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Effects of repetitive transcranial magnetic stimulation (rTMS) on Creativity

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Dedicatória

Gostava de dedicar este trabalho à minha família, em especial à minha Mãe, que sempre me apoiou ao longo da minha vida em todos os desafios, obstáculos e conquistas.

Ao meu Namorado, que me ouviu diariamente a reclamar das dificuldades e me deu força para continuar e vencer.

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A todos, um muito, muito obrigada.

Abstract

Repetitive Transcranial Magnetic Stimulation (rTMS) is based on electromagnetic induction, where an electromagnetic current is created on a specific and desired brain location. This can stimulate those neurons and change the synapse's bonds, rearranging them. This technique has been used in peripheral neural system and brain tissue as a form of treatment to both Neurologic and Psychiatric diseases.
However, the full range of applications of this technique is still being explored, so our purpose is to investigate whether it can or cannot have a positive effect on fostering creativity.
If proven effective, this can open a variety of opportunity windows concerning future research, in order to empower people to think "out of the box" and to innovate in problem solving, under an increasingly demanding and creative world.

Key Words

rTMS; Creativity; Normal subjects.

Resumo Alargado

A Estimulação Magnética Transcraniana Repetitiva (rTMS) é baseada na indução electromagnética, em que uma corrente eléctrica é criada através de campos magnéticos e direccionada para um local cerebral desejado. Isto irá estimular os neurónios e mudar as suas interligações, criando e/ou reforçando as sinapses.

Esta técnica tem sido usada no sistema nervoso periférico e central, como forma de tratamento para doenças neurológicas e psiquiátricas.

No entanto, novas aplicações para esta técnica ainda estão a ser exploradas.

O objectivo desta investigação consiste em perceber se a rTMS poderá ou não ter um efeito positivo na indução da criatividade.

Desta forma, no âmbito da investigação "Avaliação neurofisiológica em indivíduos saudáveis", subordinada ao tema "Alterações da criatividade induzidas por estimulação magnética transcraniana repetitiva em indivíduos normais" aprovada pela Comissão de Ética da FCS/UBI (Projecto 2/2011), foram recrutados alguns voluntários, alunos de Medicina da FCS-UBI, maioritariamente do primeiro ano para efeitos de realização da experiência.

Através de convite via Facebook, reuniu-se uma amostra de 24 voluntários, dos quais 11 são do sexo masculino e 13 do sexo feminino, os quais foram então divididos em dois grupos: o Grupo para Estimulação rTMS (E) com 6 homens e 6 mulheres; e o Grupo para Placebo (P) com 5 homens e 7 mulheres. A média de idades dos testados foi de 18 anos e todos receberam e assinaram um documento de Consentimento Informado e garantiram a presença dos Critérios de Inclusão: ser maior de idade; ser dextro; ser aluno de Medicina. Negaram, pelo contrário, a presença de Critérios de Exclusão: presença de elementos de metal na cabeça (excluindo região oral); diagnóstico de epilepsia ou com história pessoal de uma ou mais convulsões; história de patologia cerebral de etiologia vascular, tumoral, infecciosa ou metabólica sem controlo com medicação antiepiléptica; presença de Pacemakers ou linhas intracardíacas; doença cardíaca grave; pressão intracraniana aumentada (por exemplo: pós enfarte ou trauma; mulheres em idade concepcional sem certezas de ausência de gravidez e/ou grávidas; uso de antidepressivos tricíclicos, neurolépticos e outras drogas que diminuam o limiar convulsivo, sem concomitante toma de medicação anticonvulsiva; antecedentes de alcoolismo, e ingestão de álcool nas 24 horas previamente à rTMS ou privação de sono na noite anterior à rTMS.

A criatividade basal dos participantes foi avaliada através de uma adaptação do Teste de Torrance, em que incluímos 3 provas: 1 de escrita, com a apresentação de uma situação hipotética – "És um feiticeiro! Diz o máximo de actividades que poderias fazer com os teus novos poderes."; e 2 testes com figuras para criação de imagens, dos quais um com Losangos para desenhar e atribuir um título, e outro com uma Sequência de tarefas também para desenharem.

Devido aos efeitos da rTMS terem uma curta duração, de apenas 30 minutos, teríamos de conseguir um sistema de avaliação, um pós-teste, que permitisse a sua conclusão dentro do tempo disponível, e seria impossível utilizar o teste de Torrance completo, pelo que tivemos a necessidade de criar esta adaptação mais curta. Como pós-teste, voltamos, então, a usar as 3 provas iniciais.

A estimulação foi feita com a técnica Theta Burst Stimulation (TBS) na forma intermitente (iTBS), com o estimulador magnético MagVenture MagPro® G3 X100 5.0.1 e bobine tipo borboleta, em que após detetar o hotspot sobre a área motora primária M1 à direita e identificação do limiar motor activo (LMA), se aplicou a estimulação TBS 5 cm anteriormente a esta área, sobre o córtex pré-frontal dorsolateral direito (CPFDLD), usando intensidades de 80% do LMA. No grupo com estimulação ativa, a estimulação iTBS compreendeu séries agrupadas de três pulsos a 50Hz, aplicadas de forma repetitiva em intervalos de 200ms, sendo estas aplicadas em surtos com duração de 2 segundos, com intervalos de 8 segundos sem estimulação, totalizando um período de estimulação de 600 pulsos. No grupo placebo, utilizou-se a mesma bobine e os mesmos protocolos iniciais, sendo a bobine colocada num ângulo perpendicular sobre o crânio do voluntário e reduzindo a intensidade para 50% LMA de forma a não induzir estimulação cerebral.

