UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO

ZAHRASADAT VAZIRIKANGOLYA

Down-regulation of tinnitus negative valence through concurrent HD-tDCS and positive emotion induction: effects on neural and behavioral correlates

Ribeirão Preto

2022

ZAHRASADAT VAZIRIKANGOLYA

Down-regulation of tinnitus negative valence through concurrent HD-tDCS and positive emotion induction: effects on neural and behavioral correlates

Versão Corrigida

Tese apresentada ao Programa de Pós-Graduação em Medicina (Neurologia) da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências.

Área de Concentração: Neurociência

Orientador: Prof. Dr. João Pereira Leite

Ribeirão Preto

2022

Vazirikangolya, Zahrasadat

Down-regulation of tinnitus negative valence through concurrent HD-tDCS and positive emotion induction: effects on neural and behavioral correlates. Ribeirão Preto, 2022.
106 p.

Tese de Doutorado, apresentada à Faculdade de Medicina de Ribeirão Preto/USP. Área de concentração: Neurociência.

Orientador: Pereira Leite, João.

1.Estimulação transcraniana por corrente contínua de alta definição. 2.Indução de emoção positiva. 3.Ressonância magnética funcional. 4.Regulação emocional. 5.Modelo neurofuncional de zumbido. 6.Córtex pré-frontal dorsolateral. 7.Inventário de deficiência de zumbido

ZAHRASADAT VAZIRIKANGOLYA

Down-regulation of tinnitus negative valence through concurrent HD-tDCS and positive emotion induction: effects on neural and behavioral correlates

Tese apresentada ao Programa de Pós-Graduação em Medicina (Neurologia) da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências.

Aprovado em: ____/____/____

BANCA EXAMINADORA

Prof.(a), Dr.(a) ______________________________
Instituição ______________________________
Julgamento ______________________________

Prof.(a), Dr.(a) ______________________________
Instituição ______________________________
Julgamento ______________________________

Prof.(a), Dr.(a) ______________________________
Instituição ______________________________
Julgamento ______________________________

Prof.(a), Dr.(a) ______________________________
Instituição ______________________________
Julgamento ______________________________

AGRADECIMENTO

First, I would like to express my sincere appreciation to my supervisor, Prof. João Pereira Leite, for his constant support and encouragement during this journey. Thank you for enabling me to finalize the work, for providing this learning opportunity and for motivating me to endure the challenges I faced throughout my PhD. This would not have been possible without your support and I am grateful forever.

I would also like to acknowledge my gratitude to Prof. Miguel Angelo Hyppolito for his support in recruiting patients and facilitating this process. Special thanks to Prof. Carlos Ernesto Garrido Salmon for his countless hours dedicated to helping me with data analysis and for his patience in reviewing my work and providing constructive feedback.

I am highly thankful to the thesis committee members, Prof. Paulo Sergio Boggio, Prof. Amber Leaver and Prof. Vahid Nejati for their insightful comments, invaluable advice, and giving their time to improve my work.

I am also appreciative of Neurocognitive Engineering Lab, InBrain Lab, and CEOF staff for their help in different aspects of the work. A huge thank you to all of the tinnitus patients who have gave their time to tinnitus project. I remain deeply appreciative for their collaboration.

Most importantly, I would like to express my deepest gratitude to my family for their unconditional love and endless support throughout this thesis journey; and for always standing by my side reminding me of my strengths and keep going when it was hard and disappointing. I would never have come this far without their patience and support. My lovely family, this is dedicated to you.

“O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Código de Financiamento 001”

RESUMO

Regulação para baixo da valência negativa do zumbido através de HD-tDCS concomitante e indução de emoções positivas: efeitos sobre correlatos neurais e comportamentais

A percepção consciente do zumbido subjetivo, experimentado como uma sensação de toque ou zumbido na ausência de uma fonte externa, influencia cerca de 30% da população geral. Pacientes com transtorno clínico do zumbido experimentam uma situação altamente perturbadora e debilitante, tornando-a mais complicada do que simplesmente experimentar um som fantasma que os incita a procurar ajuda médica. Com sua alta prevalência e impacto potencialmente devastador no bem-estar psicológico de uma pessoa, a demanda por um tratamento clínico eficaz do zumbido é altamente priorizada. No entanto, atualmente não há cura universal especificamente adaptada para aliviar o sofrimento do zumbido. Nosso conhecimento do transtorno do zumbido ainda é limitado em termos de seus mecanismos neurais subjacentes e causas que exigem a necessidade de desenvolvimento de tratamentos, aliviando o sofrimento do zumbido. À luz das previsões acerca do modelo neurofuncional do zumbido e da aplicação da estimulação elétrica transcraniana, realizamos um estudo utilizando simultaneamente técnicas de estimulação transcraniana por corrente contínua de alta definição (HD-tDCS) e técnicas de indução de emoção positiva (PEI) por dez sessões consecutivas para regular a valência negativa do zumbido em pacientes com zumbido de angústia clínica. Recrutamos exames de ressonância magnética funcional em estado de repouso de doze pacientes antes e após a intervenção para examinar alterações de conectividade funcional em estado de repouso (rsFC) em regiões específicas de sementes. Os resultados mostraram rsFC reduzido no pós entre as regiões de atenção e processamento de emoção como se segue: 1) amígdala bilateral e lóbulo parietal superior esquerdo (SPL), 2) amígdala esquerda e SPL direito, 3) córtex pré-frontal dorsolateral bilateral (dlPFC) e pré-genual anterior bilateral córtex cingulado (pgACC), 4) dlPFC esquerdo e pgACC bilateral. Além disso, os escores do tinnitus handicap inventory foram significativamente menores no pós-intervenção em comparação com o pré-intervenção. Conclusão: HD-tDCS concomitante com PEI podem ser eficazes na redução da valência negativa do zumbido, aliviando assim o desconforto do zumbido.

