stimulation. Data is presented in Table 5 (*Wilcoxon* = -1.00; $p = 0.32$).

We found significant differences for suppressive imbalance between the placebo group B when compared with the group B that was actively stimulated (Mann – Whitney = 13.50, $p = 0.01$).

3.3 Group C – Normal binocular vision (NBV)

3.3.1 – Visual Acuity

Group C had 10 volunteers with normal binocular vision, which were split into 2 sub-groups: 5 were subjected to placebo stimulation (placebo group C) and 5 were subjected to active stimulation. All 10 subjects had symmetry between their eyes both in visual acuity and suppressive imbalance (Tables 2 and 3).

There were no changes in the visual acuity of either eye in the 5 volunteers with normal binocular vision that were subjected to a single session of continuous Theta Burst Stimulation. The visual acuity of placebo group C remained at its baseline values. As shown in Tables 2 and 3, the mean values for visual acuity before and after stimulation remained the same in both eyes, both for the group that was actively stimulated and for placebo group C, neither of which showed any relevant differences after Transcranial magnetic stimulation was applied.

We did not observe before-vs-after visual acuity differences in either the right (*Wilcoxon* = -1.00, $p = 0.32$) or left eyes (*Wilcoxon* = -1.00, $p = 0.32$) in the 5 volunteers who underwent placebo stimulation (placebo group C).

Concerning the 5 volunteers that were actively stimulated, right and left eye values before and after continuous Theta Burst Stimulation were not significantly different (*Wilcoxon* < 0.0001; $p > 0.99$).

No significant differences were found when the right and left eye values of the placebo group C were compared with right and left eye values of the group that was actively stimulated before and after stimulation (*Wilcoxon* = -0.153, $p = 0.88$ and *Wilcoxon* = -0.05, $p = 0.96$).

We found no significant differences for visual acuity between placebo group C when compared with the group C that was actively stimulated (Mann – Whitney = 10.00, $p = 0.32$).

Regarding suppressive imbalance, no changes were seen in the balance between eyes after a single session of continuous Theta Burst Stimulation in both the 5 stimulated and in the 5 placebo group C volunteers; subjects eyes remained completely balanced, just as they were before the stimulation (Wilcoxon < 0.0001, $p > 0.99$).

We did not find any significant differences for suppressive imbalance between the placebo group C when compared with the group C that was actively stimulated (Mann – Whitney = 12.50, $p = 1.00$).

3.4 – Comparison between the three groups (A,B,C)

3.4.1- Visual Acuity

Fifteen out of the 27 volunteers (55.6%) showed improvement in their visual acuity after one session of continuous Theta Burst Stimulation. Volunteers A3 and A9 showed no improvement in the control parameters, having maintained their visual acuity at the same level as before the session (Fig. 3). The 10 volunteers with normal binocular vision kept their baseline values of visual acuity after continuous Theta Burst Stimulation session. The mean value of visual acuity before the continuous Theta Burst Stimulation session was 0.07 logMAR (± 0.28), shifting to 0.01 logMAR (± 0.22) after continuous Theta Burst Stimulation. Given that the visual acuity values of the 10 volunteers with normal binocular vision (group C) were the same between their eyes, we used right eye values, to maintain homogeneity between subjects. Their respective values of visual acuity, before and after continuous Theta Burst Stimulation, are presented in Tables 6 and 7.

As we showed that there were no significant differences in the group of normal binocular vision (C), between the stimulated and the placebo group (Mann-Whitney = 8.50, $p = 0.40$), they were treated as only one group.

A Kruskal Wallis comparison between the three groups found significant differences between the group of amblyopes and the group of normal binocular vision (Kruskal-Wallis test = 13.03, $p < 0.0001$). In contrast, there were no significant differences between the asymmetric group and the group of amblyopes (Kruskal-Wallis = 3.85, $p = 0.96$) or between the asymmetric group and the normal binocular vision group (Kruskal-Wallis = -9.18, $p = 0.06$).