Os participantes que se encontravam numa sala afastada, nunca estrariam em contacto com os colegas já submetidos ao teste (que se encontravam no laboratório), pelo que não houve risco de contaminação dos dados.

Para avaliação da criatividade está estudado um conjunto de critérios:

1) Fluência: o número de ideias diferentes e lógicas apresentadas, que testa a capacidade de produzir alternativas;

2) Flexibilidade: o número de categorias em que as respostas se inserem, que testa a habilidade de produzir ideias com uma perspectiva ampla;

3) Originalidade: o número de ideias estatisticamente raras, que testa a habilidade de produzir ideias inovadoras e diferentes das outras pessoas, nas quais se atribuem 0 pontos às ideias comuns, e 1 ponto às restantes, de acordo com a lista de ideias Originais preparadas pelo avaliador; e

4) Elaboração: testa a habilidade de criar ideias pormenorizadas e detalhadas.

No entanto, para este trabalho de Dissertação, apenas foi avaliada a fluência e os outros parâmetros não foram contabilizados.

Apesar do grupo ser pequeno, composto por 24 elementos, e de termos optado por apenas avaliar a Fluência, obtivemos resultados muito promissores.

Com o Teste Wilcoxon, foi obtida uma similaridade nos resultados absolutos entre o grupo Estimulado e o grupo Placebo, tanto nos pré como pós testes, o que poderia transmitir que o rTMS não seria superior ao Placebo no aumento das respostas. No entanto, ao compararmos os grupos em termos de aumento, manutenção ou diminuição no número de respostas entre o Pré e o Pós-Teste em todas as provas (Teste A, Losangos, Sequência) revelou-se uma diferença significativa, sendo que o grupo submetido a rTMS mostrou um número significativo de voluntários que aumentou as suas respostas no pós-teste. ($p=0.005$; Teste Chi-Quadrado)

Assim, os resultados obtidos nesta investigação permitiram verificar que a rTMS surte um efeito positivo na criatividade, sendo que os resultados obtidos com a rTMS foram superiores aos obtidos com o grupo Placebo.

É de sublinhar que esta investigação se reveste de uma natureza pioneira, não tendo sido identificadas referências prévias na literatura que pudessem funcionar como âncora teórica ou até mesmo empírica. Assim, a presente investigação que versa a associação entre a rTMS e a criatividade, poderá servir de base ao desenvolvimento de futuros estudos conducentes à revelação de novas evidências. Esta investigação, além de ter demonstrado resultados positivos, servirá de base à produção futura de novos conhecimentos científicos, bem como à concretização de novas tentativas no sentido de melhor compreender o mistério que é o cérebro humano.

Palavras-chave

rTMS; Criatividade; Indivíduos normais.

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Lista de Acrónimos

AAS – Anabolic Androgenic Steroids

ADHD - Attention deficit-hyperactivity disorder

AMT – Active Motor Threshold

CPFDLD – Córtex pré-frontal dorsolateral direito

dACC - Dorsal anterior cingulate cortex

DLPFC - dorsolateral pre-frontal cortex

EEG – Electroencephalography

FCS – Faculdade Ciências da Saúde

fMRI - Functional magnetic resonance imaging

Ho – Null hypothesis

Hz – Hertz

iTBS – Theta Burst Stimulation at intermitent form

LC – Locus coeruleus

LMA – Limiar motor active

LSD – Lysergsäurediethylamid (dietilamida do ácido lisérgico)

NE – Norepinephrine

PFC – Prefrontal cortex

RDLPFC - Right dorsolateral pre-frontal cortex

rTMS - Repetitive transcranial magnetic stimulation

TBS – Theta Burst Stimulation

TTCT - Torrance Tests of Creative Thinking

UBI – Universidade da Beira Interior

Introduction

Creativity. What would the world be without creative people? How would we live without the Lamp, the Wheel, the Antibiotics, the X-Ray?
All of these inventions came from the brilliant minds of divergent thinkers, people who loved to take risks, to try, to discover. People who weren't afraid of failure or being different. So what makes them like this? What if we could enhance naturally creative people? Or even artificially induce creativity?
Memory, attention and creativity represent three different cognitive domains, which are interconnected and contribute to the "mental performance" of an individual. Memory is the ability to remember events or learned material; Attention is the cognitive process of selectively concentrating on one aspect while ignoring distracters; and Creativity is the ability to create things or ideas which are original and possess a social usefulness. [1]

Creativity is a complex and problematic issue, which is related to the creation of something new, original and unexpected, such as an idea, artistic work, painting or musical composition, a solution to a problem or an invention. [2,3] It plays a crucial role in our cultural life and is essential to the development and advancement of human civilization. [2,4] That's why there is an increasing interest in the potential of fostering creativity through education and formal or informal training, and brain stimulation. [2]