Palavras-chave: Estimulação Transcraniana por Corrente Contínua de Alta Definição, Indução de Emoção Positiva, Ressonância Magnética Funcional, Regulação Emocional, Modelo Neurofuncional de Zumbido, Córtex Pré-Frontal Dorsolateral, Inventário de Deficiência de Zumbido.

ABSTRACT

Down-regulation of tinnitus negative valence through concurrent HD-tDCS and positive emotion induction: effects on neural and behavioral correlates

Conscious attended awareness perception of subjective tinnitus, experienced as a ringing or buzzing sensation in the absence of an external source, influences roughly 30% of the general population. Patients with clinical distress tinnitus experience highly disruptive and debilitating situation making it more complicated than simply experiencing a phantom sound urging them to seek medical help. With its high prevalence and potentially devastating impact on a person's psychological well-being, the demand for an effective clinical treatment of tinnitus is highly prioritized. However, at present there is no universal cure specifically tailored for alleviating tinnitus distress. Our knowledge of tinnitus distress is still limited in terms of its underlying neural mechanisms and causes which necessitate the need for development of treatments, alleviating tinnitus distress. In light of the neurofunctional tinnitus model predictions and transcranial electrical stimulation application, we conducted a study concurrently utilizing high-definition transcranial direct current stimulation (HD-tDCS) and positive emotion induction (PEI) techniques for ten consecutive sessions to down-regulate tinnitus negative valence in patients with clinical distress tinnitus. We recruited resting-state functional magnetic resonance imaging scans of twelve patients before and after the intervention to examine resting-state functional connectivity (rsFC) alterations at specific seed regions. Results showed reduced rsFC at post between attention and emotion processing regions as follows: 1) bilateral amygdala and left superior parietal lobule (SPL), 2) left amygdala and right SPL, 3) bilateral dorsolateral prefrontal cortex (dlPFC) and bilateral pregenual anterior cingulate cortex (pgACC), 4) left dlPFC and bilateral pgACC. Moreover, Tinnitus Handicap Inventory scores were significantly lower at the post-intervention compared to pre-intervention. Conclusion: Concurrent HD-tDCS and PEI might be effective in reducing tinnitus negative valence, thus, alleviating the tinnitus distress.

Keywords: High-definition transcranial Direct Current Stimulation, Positive Emotion Induction, Functional Magnetic Resonance Imaging, Emotion Regulation, Neurofunctional Tinnitus Model, Dorsolateral Prefrontal Cortex, Tinnitus Handicap Inventory

List of Figures

List of Tables

List of Abbreviations

ABC	Arousal-Biased Competition
AN	Auditory Network
BOLD	Blood-Oxygenated Level Dependece
CAAP	Conscious Attended Awareness Perception
CEOF	Centro Especializado Otorrinolaringo e fonoaudiometria
COG	Center of Gravity
CON	Cingulo-Opercular Network
CS	Conditioned Stimulus
DAN	Dorsal Attention Network
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
ECL	Evaluative Conditional Learning
EEG	Electroencephalography
EST	Emotional Stroop Task
FPN	FrontoParietal Network
FRMI	Functional Magnetic Resonance Imaging
FWE	Family-Wise Error
HADS	Hospital Anxiety Depression Scale
HDTDCS	High-Definition transcranial Direct Current Stimulation
ICA	Independent Component Analysis
MDI	Major Depression Inventory
MRI	Magnetic Resonance Imaging
NAPS	Nencki Affective Picture System
NFTM	Neurofunctional Tinnitus Model
PEI	Positive-Emotion Induction
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PGACC	Pregenul Anterior Cingulte Cortex
PTA	Pure-Tone Average
ROI	Region of Interest
RS	Resting-state
RSFC	Resting-State Functional Connectivity
RSFMRI	Resting-State Functional Magnetic Resonance Imaging
SPL	Superior Parietal Lobule
STAI	State-Trait Anxiety Inventory
TDCS	Trancranial Direct Current Stimulation
THI	Tinnitus Handicap Inventory
TLQ	Tinnitus Loudness Question
TMS	Trancranial Magnetic Stimulation
US	Unconditional Stimuli
VAS	Visual Analogue Scale

Contents

Chapter 1: Preliminary Concepts

Tinnitus

Definition

The etymological origin of “Tinnitus” has been traced back to *tinnire* – a Latin word that means “to ring”. It was later defined in a much more expansive manner to refer to an “auditory phantom sensation experienced when no external sound source is present” (Eggermont and Roberts 2004). There are two aspects identified within this condition – a signal sound, and one’s response to this phantom sensation.

