# Neuromodulation of the prefrontal cortex by iTBS: effects on the entrepreneurial attitude as evaluated by TAI test

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# Resumo

**Introdução:** A investigação na área do neuroempreendedorismo tem sugerido a importância em potenciais empreendedores da existência de características como a impulsividade e um comportamento de procura de novidades, assim como uma capacidade cognitiva ambidextra e flexível para a tomada de decisões, a qual permite que empreendedores bem-sucedidos transitem eficientemente entre comportamentos exploratórios do tipo *exploitation* (associado com regiões cerebrais envolvidas na representação do valor de opções, como o córtex pré-frontal ventromedial) e do tipo *exploration* (associado com regiões frontoparietais envolvidas no controlo cognitivo e da atenção). Simultaneamente, a importância da criatividade e da capacidade para pensamento divergente têm também sido sublinhadas. A base neurobiológica para estas funções ainda está a ser esclarecida, no entanto tem apontado para a importância de várias regiões pré-frontais integradas em redes, as quais estão envolvidas em mecanismos superiores de controlo cognitivo e de controlo da atenção (tal como o córtex pré-frontal dorso-lateral e o córtex fronto-polar) , as quais permitem a mudança eficiente entre comportamentos exploratórios do tipo *exploitation* e *exploration*, a tomada de decisões, e o relaxamento de regras e constrangimentos previamente aprendidos de modo a conseguir a resolução de problemas de forma inovadora. Vários estudos de neuromodulação têm mostrado alterações em determinantes da atitude empreendedora tais como a tomada estratégia de decisões, valoração do risco e comportamento de procura de novidades. Neste estudo exploratório, analisámos os efeitos da estimulação do córtex pré-frontal dorso-lateral (DLPFC) direito num teste que avalia a atitude empreendedora (TAI) num grupo de 13 voluntários saudáveis seleccionados de forma randomizada para estimulação real ou placebo com estimulação *theta burst* intermitente (*intermitent theta burst stimulation*, iTBS).

**Materiais e métodos:** Um total de 13 voluntários saudáveis foram alocados de forma aleatória para ser submetidos a 1 sessão de estimulação real/activa (n=7) ou placebo (n=6) de iTBS sobre o DLPFC direito. Os voluntários responderam subsequentemente ao Teste de Atitude Empreendedora (TAI), o qual avalia e decompõe em 8 factores os determinantes para a atitude empreendedora e fornece também uma pontuação global, a qual permite uma classificação em 3 grupos.

**Resultados:** A pontuação média obtida pelo grupo activo no factor 3 do TAI ("adaptabilidade") foi significativamente superior à obtida pelo grupo placebo (6,64% ±

2,84%, p=0,039). De resto, não houve diferenças estatisticamente significativas nos restantes factores TAI. Os valores médios da pontuação global no teste TAI põem o grupo activo no intervalo de alta atitude empreendedora (75,71%), e o grupo placebo no intervalo de média atitude empreendedora (71,66%), embora essa diferença não seja estatisticamente significativa (4,05% ± 2,67%, p=0,157).

**Discussão:** Os mecanismos superiores de controlo da atenção (mediados pelo DLPFC via conexões com os córtices fronto-polar e parietal), os quais permitem uma transição eficiente entre comportamentos exploratórios do tipo *exploitation* ou *exploration*, podem ser uma possível base fisiológica para a mentalidade empreendedora ambidextra, e assim a causa provável para o facto de o grupo com estimulação activa /real ter tido pontuações significativamente superiores às do grupo placebo no factor 3 do TAI ("adaptabilidade"). Apesar da estimulação de uma importante região do córtex pré-frontal envolvida no controlo cognitivo *top-down*, a neurobiologia da criatividade é cada vez mais entendida no contexto da inserção das regiões relevantes em grandes redes cerebrais (como a *default mode network* e a *cognitive control network*), de tal modo que a modulação de outras regiões (como o córtex temporal anterior) pode ser importante para alcançar melhorias na criatividade, inventividade e solução de problemas por *insight*, os quais são determinantes do comportamento e atitude empreendedora. Isto, em conjunto com a nossa amostra de tamanho reduzido, possivelmente foi a causa que nos impediu de encontrar outros resultados significativos nos factores de atitude empreendedora. Contudo, o facto de que o grupo de estimulação real/activa teve, em média, uma pontuação global no teste TAI superior à do grupo placebo (embora esta diferença não seja estatisticamente significativa), possivelmente sugere que a estimulação do DLPFC direito — se aumentando a actividade dos mecanismos superiores de controlo de atenção e estimulando alguns componentes da criatividade (possivelmente o pensamento divergente e a solução de problemas por *insight*) — provavelmente teve efectivamente algum efeito líquido global nos determinantes de atitude empreendedora, certamente digna de investigação futura.

**Conclusão:** A estimulação dos mecanismos superiores de controlo cognitivo e da atenção (possivelmente a base fisiológica para uma mentalidade empreendedora ambidextra) via estimulação do DLPFC direito é reflectida num aumento da pontuação do factor 3 ("adaptabilidade") do TAI. A integração em futuros protocolos de neuromodulação no contexto da investigação no neuroempreendedorismo de questionários de resposta aberta e de jogos de azar (eventualmente permitindo análises *pre-* e *post-facto*) é uma sugestão para mais directamente avaliar a criatividade e inovação em futuras investigações sobre neuroempreendedorismo.

# Palavras-chave

Neuromodulação; Neuroempreendedorismo; Theta burst stimulation; Córtex pré-frontal dorsolateral

# Abstract

**Introduction:** Neuroentrepreneurship research suggests the importance in potential entrepreneurs of traits such as impulsiveness and novelty-seeking behaviour, along with an ambidextrous and flexible decision-making capacity that allows successful entrepreneurs to efficiently switch between exploitation behaviour (associated with regions involved in value-representation such as the ventromedial prefrontal cortex) and exploration behaviour (associated with attention- and cognitive-control frontoparietal regions). Simultaneously, the importance of creativity and ability for divergent thinking has also been underscored. The neurobiological basis for such functions is still being elucidated, but has pointed to the importance of several network-integrated prefrontal cortex regions involved in higher cognitive and attention-control mechanisms (such as the dorsolateral prefrontal cortex and frontopolar cortex) allowing the switching between exploitative and explorative behaviour, decision-making and relaxing of previous rules and constraints for innovative problem solving. Neuromodulation studies have shown changes in determinants of entrepreneurial attitude such as strategic decision-making, risk and novelty-seeking behaviour. In this exploratory study, we analysed the effects of stimulation of the right dorsolateral prefrontal cortex (DLPFC) on a test for entrepreneurial aptitude (TAI) in a group of 13 healthy volunteers randomly selected for either sham or active stimulation with intermittent theta burst stimulation (iTBS).

**Materials and methods:** A total of 13 healthy volunteers were randomly allocated for either active (n=7) or sham (n=6) one-session iTBS stimulation of the right DLPFC. They were subsequently asked to answer the Entrepreneurial Attitude Test (TAI), which evaluates the determinants of entrepreneurial attitude in 8 factors and gives a global score, classified in three groups.

**Results:** Mean TAI factor 3 scores ("adaptability") were significantly higher in the active than in the sham group (6,64% ± 2,84%, p=0,039). Otherwise, there were no statistically significant differences in most TAI scores. Mean global TAI scores put the active group in the high-entrepreneurial attitude range (75,71%), and the sham group on the mid-entrepreneurial attitude range (71,66%), although such difference was not statistically significant (4,05% ± 2,67%, p=0,157).

**Discussion:** Higher attention-control mechanisms (mediated by DLPFC via connections with the frontopolar and parietal cortices) which allow an efficient switching between exploration and exploitation behaviour may be a possible physiological basis for an ambidextrous entrepreneurial mindset, and thus the probable cause for the stimulated group having TAI factor 3 ("adaptability") scores significantly higher than non-stimulated group. Despite stimulation of a major top-down cognitive control region of the prefrontal cortex, creativity's neurobiology is increasingly understood in terms of the insertion of the relevant regions into major brain networks (such as default mode network or cognitive control network), such that modulation of other regions (such as the anterior temporal cortex) may be important for achieving improvements in creativity, innovativeness and insight problem solving, determinants for entrepreneurial behaviour. This, along our reduced sample size, possibly prevented us from finding other significant results in other entrepreneurship factors. Nevertheless, the fact that the active group had mean higher (although not significant) global TAI score, possibly suggests stimulation of the right DLPFC, if increasing activity of the higher-attention control mechanisms and stimulating some components of creativity (possibly divergent thinking and insight problem-solving), probably had indeed some overall effect in the determinants of entrepreneurial attitude, possibly worthy of future research.

**Conclusion:** Stimulation of the higher cognitive and attention-control mechanisms (possibly the physiological basis for an ambidextrous entrepreneurial mindset) by stimulation of the right DLPFC is reflected in increased TAI factor 3 ("adaptability") scores. The integration in future entrepreneurship neuromodulation protocols of open answer questionnaires or gambling tasks eventually allowing pre- and post-analysis is a suggestion to more directly evaluate creativity/innovativeness in future neuroentrepreneurship research.