Stimulating creativity has great significance for both individual success and social improvement. Although increasing creative capacity has been confirmed to be possible and effective at the behavioral level, few longitudinal studies have examined the extent to which the brain function and structure underlying creativity are plastic. [5] In order to do so, it is very important to understand the neuronal circuits, the neurotransmitters and molecular events underlined. [6]

Neuroscientific explanations of creativity were initially focused on hemispheric asymmetry. Bogen and Bogen (1969), claimed that a major obstacle to high creativity consisted in the left hemisphere inhibition on right hemisphere functions: this hemispheric lateralization model was created upon studies of patients who had had corpus callosotomies for epilepsy. [6] Later, Martindale (1999) found that creative subjects had more activity in the right than in the left hemisphere (parietal-temporal EEG), as opposed to low creative people on a creative task. [6]
However, recent advances in the field of cognitive neuroscience have identified distinct brain circuits involved in creativity. [6]

Creativity requires cognitive abilities, such as working memory, sustained attention and cognitive flexibility. [6] These abilities are typically associated with ***the prefrontal cortex***, which contributes to highly integrative computations to the conscious experience, and enables novel combinations of information to be recognized and applied to art and science. [6]

Beyond the role of the prefrontal cortex, ***the parietal lobes*** and a multitude of cortical and subcortical brain regions like ***the frontal lobes*** and the ***nucleus accumbens*** have been identified as intervenients of artistic works, such as paintings, drawings, or sculptures. [6]

The dorsolateral prefrontal cortex helps with planning and organization of the artistic effort, while ***the cingulate cortex*** modulates drive and emotion. [6]
Lastly, it has been recently reported that creative drive is controlled through interactions among ***temporal lobes***, ***frontal lobes and limbic system***. [6]
In particular, creative drive increases with dysfunctions of the temporal lobe and increasing dopaminergic tone, whereas creative block increases with deficits in frontal lobe activity, or decreasing dopaminergic tone.

So, creativity relies on the ***integrity of the prefrontal cortex (PFC)***, the brain area responsible for behavioral adaptation and highly integrated mental functions. [7] This was shown by functional neuroimaging data, showing that the PFC is playing an important role in the cognitive processes involved in creativity, as working memory, attention, planning, cognitive flexibility, and abstract thinking. So, neurological diseases in the PFC regions or their connections affect this cognitive creativity processes. [7]

More so, as the functions of the PFC are associated with control in behavioral, affective, social and cognitive spheres, an inhibition of this control, as under relaxed cognitive state, drunken states, or hypofrontality, the bottom-up information will be less filtered, causing a breaking away from rule-based thinking and favoring creativity. [7]

The PFC cannot be seen as a unitary structure, but a group of structures, as they play different roles. The lateral and ventral portions of the PFC are responsible for rule-based thinking, and the medial PFC is a default-system involved in associative thinking, spontaneous cognition and mind wandering. [7]
The rostral PFC acts as a switch between these two modes, either rule-based by the lateral part, or spontaneous-based by the medial part. However, for creativity to occur, a well-balanced contribution of the two modes of thinking is necessary. [7] Therefore, if a lesion affects the rostromedial PCT, a decrease in originality and creativity will occur. [7] However in hypofrontality, a disinhibition of the lateral and ventral PFC occurs, enhancing creativity and originality, mimicking the medial PFC actions. [7]

Creativity is also, associated with alpha activity in frontal brain areas. Alpha activity increases with internal processing demands and is involved in inhibitory top-down control, which is an important requirement for creative ideation. [8] Particularly, the generation of a creative idea is associated with increased oscillation power in the alpha band in prefrontal and parietal cortical areas and it was observed that highly creative people have a more pronounced rising in alpha activity, while creating original ideas, and while performing demanding creative tasks. [8] Alpha oscillations reflect a state of reduced mental activity. [8]

Thus, alpha power increase in the frontal cortex was hypothesized to reflect a hypoactivity of this brain area or "hypofrontality" which leads to higher creativity. [8]

Creativity varies within different people, being some more creative than others. [2] Mood represents a transient state of mind that has influence on the creative process. [9,10] Thus, acting as a facilitator, (e.g. the positive affect), producing more fluent and original responses, and revealing greater cognitive flexibility, towards implementation efficiency and creative problem solving [11]; or as an inhibitor, (e.g. the negative affect), producing the opposite. [3,12,13]

The creative process embraces four steps: (i) preparation; (ii) incubation; (iii) illumination; and (iv) verification. [14,15] It requires intelligence, skills and specific knowledge about the subject. [14] It is also possible that some people, more creative, have specific brain connections, which promotes creativity. [14] For the Creative Innovation (incubation and illumination steps) [16] it's necessary to think "out of the box" (divergent thinking), to face a constant need to experience something new (novelty seeking behavior), to reveal an absence of fear of failure (suppression of latent inhibition) and some quirkiness (subtle frontal dysfunction). [14]
Actually, the association between mental illness and creativity is very well recognized in medical and non-medical literature and a positive correlation between psychopathology and creativity has been asserted for schizophrenia, bipolar disorder, dementia, and depression. [6]