Tinnitus may vary across patients in terms of its primary identifying characteristics – it could be perceived centrally (in one or both ears), it may be an enduring condition, or an intermittent one. The phantom sound signals may vary in both pitch and loudness, commonly described in a range of variants, such as ringing, buzzing, whistling, or even humming.

Based on the etiology of the condition, tinnitus can generally be classified into objective and subjective categories. The former is associated with an uncommon condition wherein the sound perceived is related to a tangible, traceable source within the patient’s body – an auditory signal called a somato-sound, typically pathological and originating from a muscular or vascular source. The patient in this case may be detecting the pulsatile blood flow from vascular tumors in or around the middle/inner ear, leading to objective tinnitus (Sonmez, Basekim et al. 2007). This may also manifest as a “beating” sound produced by the involuntary contractions of the middle ear muscles, termed the myoclonus (Howsam, Sharma et al. 2005). While objective tinnitus refers to the common sensation of an abnormal sound source (Lanting, De Kleine et al. 2009), subjective tinnitus is much more common among patients, with no tangible or identifiable source of sound. The current thesis primarily focuses on chronic subjective tinnitus, one of the most frequently discussed conditions in the overarching context of tinnitus research.

Due to the complexity and subjective variations of tinnitus across individuals, it is typically not ascribed to a specific etiology, oftentimes even considered a symptom instead of a disease. (Henry, Dennis et al. 2005, Passi, Ralli et al. 2008). Notwithstanding this, several auditory conditions and otological diseases have been found to accompany the occurrence of tinnitus, such as retrocochlear tumors (like vestibular schwannomas) and Meniere's disease (Gimsing 2010). Extant literature has been thorough in its study of several co-morbid predictors of tinnitus common among individual patients, some of which were high-frequency hearing impairment (commonly found in age-related hearing loss as well), excessive exposure to noise, and history of discharge from the ear (Heffner and Harrington 2002). While this may be the case, the distinction between the cause of tinnitus and the factors that perpetuate its manifestations remains paramount to a specialist.

Henry, Dennis et al. (2005) conducted a study with more than 2000 patients that suffered from tinnitus to trace the causes and common factors across the cases. It was found that the most common factors observed across the group were trauma and prolonged noise exposure (22%), followed by head and neck injury (17%). Drugs and other medical conditions accounted for 13% of the total cases while 10% of the patients reported the common factor of infections and neck illness. Meanwhile, 38% of the remaining subjects failed to pinpoint a particular cause for their tinnitus; an issue common to most patients. While not as prevalent as other reported variables, the side effects of many drugs have often been associated with chronic or temporary tinnitus. Although tinnitus has been outlined as a possible side effect of over 300 over-the-counter and prescription drugs, the effect of such medications is dependent on a multitude of factors such as dosage, body size, metabolism, pharmacokinetic interactions, and genetic predispositions of the patient (Cianfrone, Pentangelo et al. 2011).

Experiences of tinnitus, as previously mentioned, may vary significantly across patients – while some may not be as challenged by it to warrant seeking out medical help, yet others may feel severely distressed by it, resulting in stress, anxiety, lack of sleep, and affected concentration, thereby impacting the overall quality of life (Halford and Anderson 1991, Dobie 2003, Hallam, McKenna et al. 2004, Crönlein, Langguth et al. 2007, Vanneste, Plazier et al. 2010). While this demarcates the urgent need for prioritizing effective clinical treatment, there is presently no licensed medication that focuses on relieving subjective tinnitus. Regardless of its centuries-old documentation as a disorder, the underpinning neural mechanisms and root causes for tinnitus are yet barely identified; this may be due to the heterogeneous nature of tinnitus itself and the possibility that it may originate from a number of etiologies. Thus, it is generally believed that no single theory of tinnitus could sufficiently explain it completely, thereby warranting further research and speculation.

Mechanisms of Tinnitus

Despite the dearth of adequate research to identify causes for various forms of tinnitus, it has generally been agreed that after damages to peripheral auditory structures (resulting in hearing loss), modifications in the central auditory system’s neuronal firing patterns may result in the precept (Eggermont and Roberts 2004, Roberts, Eggermont et al. 2010). Such peripheral damage is typically expressed as hearing loss, which is commonly associated with tinnitus. However, studies have offered that even patients without hearing loss may suffer from tinnitus (Stouffer and Tyler 1990, Jastreboff and Jastreboff 2003). This hypothesis is also brought into question, as the hearing loss may not always be completely detected during standard pure tone audiometry (PTA) (Fabijańska, Smurzyński et al. 2012). For instance, it was found that tinnitus persisted in patients following the sectioning of their eight auditory nerves; from this, it can be inferred that while peripheral damage may be considered cause for the origin of tinnitus, central mechanisms may be what facilitate its persistence (House and Brackman 1981).