Regarding the comparisons between the three placebo groups (A,B,C) for visual acuity, no significant differences between all three groups were found (Kruskal – Wallis = 2.42, $p = 0.30$).

3.4.2- Suppressive imbalance

Fourteen subjects showed improvement in their suppressive imbalance after continuous Theta Burst Stimulation, with a reduction in this control parameter; their respective suppressive imbalance values were brought closer to zero, indicating an improvement in the balance between their eyes. Volunteers A13 and A14 did not show any improvement in this control parameter (Fig. 4). The 10 volunteers with normal binocular vision remained with their eyes balanced, just as they were before the continuous Theta Burst Stimulation session. Mean suppressive imbalance values were compared: mean before continuous Theta Burst Stimulation was of 0.17 (± 0.16), shifting to 0.05 (± 0.09) after continuous Theta Burst Stimulation.

There were no significant differences between the volunteers with normal binocular vision, who were actively stimulated, and those with a normal binocular vision which were in the placebo sub-group (Mann-Whitney = 1.93, $p > 0.99$); therefore, they were all considered in the same group (C). Kruskal-Wallis Test was used to make comparisons between the three groups. No significant differences were found between the asymmetric group and amblyopic group (Kruskal-Wallis = 1.92, $p > .99$). On the other hand, we found a significant difference between the asymmetric versus the group of normal binocular vision (Kruskal-Wallis = -10.67, $p = .02$) and between the amblyopic versus the group of normal binocular vision (Kruskal-Wallis = 12.59, $p < .0001$).

Regarding comparisons between the three placebo groups (A,B,C) for suppressive imbalance, there were no significant differences found between all three groups (Kruskal – Wallis = 1.25, $p = 0.54$).

The dominant eye in the asymmetric group was tested and evaluated before and after continuous Theta Burst Stimulation, as well as the dominant eye in the amblyopic group. No significant changes were found.

4. Discussion

We found significant enhancements to visual acuity and suppressive imbalance in non-dominant eyes when compared with the baseline values, after only one session of continuous Theta Burst Stimulation, in adults with visual acuity asymmetry between their eyes, suggesting that a better balance between the eyes of each volunteer was triggered. These improvements were not found in the groups submitted to placebo stimulation. In the group with normal binocular vision, control parameters remained the same after the cTBS session. Comparing the three groups after cTBS, a clear difference can be observed between the group of amblyopic subjects and the group with normal binocular vision, with amblyopes showing improvements in visual acuity and suppressive imbalance. On the other hand, we could not find differences between the group of amblyopes versus the asymmetric group and the group with normal binocular vision versus the asymmetric group, regarding visual acuity. No significant differences were found between asymmetric versus amblyopes concerning suppressive imbalance. Significant differences were found for suppressive imbalance between the group of asymmetric subjects versus the group with normal binocular vision. In what concerns comparisons between placebo groups A, B and C, no significant differences for visual acuity and suppressive imbalance were found.

Since there was a visual acuity difference of only one line between both eyes in group A, and at least two lines between both eyes in group B, we classified group A as asymmetric and group B as amblyope. Both groups A and B showed significant improvements to their visual acuity and suppressive imbalance after continuous Theta Burst Stimulation. Other authors have also studied the use of transcranial magnetic stimulation techniques in a group of amblyopes with positive results; however, the control parameter used by those authors was contrast sensitivity, which limits the possibility of comparison between their research and our results. [9, 19] Thompson et al. further stated that, through 10Hz repetitive Transcranial Magnetic Stimulation, it may be possible that other types of visual parameters could show more pronounced effects.[19] Although our work did not rely on 10Hz repetitive Transcranial Magnetic Stimulation, and it is difficult to draw relevant comparisons between our results and the results of the aforementioned authors, it remains the case that we observed significant improvements in visual acuity and suppressive imbalance of groups A and B after continuous Theta Burst Stimulation.