Creativity is dependent on brain connectivity, and creative innovation often happens during low arousal states, as in the shower or nearly before sleeping. [14] Many scientists have mentioned experiencing complex scientific problem solving during sleep, falling asleep or awakening, as stated by Ramanujam, Kekule and Crick. [14] It was also reported that many of the most creative writers, composers and painters have suffered from depression, as Goethe, Van Gogh and Picasso. [14, 17]

This suggests a role of neurotransmitters. [14] Two catecholamines have been associated: dopamine and norepinephrine (NE). NE is a product of dopamine metabolism, and is reduced both during sleep, relaxation and depression. [14]

So, a lower level of NE is associated with higher creativity. Following this line of thought, situations with higher NE levels will lower creativity, and this is, in fact observed during stress and "flight or fight" activities. [14,18]
The locus coeruleus (LC) is the major source of NE output to the cortex. [14] Higher LC activity will increase NE levels for monitoring and attending external stimuli and increasing behavioral responsiveness to unexpected and novel stimuli. [14].Low LC activity will reduce the NE levels enhancing creativity cognition and outputs.
The frontal lobes exert an inhibitory influence on the LC. However this occurs following a relationship represented by an inverted U-shaped curve. [14] Thus, at low levels of frontal disinhibition LC activity diminishes, lowering the NE output and facilitating creative thinking. For its turn, at higher levels of frontal disinhibition the LC activity is enhanced, by rising NE output and decreasing creativity. [14]

In addition, drugs such as alcohol and opium that lower inhibition and attentional focus, have a longstanding reputation of fostering creative inspiration in the arts, for instance, artists who worked during LSD, mescalin or psilocybin intoxication often refer to feelings of either being "possessed" or "liberated" and reported significant improvements in creativity. [6]

With the advances on pharmaceuticals, there was an increased prescription of drugs for treating mental illnesses, which previously, would not receive chemical treatment. This means that many of the disorders that are classically associated with genius and creativity are being eradicated by psychiatric treatment. [6] As an example, ritalin and other drugs for attention-deficit hyperactivity disorder have helped many children to improve their focus and behavior. [6]

The increasing interest on "smart drugs" (or Nootropics) is based on the concept that some medications available to patients with mental disorders may have a positive effect also in healthy people. [6,19)
These nootropics, like Methylphenidate, are being widely used, regardless of the potential risk they carry and can be compared to the use of Anabolic Androgenic Steroids (AAS) in sports. [19] Methylphenidate is a psychostimulant and is one of the most commonly prescribed drugs for the treatment of Attention deficit-hyperactivity disorder (ADHD), however it is also abused by teenagers, young adults, and students seeking for cognitive enhancement. [19]
It acts as a dopamine-norepinephrine reuptake inhibitor, by binding and blocking dopamine and norepinephrine transporters, which reuptake them within the presynaptic neuron after

their release; however it is most effective in dopamine-modulation. [19] So, it is possible that, as acting in dopamine-modulation, it can affect creativity in subjects. [19]

Dopamine is able to induce low latent inhibition – a behavioral index of the ability to settle into sensations, which has been demonstrated to be a characteristic of creative individuals

with high intelligence. In addition, it may also play a role in creative discovery through its effect on novelty-seeking, and acts on the limbic system to increase creative drive. [6]

To test creativity, Torrance Tests of Creative Thinking (TTCT) can be used. [20] They are the most often studied and analyzed tests, validated to the Portuguese population and also very easy to perform, and do not take much time to be administrated. [2,21,22]

TTCT evaluation system relies on: [2]

a) Fluency: the number of relevant responses to the questions, testing the ability to produce and consider many alternatives;
b) Flexibility: total number of categories that answers are assigned based on a criteria table, showing the ability to produce responses from a wide perspective;
c) Originality: number of statistically infrequent ideas, showing the ability to produce ideas that differ from others, scoring the most common ideas as 0 points, and the others as 1 point, according to an originality list prepared by the examiner;
d) Elaboration: ability to produce ideas in detail. [23,24]

However, for the purpose of this study, only Fluency was evaluated and the other criteria will not be discussed.

Repetitive Transcranial Magnetic Stimulation (rTMS) is based on electromagnetic induction, where an electromagnetic current is created on a specific and desired brain location, without physical contact. [25-28] This will stimulate those neurons and change the synapse's bonds, rearranging them. Although there might be some concerns about safety and side effects, many scholars and clinicians subscribe to this technology, and it has been used in peripheral neural system and brain tissue as a form of treatment to both neurologic and psychiatric diseases, such as epilepsy, chronic pain, motor disorders and so on. [25,26,28] Although the full range of applications of this procedure is still being studied, the future of the technique seems to be promising and challenging. [25,26]

Following this line of reasoning and supported on all of the literature cited above, we aimed to identify the effects of Repetitive Transcranial Magnetic Stimulation (rTMS) on creativity, considering the following null hypothesis (*Ho*):

Ho: A stimuli of 3.5 mn of excitatory rTMS will not change the creative capacity of the subject.

And the alternative hypothesis, as follows:

H1: A stimuli of 3.5 mn of excitatory rTMS will change the creative capacity of the subject.

Methods and Materials

Study Outline

This experiment was developed in the scope of the project titled: "Neurophysiologic evaluation in healthy subjects"; which was previously approved by the Ethics Commission of FCS/UBI (Project 2/2011).