Kaltenbach (2011) offers a comprehensive model of tinnitus, alluding to evidence from studies conducted with both humans and animals. This model suggests that tinnitus may be triggered by injury to the auditory periphery, cochlear hair cell damage as a result of noise exposure, ototoxicity, or aging – altogether resulting in "plastic changes" within higher central auditory regions due to a decrease in auditory nerve activity (Salvi, Wang et al. 2000, Heffner and Harrington 2002, Guitton, Caston et al. 2003, Caspary, Ling et al. 2008). Furthermore, this is precisely what alters the balance between excitatory and inhibitory activity, causing a decrease in inhibition and a rise in hyper-excitatory activity within the central auditory system – this process has been proposed to be the neural correlate of tinnitus.

From the studies carried out on animals in the context of tinnitus, some of the several neural mechanisms identified include (1) modifications in the firing rate within the central auditory system during rest (Norena and Eggermont 2003), (2) changes in the temporal pattern of spontaneous activity (potentially manifesting as burst firing in single neurons/synchronous firing in groups of neurons – which are termed neural synchrony) (Norena, Tomita et al. 2003, Seki and Eggermont 2003) and lastly, (3) the cortical tonotopic map being reorganized (Mühlnickel, Elbert et al. 1998, Eggermont and Komiya 2000, Norena and Eggermont 2003). It is significant to note that, according to an fMRI study in human patients, it was found that the tonotopic map reorganization is not necessarily imperative for tinnitus to occur (Langers, van Dijk et al. 2007). However, Eggermont (2015) clearly indicates that the study made use of participants that were reported to have clinically normal hearing (< 20dB thresholds up to 8 kHz).

Non-Auditory Mechanisms of Tinnitus

While most models are centered on the loss of hearing, it remains ambiguous whether it is the only trigger that exists. Some make an effort to explain the reasons for which strong emotional and attentional properties may be attributed to tinnitus. For instance, the earliest models of tinnitus note that it is accompanied by emotional responses like anxiety, frustration, and depression (Hallam, Jakes et al. 1988, Jastreboff 1990). According to Jastreboff (1990), a negative valence may be assigned in correspondence with the tinnitus via interactions across auditory and emotion processing systems, thereby enabling it to receive further attention, and thus, persist as a condition.

Tinnitus may adversely impact the cognitive control of the patient, leading to attention deficit; one among the many abnormalities that can practically alter the anatomy, activity, and interactivity of the human brain. Such alterations are what lead to the experienced discomfort, or the habituation and neuroplastic adaptation that these patients use to help cope with the tinnitus. Patients can be distracted from the phantom sensation by performing cognitively demanding tasks that are non-auditory in nature. This means that the awareness of tinnitus can be altered and modulated as necessary. In line with this notion, auditory attention has been considered the primary contributor to the atypical neural changes responsible for Tinnitus (Roberts, Husain et al. 2013).

This recent model proposes that the neural circuitry of auditory attention (consisting of the primary auditory cortex, superior temporal gyrus, and prefrontal regions) is constantly activated by changes in the auditory cortex as a result of hearing loss (for instance, enhanced neural synchrony throughout the pathways of the central auditory pathways). The basal forebrain cholinergic system in this neural circuitry is imperative for conscious processing and engaged with the prefrontal and thalamic regions to form neural plasticity and filter sensory information

– the slightest failure in filtering can lead to the development of tinnitus. The performance of non-auditory activities interrupts the neural circuitry via the basal forebrain cholinergic system, thereby reducing the perceived burden of tinnitus (Roberts, Husain et al. 2013).

While tinnitus often leads to emotional responses from the patient, these emotional states can also regulate its perception itself; an interplay that has been associated with the activity of the hippocampus, amygdala, and insula, among other limbic structures (Tyler and Baker 1983, Hallam, Jakes et al. 1988, Jastreboff 1990). Just as the limbic system is neuroanatomically connected with the central auditory regions that prompt the production of emotional responses to auditory stimuli, it is also connected to the auditory areas that regulate the perception of sound, based on emotional processing.

A model proposed by Rauschecker, Leaver et al. (2010) suggests that the role of the limbic system extends beyond the emotional response to tinnitus, remaining pivotal to the persistence of tinnitus. In conjunction with the thalamus and prefrontal regions, the limbic system is capable of modifying the auditory information on the thalamic level, thereby affecting perception. The "normal" representation of auditory information is disturbed by abnormalities in the auditory cortex such as increased neural synchrony or hyperactivity. Utilizing an inhibitory gating mechanism, the limbic system alters such a disruption while relaying auditory information to the auditory cortex to "cancel out" the noise perception; failure within this process results in the production of a tinnitus sound (Rauschecker, Leaver et al. 2010).