Placebo stimulation did not affect placebo groups A (asymmetries) and B (amblyopes). As shown in tables 2 and 4, placebo subjects did not present any significant change after placebo stimulation for visual acuity. Regarding the visual parameter suppressive imbalance, the same is true, and there were no significant changes after the placebo stimulation (Tables 3 and 5). Comparisons between actively stimulated group B with placebo group B showed unavoidable differences for visual acuity and suppressive imbalance, suggesting that it seems easier to produce changes in a system that is more imbalanced.

In group B patients actively stimulated (amblyopes), despite no statistical evidence, there seems to be a suggestion for better results when the amblyogenic factor was anisometropia, rather than strabismus (graph 3 and 4). This might explain why volunteer A9 did not show any improvement in visual acuity and showed only a slight enhancement in suppressive imbalance. This better result for anisometropic amblyopes also was described by S. Clavagnier et al., although the described sample was not homogeneous.[9]

Continuous Theta Burst Stimulation technique was also applied to a group of volunteers with balanced eyes (group C), to answer the following question: if a person's visual system is balanced, will continuous Theta Burst Stimulation induce changes to their system? This group was randomly split into two sub-groups: one subjected to placebo stimulation, and the other to active stimulation. No changes were found in either visual acuity or suppressive imbalance, after continuous Theta Burst Stimulation, in either sub-group. Comparison between group C (actively stimulated) and placebo group C also showed no significant differences for visual acuity and suppressive imbalance. Therefore, it seems that, if a visual system is already balanced, continuous Theta Burst Stimulation is not able to significantly change the visual system's response; it is, therefore, reasonable to presume that continuous Theta Burst Stimulation cannot influence a system which is already symmetric, for better or for worse. Thompson et al. tested 10Hz repetitive Transcranial Magnetic Stimulation in 5 patients with normal binocular vision and found that, immediately after stimulation, their contrast sensitivity (Gabor patches) had improved.[19] Waterston et al. applied 1Hz stimulation to 5 normal subjects, and 40-second theta-burst stimulation to another 6 subjects in the primary visual cortex, and found that, after both types of stimulation, some of the volunteers had increased their capacity to discriminate Gabor patterns.[22] However, the results of our research are not in agreement with those of Thompson et al. and Waterston et al. It must be taken into consideration that we evaluated different control parameters – visual acuity and suppressive imbalance, as opposed to contrasting sensitivity or the capacity to discriminate Gabor patterns – and, in some cases, the type of stimulation that we applied was different as well. This makes it unfeasible to draw a direct comparison between our results and the results mentioned above.

We observed that continuous Theta Burst Stimulation affected groups of asymmetric and amblyopic subjects more than the group with normal binocular vision, suggesting that continuous Theta Burst Stimulation can more easily influence an unbalanced visual system. Authors like S. Clavagnier et al. also studied amblyopes with continuous Theta Burst Stimulation, presenting grating stimuli to the fellow eye to bias the effects of continuous Theta Burst Stimulation in the neural population, thereby facilitating the amblyopic eye's function. Clavagnier suggested that active neural populations are not susceptible to continuous Theta Burst Stimulation,[9] and this may explain why groups A and B showed improvement with continuous Theta Burst Stimulation, while group C did not.

D. van Versendaal and C. N. Levelt [23] suggest that inhibitory interneurons are an important regulator of plasticity, both in the critical period of childhood/adolescence and adulthood, and that they define the development period. These authors suggest that if ocular dominance plasticity is misdirected during this critical period, this can lead to amblyopia.[23] The human brain has a great capacity of adaptation to constantly changing environments, through the formation and adaptation of neuronal circuits. Even though the period of greater neuronal plasticity ends after a certain age, all human beings preserve some neuronal plasticity, which allows recovery from injuries or the capacity to learn.[23, 24] This may explain why even after the major period of neuronal plasticity has ended, it was possible to make changes to the visual system of our volunteers, after applying the continuous Theta Burst Stimulation technique. It is known that transcranial magnetic stimulation can change the neuronal excitability of the stimulated area of the brain. Continuous Theta Burst Stimulation is a variant of the traditional Transcranial Magnetic Stimulation technique, which can alter neuronal excitability faster (1-3min).[25]