Thus, 24 volunteers were selected from a group of medical students that replied to an invitation distributed through Facebook. It was then explained how the study would be conducted. The average age of the subjects was 18 years old, from which 11 were males and 13 were females.
Afterwards, the group of students was divided in 2 smaller groups: the Stimulated one (E); and the Sham one (P); undergoing rTMS or placebo, respectively.
In addition, 12 volunteers (6 males and 6 females) took part of the Stimulation Group. At the Sham Group, 12 volunteers were also considered (5 males and 7 females).

The inclusion criteria of the project were:

1- Being over 18 years old;
2- Being a medical student; and
3- Being right handed.

The exclusion criteria of the project were:

1- Presence of metal elements in the head (excluding the oral region);
2- Subject diagnosed with epilepsy or with personal history of one or more seizure;
3- History of brain pathology of vascular, neoplasic, infectious or metabolic etiology not controlled with antiepileptic medication;
4- Presence of Pacemakers or intracardiac lines;
5- Patients with severe heart disease;
6- Patients with increased intracranial pressure (eg. post infarction or trauma);
7- Doubt or confirmation of possible pregnancy;
8- Intake of tricyclic antidepressants, neuroleptics and other drugs that lower the seizure threshold, without simultaneous use of anticonvulsant medication; and
9- History of Alcoholism, alcohol intake in the 24 hours prior to rTMS or deprivation of sleep the previous night.

All subjects were healthy, over 18 years old and signed an Informed Consent Form, explaining all the activities where they would participate during the experiment and guaranteeing they didn't have any of the counter-indications cited above.

Creativity Test

Both groups performed the previously referred Torrance creativity test before the stimulation, then rTMS or placebo, and the same creativity test after it. The test was a partial Torrance Test composed of one writing and evocation part, and two drawing parts, having the subjects three minutes for performing each of them.

The volunteers waited in a separated room, then they would be called to perform the Torrance Tests in other room, and then waited to be submitted to the rTMS in the laboratory, returning then for the post-test. The subjects waiting in the Auditorium were not in touch with the already tested colleagues, guaranteeing the originality of the ideas.

We used a partial Torrance Test, compiled from the original one, due to the time we expected the cerebral response to the stimulation to remain (30 minutes). This forced us to use a short version of the total Torrance Test. The sample we used comprised a "Just suppose task", where the subject is confronted with an improbable situation and asked to predict the possible outcomes. We used the question "Imagine you have Magical Powers. What can you do?" [29]

We also used two "Picture construction task or shapes task". In one test, the subjects were given a drawing with a diamond shape and asked to complete it, creating novel pictures and forms, naming them at the bottom. In the second test, it was given a series of 3 tasks: a circle shape to complete, a selection of shapes to be part of a creation and an incomplete drawing to be completed.
For the completion of each of the tests, the subjects were allowed 3 minutes. [29]

Torrance Based Testes:

Figure 1-Just Suppose Task

És um feiticeiro!
Diz o máximo de actividades que poderias fazer com os teus novos poderes.
(apenas uma actividade por linha - sê o mais conciso possível)

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Figure 2- Diamonds

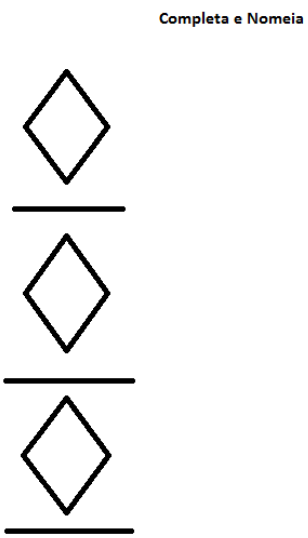
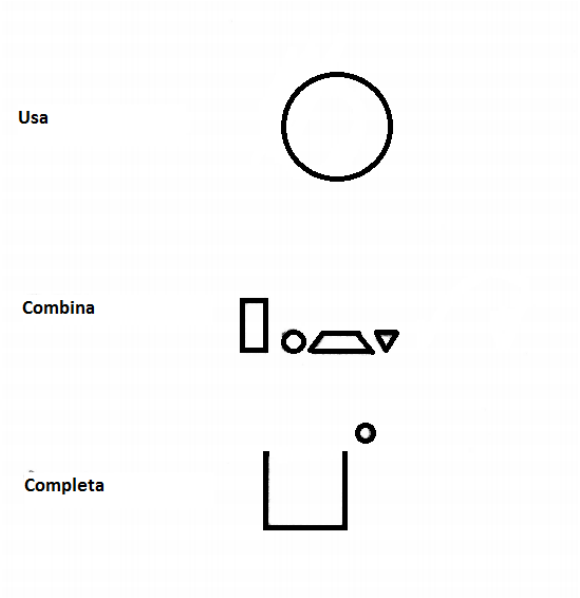


Figure 3- Use, Create and Complete/ Sequence



As only Fluency was evaluated, the number of ideas from each individual in all pre-tests were identified and counted. Then, at the post tests, the ideas which were said previously were eliminated and only the new ones were accounted for.

Again, in the scope of the current research, only Fluency was evaluated, having Flexibility, Originality and Elaboration not been considered.