Husain (2016) model is based on the framework of cognitive control of emotion, explaining the habituation and severity of tinnitus by incorporating systems of attention and emotion (Husain 2016). According to this model, the persistence of tinnitus leads to neural plasticity in the attention network, which in turn, modulates the emotional responses to tinnitus. An example of such neural reorganization is observed in the activation of the insula and the parahippocampus by the neural circuitry of the attention system, to bypass the amygdala and engage with the emotion system. While the amygdala is widely regarded as the part of the brain that assigns emotional salience to tinnitus, the insula mediates the stress caused by the condition. These changes supposedly result in habituation, followed by milder tinnitus, or the elimination of tinnitus in some cases. The lack of these changes in both attention and emotion networks is often considered a biomarker of bothersome tinnitus (Husain 2016).

The Neurofunctional Tinnitus Model (NfTM) is a recent model that classifies tinnitus patients into two groups – the "Neutral stage" and the "Clinical-Distress stage". Patients from the former group are able to perceive their tinnitus without any negative emotional responses to it, while patients from the "Clinical-Distress stage" perceive tinnitus with negative emotional responses due to the engagement and plasticity of the limbic system (Ghodratitoostani, Zana et al. 2016). Additionally, this model highlights the role of Evaluative Conditional Learning (ECL) and negative appraisals in the transition between "neutral" tinnitus and "clinical" tinnitus (Ghodratitoostani, Zana et al. 2016). ECL is a term used to denote the changes in favoring/disfavoring a particular stimulus (Conditioned Stimulus) due to the pairing of this specific stimulus with another positive/negative stimuli (Unconditioned Stimulus) (De Houwer, Thomas et al. 2001). Thus, through the ECL mechanism, the repetitive co-occurrence of tinnitus during the neutral stage (CS), when frequently paired with a negative unconditioned stimulus (US), the negative valence that is originally possessed by the US is ascribed to the CS. Following this association, the sound produced during tinnitus leads to discomfort, dislike, and annoyance (Ghodratitoostani, Zana et al. 2016).

While it is the ECL mechanism that determines the emotional value of the tinnitus, the cognitive value in this context is manifested via negative appraisals (Ghodratitoostani, Zana et al. 2016).

Examples of such appraisals are: "the noise makes my life unbearable," "it will drive me crazy" or "it will overwhelm me" (Handscomb, Hall et al. 2017). When negative appraisals and the ECL mechanism repeatedly concur, a negative cognitive-emotional value of the sound is resulted, thus leading to its persistence Conscious Attended Awareness Perception (CAAP). This is supported by the involvement of the limbic system in a valuation process of the tinnitus, resulting in the negative reactions for tinnitus in clinical distress stage (Ghodratitoostani, Zana et al. 2016).

Most data that support the above-mentioned models have been sourced from animal studies and noninvasive human brain imaging. Presently, none of these models can be refuted due to a lack of sufficient empirical evidence. However, brain imaging in general, particularly magnetic resonance imaging (MRI), has increasingly been used to delineate neural correlates of tinnitus, and offer knowledge that would allow for the elaboration of the models listed so far. Several studies that have used functional MRI (fMRI) elicited information regarding the modifications in auditory, attention, emotion, and cognitive control system, thereby outlining the characteristics of tinnitus to an extent. This would further the facilitation of the development and evaluation of interventions that help to assess the efficiency of particular methods of treatment.

Functional Magnetic Resonance Imaging

Used to capture high-resolution images of the human anatomy in terms of biological and cognitive function, fMRI is a composite technique for neuroimaging developed in the 1990s that has greatly supported research into *in vivo* brain functions (Ogawa, Lee et al. 1990, Kwong, Belliveau et al. 1992). Based on the MRI, this form of imaging is particularly sensitive to hemodynamic variations that arise from underpinning neural activity. Research using fMRI has garnered great attention over the past 20 years due to its noninvasive feature of producing high-resolution images. It cleanly replaced other fallible methods such as positron emission tomography (PET), which depended on exogenous radioactive contrast agents that are typically invasive and generally considered harmful.

The human brain is a complex network of processes. Even when it may appear to be in a state of rest, it continually processes and conveys information across anatomical areas that are spatially distributed, but functionally associated (Van Den Heuvel and Pol 2010). Patterns of brain activity during states of rest have garnered attention in the past few years; such research has been facilitated by fMRI techniques that offer novel methods to characterize such intricate networks of brain activity. Furthermore, these measures provide further insight into the strength and direction of functionally connected regions of the brain and its overall functional organization (Van Den Heuvel and Pol 2010).

Functional Connectivity

Variance in the blood oxygenation level-dependent (BOLD) signals are used to evaluate the state of neural activity in fMRI (Ogawa, Lee et al. 1990, Raichle, MacLeod et al. 2001). “Functional connectivity” refers to the relationship of various anatomical parts of the brain to exchange information; also defined as “temporal correlations between spatially remote neurophysiological events” (Friston, Frith et al. 1993). With regard to fMRI, this is evaluated by initially measuring the low frequency (~ 0.01 - 0.1 Hz) spontaneous fluctuations in the BOLD signals that are observed within varying locations in the brain (Rogers, Katwal et al. 2010). This is followed by a statistical comparison of the level of co-activation between each BOLD signal time series. Functional connectivity merely refers to the temporal correlations across neural events that take place in spatially independent areas of the brain. According to Buxton (2016), the correlation measures of BOLD signals are not inherently concerned with the amplitude of the BOLD signals.