Our results need to be interpreted with caution because of the sample size of our groups, but the effects seen are significant. In conclusion, our results suggest that continuous Theta Burst Stimulation can influence the adult neuronal visual response when there is an imbalance between the eyes, possibly by influencing cortical excitability. This suggests that continuous Theta Burst Stimulation can be a useful tool when trying to correct established neuronal imbalances that may be related to amblyopia. When a visual system is already balanced, it is apparent that the continuous Theta Burst Stimulation technique will not have any relevant influence; this allows us to state that the application of continuous Theta Burst Stimulation in a group of volunteers with normal binocular vision is safe, as it showed no negative influence on the evaluated visual parameters.

Declarations

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Tables

Table 1
Characteristics of the thirty - five volunteers and stimulation details before cTBS

ID	Age	Gender	History of Treatment	Refractive Error (OD/OS)	LogMAR Visual Acuity (OD)	LogMAR Visual Acuity (OS)	Dominant Eye	Ambliogenic Factor	Intensity (MDO)	Phosphenes
D01	23	Female	-	-0.50X60 OD -0.50 OS	-0.08	-0.18	OS	-	60%	Yes
D02	21	Female	-	-0.50X120 OD -0.25X160 OS	0.08	0.0	OS	-	55%	Yes
D03	24	Female	-	-2.50/-1.25X10 -0.75/-3.00X180	-0.1	0.0	OD	-	65%	No
D04	20	Female	-	-7.00 OD -8.50/-1.25X85 OS	-0.02	0.1	OD	-	60%	Yes
D05	22	Male	-	-1.25/-0.25X30 OD -0.25 OS	-0.04	-0.12	OS	-	50%	Yes
D06	23	Female	-	-0.25/-1.00X150 OD -0.75/-0.5X20 OS	-0.18	-0.06	OD	-	50%	Yes
A7	19	Female	No previous Treatment	-10/-1.75X90 OD -4.50/-0.25X10 OS	0.3	-0.1	OS	AM	80%	No
A8	20	Female	No previous Treatment	+1.00/-1.25X85 OD -0.50/-0.75X30 OS	0.14	-0.12	OS	AM/ST (18 ET)	70%	Yes
A9	21	Female	No previous Treatment	Plano OD Plano OS	-0.04	0.26	OD	M	60%	Yes
A10	20	Female	No previous Treatment	+0.75/-3.75X5 OD Plano OS	0.5	-0.1	OS	AM	55%	Yes
A11	24	Female	First detected age 5 Patching for 1 year	-7.00 OD -7.00 OS	0.0	0.48	OD	I	80%	Yes
A12	22	Male	No previous Treatment	+2.25/-2.00X140 OD +3.00/-2.50X60 OS	0.06	0.64	OD	ST (6 ET)	80%	Yes
A13	24	Female	First detected age 6 Patching for 1 year	Plano OD Plano OS	0.1	-0.1	OS	ST (14 ET)	55%	Yes
A14	24	Male	First detected age 3 Patching for 2 years	-1.00/-1.25X105 OD -0.75/-1.00X15 OS	-0.1	0.1	OD	ST (6 ET)	50%	Yes
A15	44	Female	No previous Treatment	+5.25 OD +6.50/-1.00X155 OS	-0.06	0.32	OD	AM/ST (6 ET)	55%	Yes