Repetitive Transcranial Magnetic Stimulation (rTMS)

The cerebral stimulation was accomplished through Theta Burst Stimulation Technic (TBS) at the intermittent form (iTBS), with the butterfly coiled MagVenture MagPro® G3 X100 5.0.1. [30]
After detecting the hotspot at the right Primary Motor Area M1 and identifying the Active Motor Threshold (AMT), TBS stimulation was applied 5 cm anteriorly, above the right dorsolateral pre-frontal cortex (RDLPFC), at 80% of the AMT. [31]

In the Stimulation Group, the iTBS comprised series of three 50Hz pulses applied repetitively in 200ms (5Hz) intervals, during 2 seconds followed by 8 seconds of non-stimulation summing up to 600 pulses of stimulation. [32]

In the Sham Group, the same coil and initial protocols were used. However, the coil was sited at a perpendicular angle above the skull at only 50% of the AMT, so that none cerebral stimulation was induced. [31]

Statistical Analysis

For our study, it was considered the following null hypothesis (*Ho*):

Ho: A stimuli of 3.5 mn of excitatory rTMS will not change the creative capacity of the subject.

And the alternative hypothesis, as follows:

H1: A stimuli of 3.5 mn of excitatory rTMS will change the creative capacity of the subject.

For inferring the hypothetical statistical differences in the data under analysis, various statistical tests were used.

Mann-Whitney U Test was used to analyze differences in variables between actively and sham-treated groups. Chi-Square Tests were also used to analyze differences in total frequencies between the both groups. Finally, Wilcoxon-Signed Rank Test was used to detect differences in parameters within each group before and after stimulation.

The significance level chosen was 0.05, for a 95% confidence interval.

Results

Overall analysis

Firstly, the number of ideas was analyzed by using the previously stated Partial Torrance Tests, both at the Pre-Test (pre-stimulation) and Post-Test (post-stimulation) stages. Analysis was broken down into Pre-Test A, Post-Test A results, Pre- and Post-Diamond Test results and Pre- and Post-Sequence Test results, which are displayed below in Table 1 (Stimulated Group results) and Table 2 (Sham Group results).

Table 1– Number of Ideas: rTMS-Stimulated Group (E)

+	Pre Test A	Post -Test A	Pre Diamond	Post Diamond	Pre Sequence	Post Sequence
E1	13	7	4	2	4	3
E2	6	8	6	4	3	6
E3	4	6	1	3	3	2
E4	7	8	3	4	4	5
E5	8	8	5	4	3	5
E6	12	9	5	6	3	3
E7	7	9	2	4	3	2
E8	8	11	3	6	2	3
E9	6	8	4	5	3	3
E10	13	18	7	8	6	5
E11	10	12	5	6	4	4
E12	13	12	3	5	3	3

Table 2– Number of Ideas: Sham-Stimulated Group (P)

+	Pre Test A	Post Test A	Pre Diamond	Post Diamond	Pre Sequence	Post Sequence
P1	14	4	6	6	6	6
P2	8	7	6	6	3	3
P3	7	15	1	3	3	4
P4	16	14	5	9	5	6
P5	5	8	4-	4-	3	3
P6	12	6	7	6	6	4
P7	10	7	3	2	3	3
P8	8	7	3	3	3	2
P9	8	7	3	3	3	2
P10	10	8	3	3	3	3
P11	8	6	4	6	2	4
P12	11	9	5	4	2	3

Concerning the rTMS-stimulated Group results (see Table 1), the subject E1 revealed the worst overall performance. The best overall performance was reached by subjects E10 and E8. E2, E3 and E5, all showed better results on the drawing tests (Diamonds and Sequence).

For the Sham-stimulated Group (see Table 2), only 2 individuals enhanced the performance at the Test A. In addition, only 3 subjects had higher scores at Diamonds Test and only 4 subjects did better at Sequence Test.
Overall there was a maintenance of the results before and after the Placebo, or even a slight decrease of ideas.
P3 subject achieved a better performance in all tests.
The worst performances were achieved by subjects P6 and P1, with a serious worsening in the written test, repeating most of the ideas.

Thus, the majority of the Sham Group kept the same number of ideas at the Post-Tests, or even decreased it.
However, the Stimulated Group had better results, coming up with new ideas. Only one of the subjects decreased the score at all tests.

Test A analysis

Then, each sub-test was thoroughly and separately analyzed.
The Results regarding Pre- and Post-Test A are shown below, in Table 3.

Table 3– Number of Ideas (Test A): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

rTMS				Sham				
+	**Pre-Test A**	**Post-Test A**	**Post-Pre**		**Pre-Test A**	**Post-Test A**	**Post-Pre**	**rTMS vs Sham**
E1	13	7	+6	**P1**	14	4	-10	P=0.49*
E2	6	8	+2	**P2**	8	7	-1	
E3	4	6	+2	**P3**	7	15	+8	
E4	7	8	+1	**P4**	16	14	-2	
E5	8	8	0	**P5**	5	8	+3	
E6	12	9	-3	**P6**	12	6	-6	
E7	7	9	+2	**P7**	10	7	-3	
E8	8	11	+3	**P8**	8	7	-1	
E9	6	8	+2	**P9**	8	7	-1	
E10	13	18	+5	**P10**	10	8	-2	
E11	10	12	+2	**P11**	8	6	-2	
E12	13	12	-1	**P12**	11	9	-2	
Total	107	116	+9	**Total**	117	98	-19	
Median (range)	8 (4-13)	8,5 (7-18)	-	**Median (range)**	9 (5-16)	7 (4-15)	-	
Mean ± SD	8,92 ± 3,18	9,67 ± 3,23	-	**Mean ± SD**	9,75 ± 3,11	8,17 ± 3,21	-	-

(*) Mann-Whitney U test

Both groups were well matched in terms of pre-stimulation Test A scores, without significant differences being observed between those that had been randomized to receive rTMS versus those that would undergo Sham-stimulation (median (range) = 8 (4-13) vs 9 (5-16), respectively; Mann-Whiney U test).