# Keywords

Neuromodulation; Neuroentrepreneuship; Theta burst stimulation; Dorsolateral prefrontal cortex

# Índice

# Lista de Tabelas

# Lista de Siglas e Acrónimos

| | |
|---|---|
| ACC | Anterior cingulate cortex |
| AMT | Active motor threshold |
| COMT | Catechol-O-methyltransferase |
| cTBS | Continuous theta burst stimulation |
| dACC | Dorsal anterior cingulate cortex |
| DLPFC | Dorsolateral prefrontal cortex |
| EEG | Electroencephalogram |
| FPC | Frontopolar cortex |
| ICD | Implantable cardiac defibrillator |
| IFG | Inferior frontal gyrus |
| IPS | Intraparietal sulcus |
| iTBS | Intermittent theta burst stimulation |
| lPFC | Lateral prefrontal cortex |
| M1 | Primary motor cortex |
| NIBS | Non-invasive brain stimulation |
| OFC | Orbitofrontal cortex |
| PFC | Prefrontal cortex |
| rTMS | Repetitive transcranial magnetic stimulation |
| TAI | Entrepreneurial Attitude Test |
| TBS | Theta burst stimulation |
| tDCS | Transcranial direct current stimulation |
| VIF | Variance inflation factor |
| vmPFC | Ventromedial prefrontal cortex |
| VS | Ventral striatum |

# 1. Introduction

Entrepreneurship is a broadly encompassing concept related to the "act of being an entrepreneur", and having autonomous initiative for accomplishing an innovative task, process, product or service, that has profound societal implications for the creation of value, innovation, economic development, and general wellbeing of the nations and populations.[1] It is widely accepted that an entrepreneur is a person with the capacity to search and discover an opportunity and to explore it by creating and innovating a solution for the problem thus identified while taking calculated risks to establish and develop a business venture based on the idea.[2] [3] Why some people are better to identify and explore market opportunities and find innovative solutions and ideas, while others could not or fail to do so, is an interesting issue.[4] In order to understand the differences in terms of behaviour, contrasting entrepreneurs and non-entrepreneurs, entrepreneurship research has moved in the last decades into a multi-disciplinary field, with a recent but increasing contribution from neuroscience, aiming to elucidate the cognitive processes that underlie the entrepreneur's activities, that is, looking into the "ultimate black box" and uncovering what lies at the basis of the entrepreneurial mindset.[4] Albeit current-day neuroscience tools are unable to correlate (much less attribute causality) all the evidence with specific neurocognitive or thought processes, it is possible, using current tools, to uncover some differences in the cognitive processing among groups and persons, which may hopefully, through systematic brain-driven entrepreneurship research, to be used in the future for constructing an integrated "big picture" of the neurobiological underpinning of the entrepreneurs' thought process.

Existing research has unveiled that an entrepreneurial mindset appears, among other traits, to be related to impulsiveness and risk-seeking behaviour.[4] From a genetic standpoint, explorative and novelty-seeking behaviour has been associated with COMT Met158Met or Val158Met polymorphism genetic variants.[5] [6] Individuals with high novelty-seeking personality traits have fewer dopamine $D_2$-like (auto)receptors in the substantia nigra/ventral tegmental area.[7] Interestingly, a mutation (DRD4-7R allele) in the dopamine $D_4$ receptor (a member the $D_2$-like family of receptors) is associated with reduced creativity and ability for divergent thinking,[8] two functions obviously essential for innovativeness and potential entrepreneurial behaviour. In an EEG study, Ortiz-Terán (2013) found that entrepreneurs have faster reaction times in a Stroop task, congruent with increasing impulsiveness and an apparent bias in entrepreneurs towards speed in lieu of accuracy in the universal decision-making's speed-accuracy dichotomy.[9] However, in the same previous study, entrepreneurs' accuracy in Stroop task were as similar to that of non-entrepreneurs, with the net overall cerebral region and circuitry activation data suggesting entrepreneurs are better able to take fast decisions in an ambiguous or noisy information environment, being particularly good in engaging in selective visual attention in a Stroop task, but that they spend more time and cognitive processing than non-entrepreneurs analysing the possible outcomes of the decision thus made and resolving residual conflicts.[9] Similarly, Zaro (2016), while using EEG in an opportunity-search/risk-assessment business simulation, found increased bilateral frontal lobe activation in entrepreneurs compared to non-entrepreneurs, and a combined brain activation pattern suggesting entrepreneurs better access working memory to process risk outcomes of the loan options presented.[2]

Bearing in mind that entrepreneurs' risk-taking traits may be adjoined by compensating traits to not totally compromise accuracy, using a gambling task Laureiro-Martinez (2014) found that entrepreneurs and managers did not have significant differences in the game's outcomes, although the entrepreneurs were able to maximise the outcomes faster than managers, owing to a better ability to switch from (a recognized unsuccessful) exploitative behaviour into an explorative one. This switch was linked to increased activation in entrepreneurs of brain regions related to explorative behaviour and higher-attention control mechanisms, namely the frontopolar cortex (FPC). Otherwise, entrepreneurs and managers did not have major differences in the activation of regions related to exploitative (meso-corticolimbic system, ventromedial prefrontal cortex [vmPFC]) or explorative actions (lateral prefrontal cortex [lPFC], dorsal anterior cingulate cortex [dACC], intraparietal sulcus [IPS]), with projections from vmPFC and dACC to *locus coeruleus* likely underpinning the balance between exploitative and explorative behaviour, respectively.[5] This efficient switching is in line with previous literature which has emphasised the importance of an ambidextrous and flexible mindset underlying successful entrepreneurial activity (both for individual entrepreneurs and at an organisational level).[10] This flexibility allows them to efficiently switch from incrementally improving their currently successful products in established market niches (exploiting) to short bursts of exploring uncertain but potentially eventually more successful other market opportunities (entrepreneurs spent an average of 78% of their time exploiting and 20% exploring).[10]

Based on the previous evidence, there is a need for deepening the still limited knowledge about the complex interconnections between frontal cortical regions (namely the prefrontal cortex [PFC]) involved in executive functions, decision-making, and setting of goal-directed behaviour, to subcortical areas (e.g. cortico-basal-thalamic loop involved in behaviour selection, meso-corticolimbic system involved in rewards) and to other cortical association areas.[11] [12] Research on modulation of frontal cortical regions suggests that the generation of new ideas is improved with reduction in activity of cortical regions responsible for inhibitory control and semantic knowledge (inferior PFC, anterior temporal lobe and middle temporal gyrus), in order to create a state less reliant on previous strategies, and mental representations.[13] Dorsolateral PFC (DLPFC) is associated with executive functions through generation of task-relevant thoughts and suppression of irrelevant ones;[13] stimulation of the left DLPFC is associated with improvements in tasks that demand selection of creative ideas and verbal convergent thinking,[14] while inhibition of the left DLPFC (and stimulation of right DLPFC) is associated with improvements in solving problems whose solution requires relaxing previous learned rules and constraints (insight problem solving, such as matchstick arithmetic tests).[15] A frontoparietal network is important for figural creativity; Huang (2013) proposes an inhibitory left-over-right mechanism whereby left PFC (namely DLPFC and inferior frontal gyrus [IFG]) inhibits right PFC during visual creative tasks in normal people.[16] Removal of this inhibition (either by a left hemisphere lesion or neuromodulation) can potentially facilitate artistic creativity and innovativeness.[16]

As reported in previous paragraphs, the current neurological theoretical background on entrepreneurship has been generally studied through a mix of traditional behavioural interventions and technologies to either directly (e.g. electroencephalogram [EEG]) or indirectly (e.g. functional magnetic resonance imaging [fMRI]) measure neuronal electric activity. Despite their undisputed importance for future research in neuroentrepreneurship under a systematic brain-driven research approach, other potentially useful technologies remain relatively unused in this research area. In particular, neuromodulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have not been significantly used in neuroentrepreneurship research, despite providing the unique capacity of manipulating the basal neural activation patterns, thus holding the potential for eventual "neuro-enhancement".[17] Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are part of the wider non-invasive brain stimulation (NIBS) techniques, which allow, through electrical or magnetic stimulation, the excitation or inhibition of discrete cortical or subcortical areas, in order to modulate certain brain functions with research or therapeutic purposes.[18] In rTMS, a coil is placed in the scalp over the desired brain cortex region, which sends rapidly alternating magnetic fields (up to 2T) at a specified frequency.[18] The fields are able to trans-synaptically activate superficial layers of the cortex, mainly by parallel-to-surface interneurons which then modulate the related neural circuitry, both on short-term or long-term periods.[19] [18] Low-frequency (<1 Hz) rTMS stimulation decreases cortical excitability, while high-frequency (usually >5Hz) increases it.[19] [18] In theta burst stimulation (TBS, a specific protocol of rTMS), three pulses at 50 Hz, repeated every 200 ms (5 Hz, theta wave frequency) are applied over a cortical area, inducing a longer-lasting after-stimulation effect when compared to regular rTMS. TBS enhances cortical excitability if applied intermittently (iTBS, 2s of stimulation every 10s), while it decreases cortical activity if applied continuously (cTBS, generally for 40s). Despite the magnetic field produced by a TMS coil being only able to directly activate the superficial layers of the cortex, the magnetic-induced electrical impulses can reach deeper brain areas owing to the brain's anatomic interconnections (e.g. activation of the primary motor cortex modulate subthalamic nucleus responses).[19] [20]

rTMS is currently used in certain neurological and psychiatric clinical settings, namely as an approved treatment for major depressive disorder (MDD) and schizophrenia resistant to usual pharmacological treatments, while TBS, a newer technique, is currently only FDA-approved for major depressive disorder (iTBS over the left DLPFC), both having a good profile of adverse effects.[21] [22] Target areas in most rTMS/TBS protocols comprise left DLPFC (in treatment-resistant depression and drug-resistant schizophrenia) and primary motor cortex (in chronic pain syndromes or stroke recovery).[18] Indeed, DLPFC is a particularly interesting area for modulation owing to the fact that it is a region involved in executive and planning functions, attention and working memory, with a large network of connections to other brain regions. The modulation of DLPFC by TBS has, for example, been shown to modulate physiological autonomic parameters such as cerebral blood flow and blood pressure,[23] as well as neural electrophysiological parameters[24] with potential impacts in cognition, decision-making[25] and working memory.[26]

Nevertheless, few studies exist on the link between neuromodulation and entrepreneurship, with none of them, to the best of our knowledge, using a TBS protocol. Van't Wout (2005) for example reported that inhibitory low-frequency repetitive TMS stimulation over right DLPFC modulates decision-making leading subjects to accept unjust offers in a gambling task, potentially underpinning the importance of DLPFC in the neurobiology of strategic decision-making.[27] Yang (2017) found that anodal tDCS (excitatory) stimulation over the right DLPFC increases the subjects' risk-seeking attitudes, with a reverse effect when stimulating the left DLPFC.[28] As previously stated, none of these studies used a TBS protocol.