Resting-state Networks

Patterns of spatially independent, temporally correlated signals that are presumed to represent functional systems underpinning primary cognitive and perception-based processes have been termed "resting-state networks" (rs networks) (Cole, Smith et al. 2010, Lee, Smyser et al. 2013). One of the first groups to identify coherent BOLD fluctuations while employing resting-state fMRI (rsfMRI) was Biswal, Zerrin Yetkin et al. (1995) who established positive correlations between spontaneous BOLD signals in the left and right somato-motor cortices. Yet, this finding was not consistently accepted by the neuroscience community, setting precedent for the current debate regarding the actual origin of the resting-state BOLD signal.

While certain researchers argue that the BOLD signals emerge from myogenic or respiratory processes (Birn, Diamond et al. 2006, Chang, Cunningham et al. 2009), it has also been reported that BOLD signal oscillations are independent of respiratory (0.1-0.5 Hz) and cardiac oscillations (0.6-1.2 Hz), which are generally higher in terms of frequency (Cordes, Haughton et al. 2001). Damoiseaux, Rombouts et al. (2006) posit that BOLD have a neuronal origin that stems from their physical original within functionally relevant areas of the cortical gray matter. A variety of rs networks have presently been identified; some of which include, attention, visual, default, and auditory mode (Damoiseaux, Rombouts et al. 2006, Mantini, Perrucci et al. 2007).

Clinical Applications

Studies that focus on rs networks have been employed with relation to clinical populations to detect various connectivity differences that underpin chronic neurological and psychological disorders (Lee, Smyser et al. 2013).

Using fMRI to Measure Resting-State Connectivity

Three widely adopted methods have been used to analyze resting-state functional connectivity (rsFC)– the independent components analysis (ICA), seed-based analysis, and graph connectivity analysis. The independent components analysis employs the time courses of voxels to generate a particular number of components that are spatially isolated and carry certain correlations with the time course of voxels.

The second type of analysis, seed-based analysis, uses a prior hypothesis concerning the seed region that can be evaluated by identifying the correlation between the selected time course of seed regions and the rest voxels of the brain.

Finally, graph connectivity analysis is used to determine the connection strength of network nodes via edges, based on selected brain regions. Various regions of the brain elicit a variety of statistical dependencies across distinct units (Van Den Heuvel and Pol 2010).

Neural Correlates of Tinnitus using rsFC

The influence of the tinnitus on the networks of auditory, default mode, attention, and emotion has been illustrated through a variety of empirical studies. However, the results of these studies remain inconsistent due to the difference in methodologies employed and the heterogeneous nature of the subject population.

Many studies have explored the role of functional connectivity in tinnitus using fMRI. As per various studies (Damoiseaux, Rombouts et al. 2006, Mantini, Perrucci et al. 2007, Smith, Fox et al. 2009), the auditory network was found to include the primary auditory cortex (within the Heschl’s gyrus) as well as the secondary cortex (situated in the superior temporal gyrus). According to Hackett (2011), subcortical auditory processing regions, part of the central auditory pathways, extending from the auditory nerve to the medial geniculate body within the thalamus make up the rest of the network.

The primary regions of the limbic network are the parahippocampus, the insula, and the amygdala, which altogether function for the processing of emotion (Stein, Wiedholz et al. 2007, Robinson, Laird et al. 2010).

Various networks operate for functions particularly associated with attention. Of these are the two major systems – the dorsal and the ventral system; while the dorsal system anatomically includes the bilateral frontal eye fields and intraparietal sulci, the ventral attention system is composed of the temporoparietal junction and the ventral frontal cortex (Fox, Snyder et al. 2005, Fox, Corbetta et al. 2006, Lee, Smyser et al. 2013). Each of these networks has been proven to be functionally varied – the dorsal attention network (DAN) operates for top-down voluntary attention while the ventral attention system is used to attend to unexpected stimuli (Corbetta and Shulman 2002, Fritz, Elhilali et al. 2007, Vossel, Geng et al. 2014).

The posterior cingulate cortex/precuneus, the medial prefrontal cortex, and the superior frontal gyrus have been considered important regions of the DMN (Mantini, Perrucci et al. 2007). An anti-correlation has been established between the DMN and task-positive networks, particularly the dorsal-attention system (Fox, Zhang et al. 2009), thereby deeming it an imperative network of focus in the context of tinnitus. As the tinnitus appears most bothersome during rest, studies on the resting state would support initiatives to distinguish tinnitus patients from control groups.

Auditory Network and Limbic System

An early study investigating altered FC among tinnitus patients with the use of fMRI compared the connectivity of auditory cortices with six healthy control patients that corresponded to the four tinnitus patients in terms of age (Kim, Kim et al. 2012). This comparison established an increase in connectivity between the limbic system and the auditory cortex among tinnitus patients using an ICA approach. This finding was in line with the theory that focused attention to the auditory system may result in heightened activity in the auditory cortex (Gu, Halpin et al. 2010).