No significant differences were observed in terms of overall responses in each group, when results before and after each type of stimulation (rTMS or Sham) were analyzed (rTMS – p=0.504; Sham – p=0.489; Wilcoxon-signed rank test).

However, when Test A results for rTMS- and Sham-stimulated groups were compared in terms of increasing, maintenance or decreasing responses (Table 4), there was a highly significant difference between the groups, with rTMS-treated group showing a significantly higher number of volunteers with increased responses (p=0.005; Chi-Square test).

Table 4– Changes in number of Ideas (Test A): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

		Stimulation		
		rTMS	Sham	
Changes in Test A responses	**Increased**	9	2	11
	Same	1	0	1
	Decreased	2	10	12
		12	12	24

Diamond Test analysis

Then it was analyzed the Pre- and Post-Diamond Test results, as can be seen below (Table 5).

Table 5– Number of Ideas (Diamond): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

rTMS				Sham				
+	**Pre-Diamond**	**Post-Diamond**	**Post-Pre**		**Pre-Diamond**	**Post-Diamond**	**Post-Pre**	**rTMS vs Sham**
E1	4	2	-2	**P1**	6	6	0	P=0.82*
E2	6	4	-2	**P2**	6	6	0	
E3	1	3	+2	**P3**	1	3	+2	
E4	3	4	+1	**P4**	5	9	+4	
E5	5	4	-1	**P5**	4	4	0	
E6	5	6	+1	**P6**	7	6	-1	
E7	2	4	+2	**P7**	3	2	-1	
E8	3	6	+3	**P8**	3	3	0	
E9	4	5	+1	**P9**	3	3	0	
E10	7	8	+1	**P10**	3	3	0	
E11	5	6	+1	**P11**	4	6	+2	
E12	3	5	-2	**P12**	5	4	-1	
Total	48	57	+9	**Total**	50	55	+5	
Median (range)	4 (1-6)	4,5 (2-8)	-	**Median (range)**	4 (1-7)	4 (2-9)	-	
Mean ± SD	4,0 ± 1,7	4,75 ± 1,6	-	**Mean ± SD**	4,17 ± 1,7	4,58 ± 2,02	-	-

(*) Mann-Whitney U test

Again, both groups were well matched in terms of pre-stimulation Diamond test scores, without significant differences occurring between those that had been randomized to receive rTMS versus those that would undergo Sham-stimulation (median (range) = 4 (1-6) vs 4 (1-7), respectively; p=0.82; Mann-Whiney U test).

No significant differences were observed in terms of overall responses in each group, when results before and after each type of stimulation (rTMS or Sham) were analyzed (rTMS – p=0.171; Sham – p=0.236; Wilcoxon-signed rank test).

However, when Diamond results for rTMS- and Sham-stimulated groups were compared in terms of increasing, maintenance or decreasing responses (Table 6), there was a highly significant difference between groups, with rTMS-treated group showing a significantly higher number of volunteers with increased responses (p=0.015; Chi-Square test).

Table 6– Changes in number of Ideas (Diamond Test): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

		Stimulation		
		rTMS	Sham	
Changes in Diamond Test responses	**Increased**	8	3	11
	Same	0	6	6
	Decreased	4	3	7
		12	12	24

Sequence Test analysis

Finally, the Pre- and Post-Sequence Test results were analyzed, as can be seen below (Table 7).

Table 7– Number of Ideas (Sequence): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

rTMS				**Sham**				
+	**Pre-Sequence**	**Post-Sequence**	**Post-Pre**		**Pre-Sequence**	**Post-Sequence**	**Post-Pre**	**rTMS vs Sham**
E1	4	3	-1	**P1**	6	6	0	
E2	3	6	+3	**P2**	3	3	0	
E3	3	2	-1	**P3**	3	4	+1	
E4	4	5	+1	**P4**	5	6	+1	
E5	3	5	+2	**P5**	3	3	0	
E6	3	3	0	**P6**	6	4	-2	
E7	3	2	-1	**P7**	3	3	0	
E8	2	3	+1	**P8**	3	2	-1	P=0.77*
E9	3	3	0	**P9**	3	2	-1	
E10	6	5	-1	**P10**	3	3	0	
E11	4	4	0	**P11**	2	4	+2	
E12	3	3	0	**P12**	2	3	-1	
Total	41	44	+3	**Total**	42	43	+1	
Median (range)	3 (2-6)	3 (2-6)	-	**Median (range)**	3 (2-6)	3 (2-6)	-	
Mean ± SD	3.42 ± 0.99	3.67 ± 1.30	-	**Mean ± SD**	3.50 ± 1.38	3.58 ± 1.31	-	-

(*) Mann-Whitney U test

Again, both groups were well matched in terms of pre-stimulation Sequence test scores, without significant differences occurring between those that had been randomized to receive rTMS versus those that would undergo Sham-stimulation (median (range) = 2 (2-6) vs 3 (2-6), respectively; p=0.77; Mann-Whiney U test).