In the present exploratory study, we analyse the effects of iTBS (excitatory stimulation) over the right DLPFC on a test for entrepreneurial aptitude (TAI scale) in a group of healthy volunteers randomly selected for either sham or active treatment. TAI is a self-report questionnaire that evaluates, through a metric scale, a wide spectrum of factors relevant to entrepreneurial behaviour and propensity for innovativeness and self-employment.[29] Introduced in the 1990s, it tries to gauge the relevant psychological characteristics, personality traits, and motivation that leads individuals to adopt an entrepreneurial attitude.[29]

# 2. Materials and methods

We conducted an exploratory study for evaluating the influence of neuromodulation of the right DLPFC on volunteers' scores in Entrepreneurial Attitude Test (TAI) score (a proxy for entrepreneurial behaviour). The study enrolled a total of 13 healthy volunteers, all of them Business Administration students at the University of Beira Interior (Covilhã, Portugal). For studying the effect of neuromodulation, the enrolees were randomly divided into two groups:

- (I) Active stimulation group: comprising 7 subjects, to whom it was applied iTBS stimulation according to the protocol; and
- (II) Sham stimulation group: comprising 6 subjects, to whom it was applied a similar protocol to the previous group, but in which coil is positioned parallel to the scalp and at a lower intensity, thus not being able of actually inducing neuronal stimulation in the underlying cortical regions of the volunteers (sham stimulation).

## 2.1. Selection process

Our study initially included a total of sixteen volunteers, aged between 19 and 25, of which nine were male and seven were female. All volunteers were Business Administration students at the University of Beira Interior (UBI), in Covilhã, Central Portugal. The study was approved by the Faculty of Health Sciences - UBI ethics board (CE-FCS-2011-001).

Inclusion criteria were the following:

- Student at the University of Beira Interior;
- 18 years old or older; and
- Right-handedness.

Exclusion criteria were the following:

- Previous history or presence of neurological or neuropsychiatric condition (e.g. epilepsy, stroke, cranioencephalic trauma);
- Metal implants on the head (except in oral region);
- Pacemaker or ICD;
- Previous history or presence of cancer;

- Previous history or presence of severe cardiac condition (e.g. acute myocardial infarction, ventricular fibrillation);
- Previous history or presence of intracranial hypertension;
- Previous history or presence of chronic alcoholism; and
- Physical or cognitive impairment preventing participation in the tests.
- Pregnancy

Volunteers were first given a written form (annex 1) for evaluating whether they fulfilled the inclusion and exclusion criteria, and answers were evaluated by a neurophysiologist. Exclusion criteria allowed to achieve a higher safety level in the neuromodulation procedure notwithstanding the fact that, according to rTMS/TBS guidelines, some of them are not absolute contraindications for this procedure. By applying the inclusion and exclusion criteria, one volunteer was excluded for being left-handed.

In accordance with the declaration of Helsinki standards, all participants were provided a written informed consent form (annex 2) before further proceeding with the study. It was provided an additional briefing on the study's primary goals, theoretical basis of the stimulation, and protocol of the ensuing practical part. They were informed about the possible adverse effects of iTBS, as reported in the literature, and that they could withdraw from the study at any time. At this point, one volunteer decided to leave the study owing to fear of the adverse effects of the stimulation protocol.

Throughout the process, data confidentiality of participants was guaranteed. Volunteers received no financial gains from the study.

## 2.2. Transcranial magnetic stimulation

Neuromodulation was done using the theta burst stimulation (TBS) protocol, in the intermittent variant (iTBS). As previously stated, iTBS is a type of TMS protocol, which is known to increase neuronal excitability of the underlying cortical region. In our study, iTBS was applied by way of a MagVenture MagPro® G3 X100 5.0.1, with a butterfly-shaped coil (MCF-B70).

In order to identify the location of the DLPFC on each volunteer, we started by locating the area on the right primary motor cortex (right M1) with the highest ability to activate the muscles of the left hand, thus identifying the active motor threshold (AMT) (i.e. the minimum stimulation required to evoke a contraction on the target muscle, in this case, the abductor pollicis brevis). After obtaining this reference point, all further pulses were applied 5 cm anteriorly, over the right DLPFC, at 80% of the AMT.

In the stimulation group, we applied iTBS over the right DLPFC following the protocol proposed by Huang (2005). Three pulses of magnetic stimulation were given at 50Hz (i.e. 20ms between each stimulus), repeated every 200 ms. A 2 s train of TBS (i.e. 30 pulses) was repeated every 10 s for 200 s (i.e. 20 TBS trains and 600 pulses).

In the sham group, using the same coil and the same location procedure, we applied a protocol of one session with the same duration, but in which the coil was rotated 90 degrees over the normal position over the volunteer's head (i.e., putting it parallel to the volunteers' scalp, instead of perpendicular, thus significantly moving away from the cortex the area of the coil with the highest magnetic field). Stimulation intensity was simultaneously decreased to 50% of AMT, thus guaranteeing the ineffectiveness of the stimulation.

## 2.3. Entrepreneurial Attitude Test (TAI)

Immediately after completing the stimulation session (either active or sham), each volunteer was requested to answer the Entrepreneurial Attitude Test (online TAI, annex 3). Although the complete version of TAI is composed of 75 multiple-choice items, a test validation in 2002–2003 allowed a reduction to 15 items.[29] In each item, volunteers have to indicate, on a five-point scale, their level of agreement or disagreement to a given statement. The shorter version of TAI scale — which we used on this study — compilates answers in order to describe entrepreneurial potential in terms of 8 factors, outlined by Cubico et al. (2010) as follows:

- *Factor 1*: Goal orientation — tendencies toward creativity and innovation, degree of determination in reaching goals, and personal perception as to overall handling of work situations.
- *Factor 2*: Leadership — aptitudes toward management and leadership.
- *Factor 3*: Adaptability — ability to perceive environmental change and adaptability.
- *Factor 4*: Need for achievement — the desire for fame, success and social affirmation and respect from others.
- *Factor 5*: Need for self-empowerment — the desire to realise oneself through one's job which, apart from any economic goals, must be enjoyable, satisfying, and interesting.

- *Factor 6*: Innovation — curiosity for what is new.
- *Factor 7*: Flexibility — tendency to reorient one's goals according to an external situation.
- *Factor 8*: Autonomy — necessity of having one's own independent space to make decisions and choices.

In accordance with the participants' answers to the relevant items, a score (from 0 to 100) is calculated for each factor. Similarly, a 0–100 global score is calculated for the whole TAI form. For calculating this global score, questions have not the same weight (each question has a multiplier factor of 1, 2 or 3). The minimum global TAI score is 30 and the maximum is 150, which is equivalent to a 20–100% global TAI score. Although TAI scale is to be understood as a continuous scale, test-takers' global scores are classified as follows:[30] [31]

- 30–70 points (20–46,7%) — low entrepreneurial attitude (or employee)
- 71–110 points (47,3–73,7%) — mid entrepreneurial attitude (or creative)
- 111–150 points (74–100%) — high entrepreneurial attitude (or leader)

## 2.4. Statistical analysis

For the statistical analysis of the previously registered data, we used IBM's SPSS 28© software. For comparing the average values of both active and sham groups in the TAI global score, and in each of the eight TAI factors, the independent samples Student's t-test (parametric test, used if there is a normal distribution pattern) and the Mann-Whitney test (non-parametric test, used if there is a non-normal distribution) were used. Due to the small sample size ($n<30$, in both active and sham groups), we used Shapiro-Wilk test for assessing whether the distributions followed a normal pattern. We also performed a regression analysis with usage of ANOVA, in order to verify whether age, gender and education/family background have effect on the TAI global scores mean differences. For all of the following statistical analysis, we considered a significance level of 5% (i.e. CI 95%), for identifying any significant results.

# 3. Results

A total of 13 volunteers (8 male and 5 female) participated in the active and sham iTBS phase of the study. The average age was 20,23 (± 1,69), ranging from 19 to 25. All volunteers were healthy with the most reported previous disease being headaches/migraine (6), followed by asthma (2) and vasovagal syncope (2 volunteers, which reported their last episodes had occurred 3 months and 3 years prior to the test, respectively).