Moreover, the left and the right primary and secondary auditory cortices represented four seed regions; correlations were evaluated across these four areas in a region of interest (ROI) analysis to find that a decreased connectivity existed between the left and right auditory cortices(Kim, Kim et al. 2012). Additionally, the computations revealed increased connectivity within the left amygdala and the dorsomedial prefrontal cortex in tinnitus patients, as opposed to healthy control subjects, thereby implying the existence of heightened intrinsic brain connectivity between the auditory networks and regions that are involved in cognitive control and emotion processing. Furthermore, the abovementioned results underpin the notion that a decrease in the balance of inputs (both excitatory and inhibitory) to the central auditory system may be associated with the occurrence of tinnitus(Kim, Kim et al. 2012). Such an imbalance may be inferred from the decreased interhemispheric coherence, wherein optimal functionality demands sufficient balance (Diesch, Andermann et al. 2010).

In a pivotal study, auditory ROI-data from 12 control subjects in terms of rsfc (identified using fMRI) was compared with data from 13 subjects that suffered from chronic tinnitus (Maudoux, Lefebvre et al. 2012). The latter group of patients exhibited high levels of coactivation between the left parahippocampal regions and auditory cortices, as compared to their control group peers. While the control group denoted normative thresholds for hearing, the tinnitus patients presented with differing degrees of severity and hearing loss (Maudoux, Lefebvre et al. 2012)

A study exploring a similar area of research established a high level of connectivity between the auditory networks and the left parahippocampal regions as compared with the control group. While such a trend has been observed among these patients upon comparison with their age/hearing-matched control group peers, the data elicited was not statistically significant. (Schmidt, Akrofi et al. 2013). The parahippocampal regions (in neuroanatomical conjunction with the secondary auditory cortices) carry an imperative role in the assessment of the salience of auditory input. This increase in functional connectivity between the auditory areas and the parahippocampal areas is indicative of the changes that take place in the neural circuitry of the limbic system to adjust and retain the salience of tinnitus during chronic tinnitus (Schmidt, Akrofi et al. 2013). This inference is closely aligned with the assumption of the tinnitus habituation model, which suggests that in response to tinnitus, the cognitive control of emotion undergoes some amount of change (Husain, 2016). Furthermore, it indicates the significance of the engagements between the auditory and the limbic system, which was initially posited by Rauschecker, Leaver et al. (2010).

Auditory Network and Visual System

Among patients with bilateral or unilateral bothersome tinnitus with slight hearing loss, a negative correlation was established between visual and auditory networks during states of rest (Burton et al., 2012). Participants that scored ≥ 18 on the Beck Depression Inventory questionnaire (Beck, Ward et al. 1961) and those who suffered from hyperacusis were excluded from the study. The established negative correlation is indicative of a dissociation between the two sensory modalities of sight and hearing, thereby evidencing the existence of an inhibitory mechanism used to block out sensory information irrelevant to the process of a sensory-specific modality. However, this dissociation had not been observed among patients that suffered from non-bothersome tinnitus (Wineland, Burton et al. 2012).

Attention-Related Networks

Potentially due to the interruption caused by the prolonged phantom auditory sensations that occur when the patient performs attention-demanding tasks, they may experience certain difficulties in terms of cognition and concentration. As previously mentioned, the dorsal and ventral systems are among the many various networks that are involved in the processes of attention. Atypical variables were recognized within the prefrontal cortices observed in tinnitus patients.

According to a group of researchers, the prefrontal cortex typically regulates the potential to switch attention across salient phantom auditory sensations and other states that are non-auditory in nature; furthermore, they discovered and identified various disruptions in the ventral attention network in subjects with bothersome tinnitus (Burton, Wineland et al. 2012). Such changes indicate that tinnitus leads to modifications in the composition of the attention systems, thereby influencing the involuntary reorientation of attention to salient sensory events – this remains in line with the attention model of tinnitus as well as the tinnitus habituation model based on cognitive control of emotion (Roberts, Husain et al. 2013, Husain 2016).

In a previously mentioned study that focused on experimental and control groups of subjects with non-bothersome tinnitus and age/hearing-matched peers, respectively, Schmidt, Akrofi et al. (2013) reported heightened levels of co-activity between the DAN and the left parahippocampal regions; which has been associated with responses to attend to or ignore the phantom noise, indicating the relationship between systems of attention and emotion proposed by Husain's model of tinnitus habituation (Husain 2016).

The previous study by Schmidt, Carpenter-Thompson et al. (2017) noted a pairing association between the DAN and the precuneus, a vital component of the DMN, among tinnitus patients. The connectivity between the two components is greatly influenced by prolonged and bothersome tinnitus, thus encouraging the hypothesis that a true state of rest is difficult to achieve among patients that endure chronic tinnitus.

Default Mode Network

The DMN remains active during states of rest and less active during the performance of a task. The operations of the DMN are associated with reflexive thinking, thinking about others, and thinking about the past or the future (Van Den Heuvel and Pol 2010).