No significant differences were observed in terms of Sequence test responses in each group, when results before and after each type of stimulation (rTMS or Sham) were analyzed (rTMS – p=0.374; Sham – p=0.288; Wilcoxon-signed rank test).

When Sequence test results for rTMS- and Sham-stimulated groups were compared in terms of increasing, maintenance or decreasing responses (Table 8), no significant differences were observed between groups (p=0.881; Chi-Square test).

Table 8– Changes in number of Ideas (Sequence Test): rTMS-Stimulated (E) and Sham-Stimulated (P) groups

		Stimulation		
		rTMS	Sham	
Changes in Diamond Test responses	**Increased**	4	4	8
	Same	4	5	9
	Decreased	4	3	7
		12	12	24

Discussion

Our study aimed to investigate if the creativity of a group of right handed individuals could improve through rTMS stimulation.
Being rTMS used in many pathologies, as neurological and psychiatric, with good results, [33] we aimed to assess if it would also improve individual creativity.

This study is a first attempt to assess the role played by rTMS stimulation in fostering creativity, so it assumes a pioneering nature. Although the sample had few individuals, it produced promising results and shall support further research on this challenging topic.

Despite the results revealed an absolute enhance in the number of creative responses after the stimulation, no significant differences were observed in terms of overall responses in each group, when results before and after stimulation (rTMS or Sham) were analyzed, possibly due to the small sample's dimension, comprised of only 24 subjects.
However, when comparing if the responses between both groups in the Post-Tests had decreased, maintained or increased, the difference was very clear, with the rTMS-Stimulated Group individuals showing a significantly higher number of responses after the stimulation, in both Test A and Diamonds Test. This fact was not observed in the Sequence Test.

Creativity has been attempted to be achieved and enhanced by various means, as can be seen previously in introduction. That is because of the possible dopaminergic mediation, pre-frontal-cortex intermediation and alpha activity association.

It is possible that the use of rTMS increases the dopaminergic flow in the DLPFC, thereby mimetizing the same effects that occurred with the use of behavioral training sessions [5] or inducing alpha band oscillations. [8] Cortical oscillations in the alpha frequency band are correlated with better creative ideation or possibly, a better cognition process. [8] A possible aspect would be to evaluate a group after rTMS with EEG in order to confirm changes in the alpha frequency band.

We do know that rTMS can improve excitability in cortical neurons releasing dopamine and NA [6] and it is possible that it acts similarly as Methylfenidate or other smart drugs, [19] by increasing dopamine levels and inducing creative thinking.

Stimulation of the dorsal lateral prefrontal (DLPFC) probably would produce the same changes that were observed in neurobehavioral training: when a cognitive stimulation (with 20 sessions) method was used, the results revealed that both the originality and the fluency of divergent thinking were significantly improved showing functional changes in the dorsal anterior cingulate cortex (dACC), dorsal lateral prefrontal cortex (DLPFC), and posterior brain regions. [5]. As the DLPFC is involved in the top-down cognitive control, its stimulation may have reduced inhibitory functions and hence improved creative thinking. [5]

Another study showed that rTMS improved cognitive performance by influencing the dynamics of alpha desynchronization. [1]
This study delivered rTMS to the mesial frontal and right parietal cortexes and concluded that after rTMS there is a functional relevance of oscillatory neural activity in the alpha band with implementation of cognitive performance. [1]

Therefore, if,as seen before, the alpha waves are correlated with creative states, and by this study, it is possible to produce alpha waves by rTMS, we can conclude that rTMS, inducing alpha wave power, can foster creativity.

In future studies, additional creativity variables like Flexibility, Originality and Elaboration, should be considered and assessed. [29,34]
Although this system can be more subjective and judge dependent, it would account for more variables of evaluation, and maybe that way, the rTMS effectiveness on enhancing creativity would show stronger results, because not only the fluency would be checked but also originality, which would be more relevant to our original purpose of application. [34]

Maybe, combining rTMS with functional magnetic resonance imaging (fMRI) or with electroencephalography (EEG) we would see the exact brain parts used by each individual to perform a creativity related tasks and, this way, we could direct the beam of iTBS to those locations and see if the post-results would improve. [33,35] Because not all individuals work and think the same way, maybe our investigation's results could have been better if we have attended to these differences. [35]

Although, as far as we know, there are no other studies regarding the use of rTMS to enhance creativity, for comparing and benchmarking purposes, and being our study the first of his kind, with the promising results obtained, I believe this investigation should be thoroughly explored, with other samples of the community, bigger ones, perhaps even using a different evaluation system, or even with a different locus of stimulation.

Even if with future studies, the results remain the same, the end point will always be our attempt to try to understand the amazing challenge, which is the Human Brain.

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