**Table 1 – Previous or current diseases reported by volunteers**

| **Previous or current disease** | **N=13** |
|---|---|
| Headaches/migraine | 6 |
| Vasovagal syncope | 2 |
| Asthma | 2 |
| Rhinosinusitis | 1 |
| Thyroid nodules (not otherwise specified) | 1 |
| Tachyarrhythmia (not otherwise specified) | 1 |
| Herpes-zoster | 1 |

Regarding current medication, 3 female volunteers were taking an oral contraceptive. Other reported current treatment regimens included methylphenidate (1), azithromycin (1) and an unspecified anti-migraine drug (1). Three volunteers had previously undergone surgery, all of which were tonsillectomies.

**Table 2 – Volunteers' current medication**

| **Current medication** | **N=13** |
|---|---|
| Oral contraceptive | 3 |
| Methylphenidate | 1 |
| Azithromycin | 1 |
| Anti-migraine drug (not otherwise specified) | 1 |

**Table 3 – Volunteers' surgical history**

| **Previous surgery?** | **N=13** |
|---|---|
| Yes | 3 |
| Tonsillectomy | 3 |
| No | 10 |

Five volunteers had a parent or grandparent which was owner of a business (3 in the active group and 2 in the sham one). One volunteer (in the sham group) had a prior educational background on entrepreneurship.

**Table 4 – Entrepreneurial background**

| **Entrepreneurial background?** | **N=13** |
|---|---|
| Parent or grandparent is owner of a business | 5 |
| Prior educational/labour background on entrepreneurship | 1 |

Volunteers reported no adverse events from the stimulation session, namely headaches, paraesthesia in the scalp or even syncope.

In tables 5 and 6, we present the descriptive statistics of the results of TAI form (both for global score and for each of the 8 factors) for sham and active groups, respectively:

**Table 5 – Descriptive statistics for the sham group**

| **TAI score** | **N** | **Mean** | **Std. deviation** | **Minimum** | **Maximum** |
|---|---|---|---|---|---|
| Factor 1 | 6 | 73,17% | 4,17% | 69,00% | 78,00% |
| Factor 2 | 6 | 66,17% | 7,57% | 54,00% | 74,00% |
| Factor 3 | 6 | 60,50% | 4,18% | 56,00% | 67,00% |
| Factor 4 | 6 | 60,67% | 9,61% | 44,00% | 72,00% |
| Factor 5 | 6 | 77,67% | 7,15% | 65,00% | 85,00% |
| Factor 6 | 6 | 76,67% | 9,89% | 67,00% | 93,00% |
| Factor 7 | 6 | 80,83% | 8,61% | 65,00% | 90,00% |
| Factor 8 | 6 | 60,00% | 16,78% | 32,00% | 80,00% |
| TAI (global score) | 6 | 71,67% | 4,41% | 66,00% | 76,00% |

**Table 6 – Descriptive statistics for the active iTBS group**

| TAI score | N | Mean | Std. deviation | Minimum | Maximum |
|---|---|---|---|---|---|
| Factor 1 | 7 | 75,14% | 4,10% | 72,00% | 83,00% |
| Factor 2 | 7 | 73,43% | 17,25% | 49,00% | 97,00% |
| Factor 3 | 7 | 67,14% | 5,76% | 58,00% | 73,00% |
| Factor 4 | 7 | 68,00% | 22,39% | 20,00% | 88,00% |
| Factor 5 | 7 | 72,71% | 13,94% | 58,00% | 90,00% |
| Factor 6 | 7 | 82,86% | 13,28% | 60,00% | 100,00% |
| Factor 7 | 7 | 76,43% | 6,90% | 65,00% | 85,00% |
| Factor 8 | 7 | 62,86% | 9,44% | 52,00% | 80,00% |
| TAI (global score) | 7 | 75,71% | 5,09% | 70,00% | 84,00% |

According to the previous tables (and before proceeding for analysing the statistical significance of such differences), it can be seen that mean TAI scores were higher in the active than sham stimulation group in all but two factors in analysis (TAI factors 5 and 7). Mean global TAI scores were also 4,04 pp higher in the active than in the sham group (71,67% vs 75,71%), which put the two groups in different entrepreneurial attitude levels as evaluated by the TAI scale, with the active group scoring in the high-entrepreneurial attitude range (75,71%), while the sham group scores are in the mid-entrepreneurial attitude range (71,66%).[30] [31] Caution should be emphasised in interpreting the relevance of such result, as TAI scale is due to be interpreted as a continuous scale.

We then analysed whether there is any statistically significant difference (and the direction of it) of the average value of any of the TAI scores between active and sham iTBS groups. Due to our small sample size (n<30 in both active and sham groups), we used Shapiro-Wilk test to find whether each means' distributions followed a normal pattern.

Considering that we have independent samples in all of the 9 variables for analysis, we then used the independent samples Student's t-test (parametric) if there was a normal distribution pattern and the Mann-Whitney test (non-parametric) if there was no normality, in order to compare means (or medians, for the case of Mann-Witney test).

For assessing the statistical significance, a 5% level was considered in all subsequent calculations.

**Table 7 – Shappiro-Wilk test for assessing normality of distributions**

| | Stimulation group | p-value# |
|---|---|---|
| TAI (global score) | Sham | ,241 |
| | Active | ,541 |
| Factor 1 | Sham | ,150 |
| | Active | ,065 |
| Factor 2 | Sham | ,301 |
| | Active | ,776 |
| Factor 3 | Sham | ,450 |
| | Active | ,145 |
| Factor 4 | Sham | ,312 |
| | Active | ,015 |
| Factor 5 | Sham | ,467 |
| | Active | ,168 |
| Factor 6 | Sham | ,373 |
| | Active | ,864 |
| Factor 7 | Sham | ,210 |
| | Active | ,456 |
| Factor 8 | Sham | ,845 |
| | Active | ,489 |

#1 — Shapiro-Wilk test

As such, according to Shapiro-Wilk test, only the active group of TAI factor 4 ($p=0,015<0,05$) does not follow a normal distribution pattern at our chosen significance level. We thus used the Mann-Witney test for comparing means between the active and sham group in the TAI factor 4 scores, and the independent samples t-test in the remaining 8 groups. It is noteworthy that, at a slightly lower significance level (10%) we could not assume normality for the distribution of the active group of TAI factor 1 ($p=0,05<0,065<0,1$). As such, we will also present the results for an evaluation of the significance of the mean differences between the active and sham group of TAI factor 1 using Mann-Whitney test.

The results concerning the Mann-Witney test and the mean differences are presented below in Tables 8 and 9.

**Table 8 – Mann-Witney test ranks (for TAI factor 1 and 4 scores)**

| Mann-Witney test ranks | | | | |
|---|---|---|---|---|
| | **Stimulation** | **N** | **Mean Rank** | **Sum of Ranks** |
| Factor 1 | Sham | 6 | 5,92 | 35,50 |
| | Active | 7 | 7,93 | 55,50 |
| | Total | 13 | | |
| Factor 4 | Sham | 6 | 5,08 | 30,50 |
| | Active | 7 | 8,64 | 60,50 |
| | Total | 13 | | |

**Table 9 – Significance of mean differences between the active and sham groups**

| TAI score | Stimu-lation | N | Mean | Std. dev. | Mann-Witney test | Levine test | T test for ind. samples | Mean diff. | Std. error diff. | CI 95% | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | p-value | p-value | p-value | | | Min. | Max. |
| Factor 1 | Sham | 6 | 73,16% | 4,16% | N/A | 0,715 | 0,408 | -1,98% | 2,30% | -7,03% | 3,08% |
| | Active | 7 | 75,14% | 4,09% | | | | | | | |
| | Sham | 6 | 73,16% | 4,16% | 0,402 | N/A | N/A | N/A | N/A | N/A | N/A |
| | Active | 7 | 75,14% | 4,09% | | | | | | | |
| Factor 2 | Sham | 6 | 66,16% | 7,57% | N/A | 0,118 | 0,362 | -7,26% | 7,64% | -24,07% | 9,55% |
| | Active | 7 | 73,42% | 17,25% | | | | | | | |
| Factor 3 | Sham | 6 | 60,50% | 4,18% | N/A | 0,164 | 0,039 | -6,64% | 2,84% | -12,89% | -0,40% |
| | Active | 7 | 67,14% | 5,76% | | | | | | | |
| Factor 4 | Sham | 6 | 60,67% | 9,61% | 0,111 | N/A | N/A | N7A | N/A | N/A | N/A |
| | Active | 7 | 68,00% | 22,39% | | | | | | | |
| Factor 5 | Sham | 6 | 77,66% | 7,15% | N/A | 0,029 | 0,432[a] | 4,95%[a] | 6,02%[a] | -8,62%[a] | 18,53%[a] |
| | Active | 7 | 72,71% | 13,94% | | | | | | | |
| Factor 6 | Sham | 6 | 76,66% | 9,89% | N/A | 0,508 | 0,368 | -6,19% | 6,60% | -20,72% | 8,34% |
| | Active | 7 | 82,85% | 13,28% | | | | | | | |
| Factor 7 | Sham | 6 | 80,83% | 8,61% | N/A | 0,903 | 0,327 | 4,40% | 4,30% | -5,06% | 13,86% |
| | Active | 7 | 76,42% | 6,90% | | | | | | | |
| Factor 8 | Sham | 6 | 60,00% | 16,78% | N/A | 0,297 | 0,707 | -2,86% | 7,39% | -19,13% | 13,42% |
| | Active | 7 | 62,85% | 9,44% | | | | | | | |
| TAI (global score) | Sham | 6 | 71,66% | 4,41% | N/A | 0,775 | 0,157 | -4,05% | 2,67% | -9,92% | 1,82% |
| | Active | 7 | 75,71% | 5,09% | | | | | | | |

[a] — According to the Levine test, equal variances cannot be assumed (p-value_Levine=0,029<0,05). As such, we used the p-value of the t-test where equal variances had not been assumed (otherwise, p-value would be 0,450).