ID	Age	Gender	History of Treatment	Refractive Error (OD/OS)	LogMAR Visual Acuity (OD)	LogMAR Visual Acuity (OS)	Dominant Eye	Ambliogenic Factor	Intensity (MDO)	Phosphenes
A16	41	Female	First detected age 5 Patching for 1 year	+ 1.25/-0.25X175 OD + 3.00/-0.75X170 OS	0.7	-0.08	OS	AM	50%	No
A17	45	Female	No previous Treatment	-6.00/-1.25X180 OD -5.00/-0.75X30 OS	0.22	0.0	OD	AM	55%	Yes
AS1	21	Female	No previous Treatment	Plano OD Plano OS	-0,1	0,2	OD	M	30%	Yes
AS2	22	Female	No previous Treatment	-11 OD -9,50 OS	0,28	0,0	OS	AM	25%	Yes
AS3	24	Male	No previous Treatment	Plano OD Plano OS	0,58	0,1	OS	ST (20 XT)	25%	Yes
AS4	20	Female	No previous Treatment	-3.00/-0.75X180 OD -5,25/-0,75X180 OS	0,0	0,2	OD	AM	30%	Yes
AS5	21	Male	No previous Treatment	Plano OD Plano OS	-0,1	0,16	OS	ST (10 XT)	35%	Yes
AS6	51	Female	No previous Treatment	-1,50/-2,75X110 OD + 0,75/-0,25X130 OS	0,14	-0,04	OS	AM	25%	Yes
AS7	39	Female	No previous Treatment	-10,50/-1,25X90 OD -1,50/-0,75X90 OS	0,2	-0,1	OS	AM	25%	Yes
AS8	29	Female	First detected age 4 Surgery at age 5	-0,50/-3,75X160 OD -0,75/-4,75X175 OS	-0,1	0,2	OD	AM/ST (6 XT)	25%	Yes
NP1	22	Female	-	-1.00 OD -0.5X160 OS	-0.2	-0.2	None	-	40%	No
NS2	22	Female	-	-1.75/-0.25X30 OD -1.00 OS	-0.08	-0.1	None	-	30%	Yes
NS3	22	Female	-	-8.50 OD -8.00 OS	-0.1	-0.1	None	-	15%	Yes
NS4	21	Female	-	-	-0.1	-0.1	None	-	40%	Yes
NS5	23	Female	-	-3.00/-0.50X90 OD -2.00 OS	-0.28	-0.3	None	-	35%	Yes
NP6	21	Female	-	-	-0.16	-0.16	None	-	20%	Yes
NP7	27	Male	-	-	-0.3	-0.3	None	-	30%	No

ID	Age	Gender	History of Treatment	Refractive Error (OD/OS)	LogMAR Visual Acuity (OD)	LogMAR Visual Acuity (OS)	Dominant Eye	Amblyogenic Factor	Intensity (MDO)	Phosphenes
NS8	25	Male	-	-1.75/-0.50X130 OD -1.50/-0.50X40 OS	-0.3	-0.3	None	-	50%	Yes
NP9	23	Female	-	+ 3.50/-1.75X20 OD + 3.75/-2.25X180 OS	-0.12	-0.1	None	-	40%	No
NP10	23	Male	-	-	-0.14	-0.16	None	-	30%	No

AM = Anisometropia, AS = Anisometropia and Strabismus, M = Microstrabismus, I = Isometropia, ST = Strabismus. ET = Esotropia, XT = Exotropia, DO = Group with an asymmetry, A = group of amblyopes, NS = Group with normal binocular vision - stimulated; NP = Group with normal binocular vision – sham, MDO = Maximal Device Output

Table 2
Visual Acuity of the non – dominant eye before and after stimulation (placebo group A)

	Visual Acuity (Before Placebo Stimulation)	Visual Acuity (After Placebo Stimulation)
DO2	0.06	0.06
DO3	0.00	0
DO4	0.10	0.06
DO5	-0.02	-0.06
DO6	-0.12	-0.12
Average	0.01	0.01
STDEV	0.08	0.08

Table 3
Suppressive Imbalance before and after stimulation (placebo group A)

	Suppressive Imbalance (Before Placebo Stimulation)	Suppressive Imbalance (After Placebo Stimulation)
DO2	-0.10	-0.10
DO3	0.08	0.08
DO4	0.05	0.05
DO5	-0.08	-0.08
DO6	0.09	0.09
Average	0.08	0.08
STDEV	0.02	0.02

Table 4
Visual Acuity of the amblyopic eye before and after stimulation (placebo group B)