As such, by way of the independent samples t-test and the Mann-Witney (for TAI factor 4 comparison group), we found that, at our chosen significance level (5%), there is only a statistically significant difference in the TAI scores regarding factor 3 ("adaptability") (p=0,039**)**, with the active iTBS group having a mean score 6,64 pp higher than that of the sham group (CI 95% -12,89 – -0,39). Otherwise, no other comparison group has a statistically significant difference in the mean TAI scores. Regarding the comparison of TAI factor 1 scores, the use of the (non-parametric) Mann-Whitney test instead of the (parametric) independent samples t-test does not change the result of a lack of statistically significant difference between the active and sham groups at 5% or even 10% significance level (p=0,715>0,05 for t-test and p=0,402>0,05 for Mann-Whitney).

As already mentioned, mean global TAI scores were 4,04 pp higher in the active than in the sham group (mean difference -4,04, CI 95% -9,91 – 1,82), putting the two groups in different entrepreneurial attitude levels as evaluated by the TAI scale (active group in the high-entrepreneurial attitude range [75,71%] and sham group in the mid-entrepreneurial attitude range [71,66%]). This difference however is not statistically significant at our chosen significance level (p=0,157>0,05).

By way of regression analysis, we found that global TAI scores are not related with age, gender, having a family member owner of a business, or having previous labour/educational background on entrepreneurship (p-value ANOVA=0,582>0,05).

**Table 10 – Linear regression analysis (ANOVA) for variables gender, age, familial entrepreneurial background and educational/labour entrepreneurial background**

| | Coefficients | p-value | 95% Confidence Interval | | VIF |
|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | |
| (Constant) | 91,084 | ,055 | -2,480 | 184,648 | |
| Gender | -3,763 | ,313 | -11,949 | 4,423 | 1,151 |
| Age | -,533 | ,799 | -5,291 | 4,224 | 1,289 |
| Parent or grandparent owns a business | -2,996 | ,433 | -11,521 | 5,528 | 1,249 |
| Prior educational/labour back-ground on entrepreneurship | -,121 | ,986 | -16,134 | 15,892 | 1,385 |
| Adjusted $R^2$: 0,095<br>p-value ANOVA: 0,582 | | | | | |

# 4. Discussion

Our study intended to assess whether modulation of the electrical activity of a region of the prefrontal cortex (PFC) through iTBS would have any effect in the volunteers' attitude towards entrepreneurship and its determinants (such as innovativeness and novelty-seeking) as evaluated by the TAI scale. We did not find statistically significant differences in most TAI scores at our chosen significance level between the group which had received iTBS stimulation and the one which not. We found however a statistically significant difference in the mean TAI factor 3 scores ("adaptability") between the active and sham group, with the stimulated group having significantly higher scores than the sham group. Although the 4,04-pp difference between the means of the two groups' global TAI scores was not statistically significant at our chosen significance level, it is noteworthy that the two groups' means are in different entrepreneurial attitude levels, with the active group's mean (75,71%) in the high-entrepreneurial attitude range, while mean global TAI scores in the sham group (71,66%) in the mid-entrepreneurial attitude range. This result should however be interpreted with caution, as TAI scale is due to be interpreted as a continuous scale. In either case, it is noteworthy that both in overall TAI scores and in all individual factors (except factors 5 and 7), mean TAI scores were always higher in stimulated group versus the sham group, but — as stated — only regarding TAI factor 3 where such differences worthy of statistical significance.

TAI has been successfully used since the 1990s as an evaluation tool for entrepreneurial attitude and self-employment propensity. Although we found no neuromodulation study evaluating eventual TBS effects on entrepreneurial-relevant traits, previous studies using rTMS showed that inhibition of right DLPFC impairs subject's strategic decision-making,[27] while its stimulation increases risk and novelty-seeking behaviour,[28] which are personality traits evaluated by TAI scale. Besides that, previous studies posit the existence of left-to-right PFC inhibition mechanism regarding creativity.[16]

Considering this, several factors may explain our results. The set of influencers of what make a person an entrepreneur is diverse and have complex inter-relationships, including also the external environment, institutional context, and past experiences. As previously stated, research suggests that the entrepreneurial mindset may be facilitated by some personality traits such as high-novelty-seeking behaviour and impulsiveness.[4] [9] Also, entrepreneurs may have better ability to perceive and make use of potential business opportunities, and further flexibility in their decision-making is required, in order to keep their business afloat and growing (e.g. realizing if a company should continue to invest in the market area where it is growing, or if it should expand/move to other business areas).[5] [32] [33] On the basis of this flexible cognition mindset able of maintaining focus on long-term and more day-to-day goals, is the ability to develop an ambidextrous entrepreneurial mindset that is able to efficiently switch between exploitation and exploration behaviours, i.e. the ability of knowing when is it better to continue exploiting a business opportunity that one knowns is currently successful, or when is it better to explore new business opportunities (whose outcome is naturally uncertain at the time of the decision).[33] Successful entrepreneurs are better at knowing when to switch from exploitation to exploration behaviour, thus achieving a superior decision-making performance by capturing the best business opportunities and continuing to exploit them until better opportunities arise.[33] That switch engages higher cognitive and attention-control regions (namely the DLPFC, via connections to frontopolar and the parietal cortices), as it is necessary to trade-off an option whose outcome is currently known, for an option whose outcome may possibly be better, but is currently unknown, putting the individual in a state of uncertainty about his future.[33] As such, if exploitation behaviour is strongly associated with activation of reward-related (orbitofrontal cortex, ventral striatum and hippocampus) and value-representation-related (ventromedial PFC) regions under the framework of the meso-corticolimbic system, explorative behaviours engage attention- (parietal cortices, namely intraparietal sulcus) and cognitive-control systems (PFC, namely frontopolar cortex), which disengage attention from current choices and increase attention for new opportunities in the environment, at the cost of uncertainty.[33] Without such higher-order mental process, an individual may prosecute the currently rewarding and reassuring choices, independent of a potential worse long-term outcome, as it is seen — in an extreme case — in addiction disorders.

Under this framework, stimulation (by iTBS in our case) of the DLPFC might have increased the volunteers' higher attention-control mechanisms, which is a necessary component for an entrepreneur (or any potential entrepreneur) to realise the need for changes in the business choices they take, and thus to adapt to the constantly evolving market landscape. As such, we may hypothesize this mechanism, the possible physiological basis for an ambidextrous entrepreneurial mindset, as the probable cause for the stimulated group having TAI factor 3 scores significantly higher than non-stimulated group. It is possibly worthwhile in this context to also note that previous literature on entrepreneurial mindset has emphasized the importance of sense-making processes in the entrepreneurial cognition, i.e. the ability to process information in a noisy and changing environment in order to make sense of what is relevant, thus achieving a “a manageable level of uncertainty”.[34] This may be another way by which increased activity of the higher-order PFC attention-control mechanisms stimulates a more flexible mindset, and is thus possibly also on the basis of increased TAI factor 3 on the stimulated group.

However, as stated, in the remaining TAI factors no statistically significant differences were found between the active and sham group. One of the potential reasons for such absence of differences relies in the complex circuitry and regional activation patterns involved in the multiple determinants of entrepreneurial aptitude,[11] [35] so that stimulation of a single region of the PFC (DLPFC in our case) may not be significant for inducing significant changes in the thought process. Regarding decision-making, there are multiple ways by which the switch from exploitative to explorative behaviour is computed by the brain: for example, a computation between the ventromedial PFC (which monitor the value of the current decision) and the frontopolar cortex (which monitor the value of foregone options) is performed by the dorsal anterior cingulate cortex (dACC) such that when inputs from the frontopolar cortex (FPC) are higher than those from ventromedial PFC, then the intra-parietal sulcus disengages attention from the current choice.[33] However, other major pathway for regulating the parietal cortex’s attentional engagement involves output from the orbitofrontal cortex and the anterior cingulate cortex (regions with prominent sensorimotor inputs and which represent the outcome of previous decision processes) which regulate the *locus coeruleus*-norepinephrine system, which will itself regulate the parietal attention-engagement regions for either an explorative or exploitative behaviour.[33] [36] [37] None of these regions were directly modulated by our study, which may explain the absence of significant differences between the stimulated and non-stimulated groups in the remaining entrepreneurial determinants.

Creativity (including divergent thinking and insight problem solving), an essential asset for entrepreneurial mindset (with TAI factors 6 and 7 as an indirect measure), is also a complex and multifaceted phenomenon, difficult to study in the brain.[38] Creativity requires multiple cognitive abilities such as working memory, sustained attention and cognitive flexibility, for which the prefrontal cortex plays a central role.[35] However, as expected, other cortical and subcortical structures play also important roles, namely regarding attention engagement (parietal lobes), modulating emotional drive (anterior cingulate cortex, limbic system) and controlling precise motor movements necessary for putting in practice the chosen actions (premotor cortex, basal ganglia, cerebellum).[35] Research suggests improvement in several creativity task scores after modulation of DLPFC, namely improvement of visual divergent thinking (DT) and insight problem solving after right DLPFC stimulation[15] and improvements in verbal convergent thinking (CT) in stimulation of the left DLPFC.[14] [39] Nevertheless, results in literature are somewhat inconsistent.[39] Indeed, for example, improvements in visual creativity have been reported after inhibition of the right DLPFC,[40] apparently in contradiction with the proposed left-over-right PFC inhibitory dominance mechanism over visual creativity tasks,[16] but possibly explained under a framework of paradoxical functional facilitation[41] and the not total compartmentalisation of the creativity components in strict brain areas.[40] In line with the previously stated, also important is the involvement of other brain regions in the modulation of these and other creativity components: creativity's neurobiology is increasingly understood in terms of the insertion of the relevant regions into major brain networks such the default mode network (DMN) and cognitive control network (CCN).[35] [38] As such, modulation of other regions is important in achieving improvements in creativity task scores relevant for entrepreneurial attitude, such as possibly modulation of the anterior temporal cortex in improving insight problem solving.[42] [39] As such, it is possible that stimulation of the DLPFC, despite the region's importance in top-down cognitive and attentional control, planning and organisation, and emotional regulation, is not sufficient in itself to increase innovativeness and divergent thinking capabilities.

Despite the previous considerations, we find it noteworthy that, although the difference between the two groups' mean global TAI scores was not statistically significant, such means were on different entrepreneurial attitude levels as evaluated by TAI scale, with the group which received iTBS stimulation over the right DLPFC having a mean global TAI score in the high-entrepreneurial attitude range (75,71%), while the group which did not receive stimulation had a mean global TAI score in the mid-entrepreneurial aptitude range (71,66%). Also, all TAI factors' means (except for TAI factor 5 ["need for self-empowerment"]) were higher in the stimulated than in the sham group, despite — as already noted — of the lack of statistically significance in all but TAI factor 3 ("adaptability"). This possibly suggests that the stimulation of the right DLPFC, if increasing activity of the higher-attention control mechanisms and stimulating some components of creativity (possibly divergent thinking and insight problem-solving) probably had indeed some overall effect in the determinants of entrepreneurial attitude, although this did not reach statistical significance with our (one-session) protocol. As such, is also noteworthy that regarding TAI factor 6, the most appropriate in TAI scale to evaluate creativity and innovativeness, the stimulated group achieved a 6,21 pp higher mean than the non-stimulated one.

Other reason for the lack of statistically significant differences in most TAI factors is related to the reduced number of stimulation sessions and short time from the stimulation to the application of the questionnaire. As such, our protocol consisted of only one session of iTBS, which may not have been sufficient to produce long-lasting changes in the volunteer's cortical activation patters. The effects of transcranial stimulation in the nervous system after the end of the stimulation proper are mediated by way of the metabolic and genetic expression changes underlying long-term potentiation (LTP) and long long-term depression (LTD).[19] Under this framework, protocols comprising multiple sessions of transcranial stimulation are associated with longer and more marked changes in cortical activation and synaptic strength. For example, rTMS protocols for treatment-resistant depressant include 10–30 sessions, with increasing number of sessions or of the number of pulses per session associated with increased antidepressant effect of high-frequency rTMS stimulation over the left DLPFC.[22] It is thus possible to speculate that more marked neuronal changes would be necessary in order to elicit changes in the determinants of entrepreneurial behaviour, which could possibly only be achieved by more stimulation sessions. As such, it is likely that a stimulation protocol consisting of multiple sessions could lead to significant differences in the determinants for entrepreneurial behaviour. Nevertheless, it should be remarked that iTBS protocols similar to our own produces significant intracortical facilitation for around 15-20 min after each stimulation session, with return to the baseline thereafter.[20] As such, the application of the TAI form to the volunteers immediately after the stimulation session possibly granted us the opportunity to evaluate the cortical activation changes induced by iTBS when these were more pronounced, despite a multiple session protocol likely producing deeper changes in neurocircuitry. As stated previously, it is noteworthy the group's mean global TAI scores put them in different entrepreneurial attitude levels; we can speculate that this non-statistically significant difference has its basis on the neurocircuitry and cortical activation pattern changes induced by one-session of iTBS stimulation over the prefrontal cortex, and that such changes would possibly be more marked had a longer protocol been applied.

Other possibility is that the TAI questionnaire, as a self-evaluation questionnaire, is not the best tool of evaluating creativity task scores relevant for entrepreneurial mindset, which may explain the lack of significant different in TAI factors related to innovativeness and flexibility. Studies regarding creativity tend to use open-answer questionnaires such as Remote Associates Test (RAT) and Torrance Tests of Creativity Thinking (TTCT). These allow to evaluate actual and individual ideas regarding, for example, their number and originality. Another limitation in the use of TAI scale in our study, is the fact that the scale and its subcomponents have been successfully validated for an Italian population, albeit not for a Portuguese one.

We did not find any significant correlation between entrepreneurial attitude (as measured by global TAI scores) and volunteers' having a family member owner of business or an education background on entrepreneurship. Research suggests a positive correlation between entrepreneurial intention and passion, and an entrepreneurial educational or familial background.[43] [44] Possibly the lack of results in our study is related to the reduced size of our sample: as such, for example, Lee (2021) used a sample of 160 students to test the relationship between these variables. We also did not find a significant correlation between entrepreneurial attitude and volunteers' gender and/or age. There appears to exist a negative correlation between female gender and entrepreneurial intention,[45] but our sample is too small to potentially contribute to that research area. Older employees tend to have a reduced entrepreneurial intention, but our sample consisted of young adults aged between 19 and 25, while literature regarding the effect of age includes samples comprising both young, middle-aged and older adults.[46] As such, no population-level conclusions can be drawn from our study. Volunteers' global TAI scores ranged in the mid- to high-entrepreneurial attitude. This is probably influenced by the fact that the sample is composed solely of Business Administration students, i.e. persons which probably have higher interest and passion in business and entrepreneurial-related subjects. However, as previously discussed, the mean global TAI scores in the stimulated group were in the high-entrepreneurial attitude range, while those of the sham group were in the mid-attitude range. The TAI scores of the volunteers in our study are generally in line, for example, with those from senior and junior entrepreneurs in a study for the validation of TAI.[29] As such, regarding mean TAI factor 3 scores, for example, volunteers' in our study registered scores ranging from 60,50–67,14%, while a sample of 94 father and son entrepreneurs by Cubico (2010) registered mean scores of 64,74–66,34%.[29]

Our study had several limitations. First, we add a relatively reduced sample size. As such, we enrolled a total of 13 volunteers in the active/sham stimulation part of the study, with 6-7 volunteers in each arm, which is however not dissimilar with the average sample in cognitive neuroscience studies, which averages around 15–20 persons.[47] However, it is undeniable that a small sample turns more difficult to apply the results eventually found to the general population.[47] This small sample size may also be on the basis of e.g. the non-normal distribution of the scores in the active group of TAI factor 4 (at 5% significance level) and of the active group of TAI factor 1 (at 10% significance level). Also, owing to its composition, the sample may be biased owing to its members not being representative of the population. Our sample was relatively homogenous, composed of young persons (mean age 20,2; range 19–25) and — owing to the concerns on adverse effects of transcranial stimulation — healthy persons. Furthermore, all volunteers had the same occupation, and despite them being studying Business Administration, i.e., a subject with intimate connections related to entrepreneurship and business creation, none of them were entrepreneurs, or were owners of current or previous business ventures. A study with more persons and with a more representative sample of the entrepreneurial population could have obtained significant results.

Second, another limitation that also may have precluded the finding of statistically significant results regarding most TAI factors is related to the fact that we did not make a pre- and post- analysis, thus evaluating the volunteers' entrepreneurial attitude both before and after the stimulation protocol. As such, for example, it might be that such attitude underwent significant changes owing to the effects of iTBS stimulation, which was not found by our study, despite the difference between the groups (*post-facto*) not being statistically significant, as found in our study. We intentionally wanted volunteers to be naïve to TAI questionnaire after applying the stimulation protocol, because answers from the second time would likely be affected by the first answering of the form. The integration in protocols of open answer questionnaires (such as the Alternates Uses Task [AUT] or the Insight Task [IT])[48] which can have two or more versions and evaluate creativity/innovativeness is a possible solution for, in future studies, allowing a pre- and post-analysis in entrepreneurship research.

# 5. Conclusion and suggestions for future research

As far as we known, our study was the first to use neuromodulation techniques to analyse entrepreneurial determinants as evaluated by the Entrepreneurial Attitude Test (TAI). Our study found that stimulation of the right DLPFC by a one-session iTBS protocol does not lead to statistically significant differences in most factors of the TAI test when the test is applied immediately after the stimulation session. The only exception occurs in TAI factor 3 ("adaptability"), where stimulation leads to higher scores in the active than in the sham stimulation group, which is possibly related to increased activation of the higher attention-control mechanisms modulated by the DLPFC and important in developing an ambidextrous entrepreneurial mindset, which is able to switch from exploitative to explorative behaviour. Although the difference between the two groups' mean global TAI scores was not statistically significant at our chosen significance level, the two means put the active and the sham group on different entrepreneurial attitude levels (high- and mid-entrepreneurial attitude respectively) as evaluated by the TAI scale. This possibly suggests that the stimulation of the right DLPFC, if increasing activity of the higher-attention control mechanisms and stimulating some components of creativity (possibly divergent thinking and insight problem-solving) probably had indeed some overall effect in the determinants of entrepreneurial attitude, although this did not reach statistical significance with our (one-session) protocol.