	Visual Acuity (Before Placebo Stimulation)	Visual Acuity (After Placebo Stimulation)
AS1	0.20	0.20
AS2	0.28	0.30
AS3	0.58	0.56
AS4	0.20	0.20
AS5	0.16	0.16
AS6	0.14	0.14
AS7	0.20	0.20
AS8	0.20	0.20
Average	0.25	0.25
STDEV	0.14	0.14

Table 5
Suppressive Imbalance before and after stimulation (placebo group B)

	Suppressive Imbalance (Before Placebo Stimulation)	Suppressive Imbalance (After Placebo Stimulation)
AS1	0.13	0.13
AS2	-0.10	0.00
AS3	-1.00	-1.00
AS4	0.17	0.17
AS5	0.33	0.33
AS6	-0.03	-0.03
AS7	-0.04	-0.04
AS8	0.03	0.03
Average	0.23	0.22
STDEV	0.33	0.34

Table 6
Values for visual acuity for the volunteers with normal binocular vision submitted to placebo stimulation

	Visual Acuity (Before Placebo Stimulation)		Visual Acuity (After Placebo Stimulation)	
	OD	OS	OD	OS
NP1	-0.2	-0.2	-0.2	-0.2
NP6	-0.16	-0.16	-0.18	-0.18
NP7	-0.3	-0.3	-0.3	-0.3
NP9	-0.12	-0.1	-0.12	-0.1
NP10	-0.14	-0.16	-0.14	-0.16
Average	-0.184	-0.184	-0.188	-0.188
STDEV	0.071	0.074	0.070	0.073

OD – Right eye; OS – Left eye

Table 7
Values for visual acuity before and after cTBS for volunteers with normal binocular vision

	Visual Acuity (Before cTBS)		Visual Acuity (After cTBS)	
	OD	OS	OD	OS
NS2	-0.08	-0.1	-0.08	-0.1
NS3	-0.1	-0.1	-0.1	-0.1
NS4	-0.1	-0.1	-0.1	-0.1
NS5	-0.28	-0.3	-0.28	-0.3
NS8	-0.3	-0.3	-0.3	-0.3
Average	-0.172	-0.18	-0.172	-0.18
STDEV	0.108	0.109	0.108	0.109

OD – Right eye; OS – Left eye

Table 8
Individual group data and group comparisons for groups actively stimulated

	Difference of Means VA		Difference of Means SI	
	(Mean ± SD)	p-value	(Mean ± SD)	p-value
A	0.077 ± 0.061	.04*	0.055 ± 0.021	0.03*
B	0.121 ± 0.079	.01*	0.122 ± 0.145	0.01*
C	0.002 ± 0.006	> .99*	0.000 ± 0.000	> .99*
A vs B		.96**		> .99**
A vs C		.06**		.02**
B vs C		< .0001**		< .0001**

A: Asymmetrics; B: Amblyopes; C: Normal Binocular Vision. *With Wilcoxon Test. **With Kruskal-Wallis Test.

Figures

Figure 1

Visual Acuity of the non dominant eye before and after continuous Theta Burst Stimulation in group A. Average $\pm$ SD (Before cTBS) = -0.02 ± 0.07 ; Average $\pm$ SD (After cTBS) = -0.10 ± 0.09

Figure 2

Suppressive Imbalance before and after continuous Theta Burst Stimulation in group A. Average $\pm$ SD (Before cTBS) = 0.07 ± 0.04 ; Average $\pm$ SD (After cTBS) = 0.02 ± 0.03

Figure 3

Visual Acuity of the amblyopic eye before and after continuous Theta Burst Stimulation in group B. Average $\pm$ SD (Before cTBS) = 0.34 ± 0.21 ; Average $\pm$ SD (After cTBS) = 0.22 ± 0.17

Figure 4

Suppressive Imbalance before and after continuous Theta Burst Stimulation in group B. Average $\pm$ SD (Before cTBS) = 0.25 ± 0.17 ; Average $\pm$ SD (After cTBS) = 0.12 ± 0.12

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