Indeed, one of the limitations of our study was our short stimulation protocol, consisting of just one session, and we think that more interesting results could be achieved in future studies with longer stimulation protocols. Also, our reduced sample size and the lack of a pre-/post- analysis (as the TAI test was not developed for allowing such analysis) likely prevented us from finding significant differences in other factors related to creativity and entrepreneurial mindset. Larger samples, preferentially including entrepreneurs and non-entrepreneurs, would also likely be useful for producing more population-level-applicable results. The integration in future entrepreneurship neuromodulation protocols of open answer questionnaires (such as the Alternates Uses Task [AUT] or the Insight Task [IT]), which can have two or more versions, is a suggestion for making pre- and post-analysis and — in the examples given — to more directly evaluate creativity/innovativeness in future neuroentrepreneurship research. Also, highly interesting would be to integrate tasks which, like in an entrepreneurial career, require a superior ambidextrous decision-making capacity (e.g.

gambling tasks such as a multi-armed bandit task) in neuromodulation protocols. In these gambling tasks, each options' reward probability is unknown to the player beforehand, and may even change throughout the game, thus needing an optimised exploration-exploitation balance. As such, for example, a researcher could compare the outcomes in such gambling tasks of two groups, one which was not subjected to neuromodulation and another which was (the DLPFC or other cortical regions involved in the higher-attention control mechanisms involved in such ambidextrous mindset such as the frontopolar cortex could be possible targets). These gambling tasks can also be integrated in protocols in such a way that they allow for a pre- and post-facto analysis, thus allowing a researcher to directly evaluate the effect of such neuromodulation in the volunteers' decision-making capacity.

Finally, in future neuroentrepreneurship studies, TAI scale may still be used as it provides a single tool for analysing multiple determinants of the entrepreneurial behaviour. As it, however, is not developed for a pre-/post- analysis, it would be interesting to design a protocol with two control groups, both subjected to the TAI test, but one with sham stimulation and the other without any suggestion of stimulation. This would allow the researcher to evaluate whether the volunteers' perceived subjection to neurostimulation would have any effects in the ensuing TAI scores. Comparison of the differences between the active and non-stimulation TAI scores and those of between the sham and non-stimulation group could then be used as proxy for a pre-/post- analysis.

The literature regarding the effects of neuromodulation on entrepreneurial, decision-making and creativity factors is steadily increasing. Our study is a small contribution in such brain research, and we expect it can contribute to helping understating a part of the functioning of such delicate and marvellous ultimate black box.

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# Annex 1 — Written form on socio-demographic data and fulfilment of the inclusion and exclusion criteria

## Inquérito aos Voluntários

*A informação cedida neste documento é para uso exclusivo do projecto, e todas as respostas dadas serão mantidas em extrema confidencialidade e só serão ligadas ao nome da pessoa em casos de dúvida ou esclarecimento de alguns parâmetros.*

***CÓDIGO*** ____________

**Data de nascimento** ____________________

**Sexo**: Feminino ☐ Masculino ☐

**Profissão** ____________________________________

**Escolaridade** ____________________________________

1. **Já lhe foi diagnosticada algum tipo de doença?**

Sim ☐ Não ☐

Em caso de resposta afirmativa indique qual(ais): ____________________

________________________________________

2. **Alguma vez sofreu de algum destes sintomas (preencha em caso afirmativo)?**

Síncopes ☐

Palpitações ☐

Tonturas ☐

Alterações da fala ☐

Convulsões ou outras crises epilépticas ☐

Acufenos/zumbidos/problemas auditivos ☐

Disestesias ☐

Parestesias ☐

Alterações da visão ☐

Cefaleias ☐

Alt. da força ☐

Outro(s) ☐ ____________________________________

________________________________________

*Se preencheu algum parâmetro nos pontos **1** e **2**, por favor responda às seguintes questões, especificando qual dos sintomas a que se refere:*

**Em que circunstâncias ocorreu o episódio?** ____________________

________________________________________

**Quanto tempo decorreu desde a última sintomatologia?** ____________________

________________________________________

Com que frequência (diário/semanal/mensal/ anual)? ______________________________
_________________________________________________________________________

Quanto tempo costumam durar os episódios? ______________________________
_______________________________________________________

Já consultou um médico, pelas condições acima referidas?

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

Qual o diagnóstico final? ______________________________________________
_________________________________________________________________________

3. **Sofre de alguma patologia cardíaca?**

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

Qual? ____________________________________________________________
_________________________________________________________________________

4. **Sofre de alguma patologia respiratória?**

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

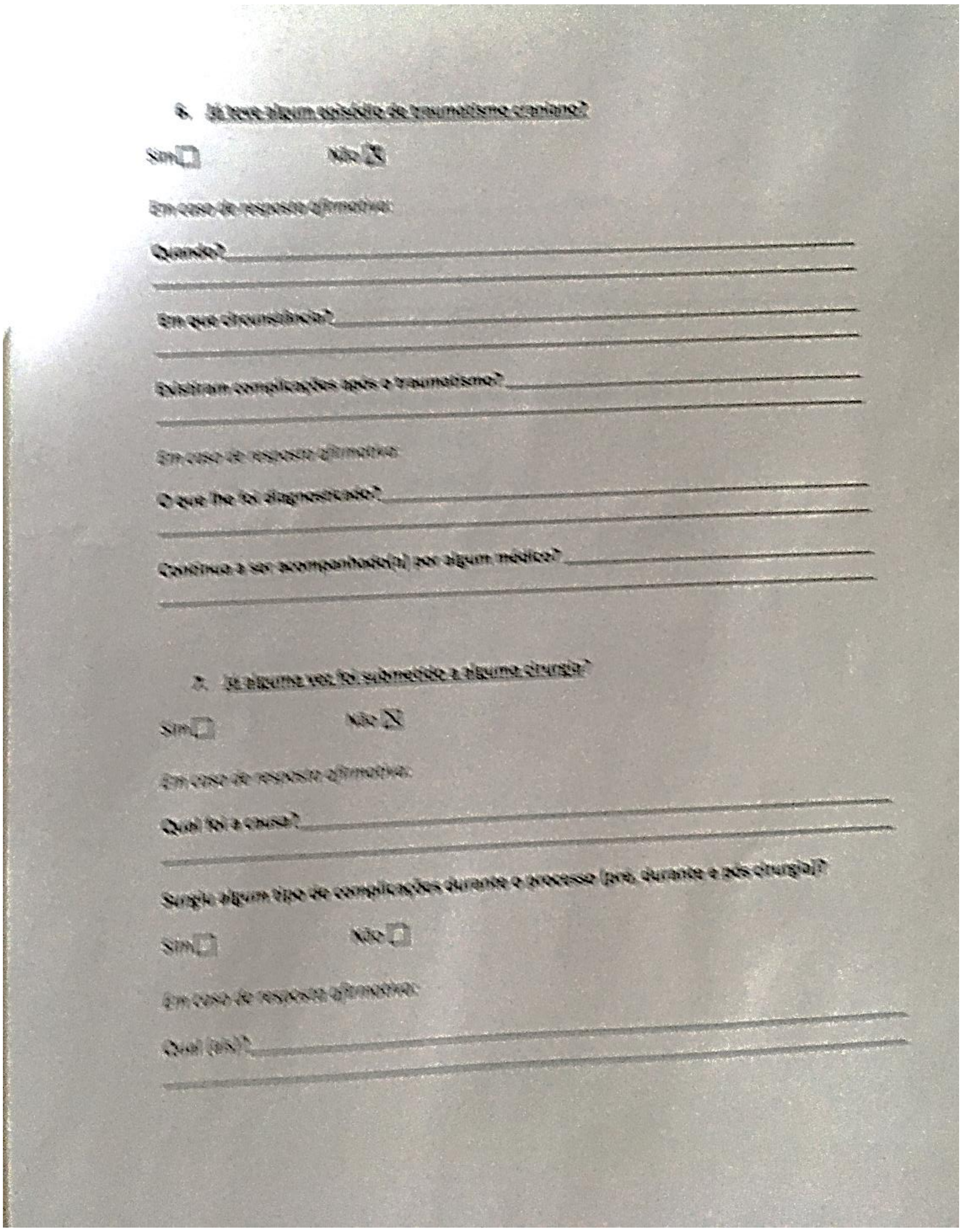
Qual? ____________________________________________________________
_________________________________________________________________________

5. **Sofre de alguma patologia neurólogica / psiquiátrica?**

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

Qual? ____________________________________________________________
_________________________________________________________________________



6. Já teve algum episódio de traumatismo craniano?

Sim ☐ Não ☒

Em caso de resposta afirmativa:

Quando? ______________________________

______________________________

Em que circunstância? ______________________________

______________________________

Existiram complicações após o traumatismo? ______________________________

______________________________

Em caso de resposta afirmativa:

O que lhe foi diagnosticado? ______________________________

______________________________

Continua a ser acompanhado(a) por algum médico? ______________________________

______________________________

7. Já alguma vez foi submetido a alguma cirurgia?

Sim ☐ Não ☒

Em caso de resposta afirmativa:

Qual foi a causa? ______________________________

______________________________

Surgiu algum tipo de complicações durante o processo (pré, durante e pós cirurgia)?

Sim ☐ Não ☐

Em caso de resposta afirmativa:

Qual (ais)? ______________________________

______________________________

**8. Faz, actualmente, alguma medicação?**

Não ☐

Sim ☐ Qual? ______________ Causa: ______________

Qual? ______________ Causa: ______________

Qual? ______________ Causa: ______________

**9. Quanto aos seus hábitos**

**Na última semana, em média, quantas horas dormiu por noite?**

>8h ☐ 8h a 7h ☐

6h a 5h ☐ 5h a 4h ☐

<4h ☐

**Na última semana, em média, quantos dias saiu à noite?**

0 ☐ 1 a 2 ☐

3 a 4 ☐ 5 a 6 ☐

7 ☐

**Consome álcool?**

Não consumo álcool ☐

Sim ☐

*Em caso afirmativo responda aos dois pontos abaixo,*

Diariamente ☐ Semanalmente ☐ Ocasionalmente ☐

O que consome/consumiu e em que quantidades.______________________________________________

______________________________________________________________________

______________________________________________________________

**Consome drogas?**

Não consumo drogas ☐

Sim ☐

*Em caso afirmativo responda aos dois pontos abaixo,*

Diariamente ☐ Semanalmente ☐ Ocasionalmente ☐

O que consome/consumiu e em que quantidades______________________________________________

______________________________________________________________________

______________________________________________________________

**Tem algum tipo de prótese metálica? ( no cérebro, implantes cocleares, neuroestimulador, pace-maker ou linhas cardíacas, aparelho de infusão de medicação).**

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

Onde?_________________________________________________________________

______________________________________________________________________

**Tem alguma derivação ventricular ou medular?**

Sim ☐ Não ☐

**Usa aparelho dentário?**

Sim ☐ Não ☐

**Usa piercings?**

Sim ☐ Não ☐

*Em caso de resposta afirmativa:*

Onde?________________________________________

____________________________________________

**Está grávida ou tem possibilidade de estar grávida?**

Sim ☐ Não ☐

**Tem-se sentido deprimido(a), em baixo, sem motivação, nas últimas duas semanas?**

Sim ☐ Não ☐

Outro ☐ ________________________________________

____________________________________________

**Já fez RMN-CE ou medular alguma vez?**

Sim ☐ Não ☐

**Já fez ETM alguma vez?**

Sim ☐ Não ☐

Covilhã, _____/__________/_____

________________________ ________________________

(Assinatura do Voluntário) (Assinatura do Responsável)

# Annex 2 — Written consent form

1

## CONSENTIMENTO INFORMADO

O/a voluntário/a Sr./Sra.______________________________________________, nascido/a a ___/___/______, aluno da Universidade da Beira Interior, foi DETALHADAMENTE INFORMADO SOBRE o projecto de investigação que vai fazer parte, intitulado "ESTUDO PILOTO SOBRE O EFEITO DA ESTIMULAÇÃO MAGNÉTICA TRANSCRANIANA SOBRE A CAPACIDADE CRIATIVA E EMPREENDEDORA EM ALUNOS UNIVERSITÁRIOS.", que de forma resumida consiste no seguinte protocolo:

FASE I

- Avaliação dos critérios de inclusão e exclusão.

FASE II

- Aplicação de escalas sobre criatividade e empreendedorismo associadas a uma única sessão de estimulação magnética transcraniana, nomeadamente TBS.

Informamos que a sua participação é voluntária, podendo desistir a qualquer momento sem que por isso venha a ter qualquer prejuízo; informamos ainda que todos os dados recolhidos serão confidenciais.

O/a voluntário/a foi informado/a sobre os riscos e possíveis efeitos secundários INERENTES às técnicas que serão usadas – anexo I.

O/a voluntário/a declara não fazer parte de nenhum grupo de risco de acordo com as informações referidas no anexo I.

O/a voluntário/a declara não usar, publicar nem de outra forma revelar, pessoalmente ou por interposta pessoa, quaisquer informações ou documentos directa ou indirectamente ligados à investigação em causa.

- - - - -

Com tudo isto e tendo o direito à liberdade de todos os cidadãos, o voluntário entende e aceita os anteriores pontos, de forma a assinar o presente CONSENTIMENTO INFORMADO de livre e espontânea vontade, sem receber qualquer benefício em troca.

______________________________ Covilhã, ____/________/ ______

(Assinatura do Voluntário)

---

O investigador declara que forneceu a informação necessária e explicou e respondeu a todas as questões e dúvidas apresentadas pelo voluntário.

______________________________ Covilhã, ____/________/ ______

(Assinatura do Investigador)

Equipa de investigação FCS-UBI

Maria da Assunção Vaz Patto; João Carlos Correia Leitão; Nuno Filipe Cardoso Pinto;

*Os investigadores declaram não existir nenhum conflito de interesses ou auferirem incentivos financeiros para esta investigação.*

*Contactos: 275329002/916101225*

# Anexo I

Objectivo Primário do projecto:

Avaliação da capacidade de intervenção da estimulação magnética transcraniana na modulação da actividade das redes neuronais intervenientes nos processos de criatividade e capacidade empreendedora, em alunos universitários saudáveis.

**Critérios de inclusão:** Idade superior a 18 anos; Aluno/a da Universidade da Beira interior; Ser destro.

**Critérios de exclusão:** Antecedentes de epilepsia ou outras doenças neuropsiquiátricas não controladas. Presença de elementos de metal na cabeça (excluindo região oral). Antecedentes de patologia tumoral. Presença de Pacemakers ou linhas intracardíacas. Antecedentes de patologia cardíaca grave. Pressão intracraniana aumentada. Antecedentes de alcoolismo crónico. Voluntários que não possam submeter-se aos testes (limitação física ou cognitiva).

Possíveis efeitos secundários INERENTES apenas para a técnica de Estimulação Magnética Transcranina *(fenómenos muito raros, de acordo com as guidelines do último consensus de segurança em EMT - Rossi et al, 2009):*

Algum ruído junto do ouvido na altura da aplicação dos pulsos magnéticos e que alguns sujeitos podem achar desagradável. Desconforto local transitório (escalpe, face ou pescoço). Ocasional cefaleia transitória. Ocasionais parestesias de curta duração no hemicorpo contralateral e dependendo do local de estimulação. Convulsão – *evento possível mas muito raro (apenas 1 caso reportado desde 2005, num sujeito com privação de sono e estimulação com intensidade superior ao protocolado neste estudo).* Síncope – *evento possível mas como epifenómeno – não resultante directamente do efeito da EMTr.*

# Annex 3 — Entrepreneurial Attitude Test (Portuguese version)

**Note:** In our study, volunteers answered on a computer the following Portuguese version of the online TAI form. The following table presents the 15 questions they declared their level of agreement with (on a 1-to-5-point scale). The multiplying factors used by the software to calculate the global TAI score are presented in the second table.

Adapted from Rocha, C.; Caetano, L.; Santos, HL. Manual sobre Empreendedorismo Social. Conversas Associação Internacional; 2020. pps. 49-50. Available in https://socialentrepreneur.eu/wp-content/uploads/2021/11/Manual_PT.pdf

| **Item** | **Declaração** | **Pontuação (1 a 5)** |
|---|---|---|
| 1 | Tento frequentemente organizar e gerir o trabalho de outras pessoas. | |
| 2 | Sinto que tenho constantemente novas ideias. | |
| 3 | Sinto que tenho controlo total sobre o que me acontece. | |
| 4 | Quando não se pode vencer alguém por ser mais forte, é bom formar uma equipa com ele em antecipação de tempos melhores. | |
| 5 | Não tenho medo de perseguir objectivos ambiciosos, mesmo que estes exijam esforços consistentes e contínuos. | |
| 6 | A pessoa que quer ser bem-sucedida na vida deve esconder os seus sentimentos dos outros. | |
| 7 | Se me proponho um objectivo, quero alcançá-lo a qualquer custo. | |
| 8 | Posso estar satisfeito com o meu trabalho mesmo que outras pessoas o desprezem ou ignorem. | |
| 9 | O sucesso social fascina-me, adoro a fama e a notoriedade. | |
| 10 | Posso sempre encontrar o lado positivo em situações indesejadas. | |
| 11 | Sinto que posso sempre fazer com que as coisas corram como eu quero. | |
| 12 | O que é diferente e invulgar estimula a minha curiosidade. | |
| 13 | Admiro as pessoas que podem dizer coisas desagradáveis de forma a ter graça. | |
| 14 | As minhas decisões sempre tiveram consequências positivas. | |
| 15 | Faço o meu trabalho principalmente porque estou interessado no seu conteúdo. | |

| Item | Resposta | Factor Multiplicativo | Pontuação Ponderada |
|---|---|---|---|
| 1 | | 3 | |
| 2 | | 2 | |
| 3 | | 1 | |
| 4 | | 3 | |
| 5 | | 1 | |
| 6 | | 1 | |
| 7 | | 2 | |
| 8 | | 2 | |
| 9 | | 1 | |
| 10 | | 3 | |
| 11 | | 3 | |
| 12 | | 1 | |
| 13 | | 3 | |
| 14 | | 2 | |
| 15 | | 2 | |
| **Pontuação total** | | | |