Several studies have observed the differences in the coherency of the DMN. For instance, one study found that patients with non-bothersome tinnitus, in comparison with hearing loss control groups, presented weaker connectivity with the precuneus – an effect that was associated with the duration of the tinnitus (Schmidt, Akrofi et al. 2013).

Furthermore, the connectivity decreased further for patients with increased severity of tinnitus (chronic and bothersome). These results positively concurred with the study of Carpenter-Thompson, Schmidt et al. (2015), who had compared effects endured by patients with mild tinnitus (for over a year) with those who were recently diagnosed with the condition (between 6 and 12 months), to find similar results. Similarly, two studies in 2016 also demonstrated lower DMN connectivity among patients with tinnitus, in comparison with control groups that were hearing-matched (Lanting, WoźAniak et al. 2016, Leaver, Turesky et al. 2016). Deficiency in DMN coherency, which is typically associated with the extent of the rest-state, is indicated by a weakness in connectivity between the DMN and the precuneus or the posterior cingulate cortex. Due to the prolonged tinnitus that restricts patients from experiencing rest states as they are constantly required to suppress tinnitus sounds, the diminished coherency within tinnitus patients is justified (Shahsavarani, Khan et al. 2019)

Salient network

The framework of the salience network that is mainly composed of the dorsal anterior cingulate cortex and the anterior insula, may provide a different explanation for the engagements between the limbic and attention networks. The salience network is responsible for mediating attention to external stimuli that are considered relevant and operate in terms of the associated processing for cognition and emotion (Menon and Uddin 2010, Elton and Gao 2014).

Unlike the salience network, the executive network is composed of the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and inferior parietal lobules, functioning during states of rest as well as task (Dosenbach, Fair et al. 2007, Seeley, Menon et al. 2007, Sadaghiani, Hesselmann et al. 2009, Elton and Gao 2014).

Both these networks operate in different ways when paired with the DAN and the DMN. While it was reported that the salience network was associated with an increase in connectivity with the DMN while transitioning from a rest-state to a performance-related attention state, a heightened level of connectivity to the areas of the DAN was observed in the same conditions for the control network (Elton and Gao 2014).

In comparison with controls, variations in connectivity for the right anterior insula were found in patients suffering from tinnitus, thereby indicative modifications in terms of the functional connectivity of the salience network in cases of bothersome tinnitus (Burton, Wineland et al. 2012). Meanwhile, in a similar study with non-bothersome, there were no differences upon experiment-control comparison (Wineland et al., 2012) suggesting that differences in salience nwtrok is associated with tinnitus distress. A study in 2015 observed heightened levels of activation for the anterior insula while the tinnitus patient performed a visual attention task – this highlights the pivotal role that the salience network played in the development of tinnitus (Amaral and Langers 2015). Therefore, it is necessary to associate changes in the salience network, particularly in relation to the insula, during rest-states and task-states to bothersome tinnitus.

De Ridder, Vanneste et al. (2014), in their model-based explanations of the association between tinnitus distress and the salience network, mention that the anterior insula and the anterior cingulate play a key role in the production of such distress; While, it was later found that they are often increased in terms of activity in cases of chronic tinnitus (Vanneste and De Ridder 2011, De Ridder, Vanneste et al. 2014). According to Husain (2016), such contradictions may be attributed to the dual role played by the insula within the limbic system and salience network, warranting further investigation.

Taken together, as per the observations of Schmidt, Carpenter-Thompson et al. (2017), common trends noted by extant literature are illustrative of the modifications within the coherency of the DMN, the pairing of the default network with other networks, alterations that are typically observed in the attention networks and the engagements across the limbic and auditory systems (Husain 2016).

Nevertheless, studies that employ functional imaging typically adopt a correlational approach, due to which it would only succeed in outlining changes within the neuronal activity that are specifically associated with tinnitus. Thus, it fails to distinguish the alterations that are relevant in terms of causation as opposed to epiphenomena. Non-invasive brain stimulation techniques may further contribute with relation to such a limitation by modulating neural activity in the relevant regions.

Transcranial Direct Current Stimulation

Nitsche, Cohen et al. (2008) define transcranial direct current stimulation (tDCS) as a "non-invasive brain stimulation (NIBS) technique" used for cortical modulation. In 1800, the influence of electric currents on brain-related processes had been demonstrated practically, later studied objectively in academia in the 1960s (Bindman, Lippold et al. 1962, Creutzfeldt, Fromm et al. 1962, Bindman, Lippold et al. 1963, Purpura and McMurtry 1965). Regardless of the positive results acquired during these periods, tDCS has generally been discarded due to the nature of the findings it produces, in addition to the emergence of innovations in pharmacotherapy and transcranial magnetic stimulation. It was only around twenty years ago that the domain of NIBS was reinvented as an application for clinical neurophysiology with the advent of tDCS (Nitsche and Paulus 2000). Thus, the method has been widely popular among most clinical practitioners and neuroscience specialists (Dubljević, Saigle et al. 2014, Bestmann, de Berker et al. 2015).

Action mechanisms of tDCS – A Mechanistic View

Using two surface electrodes (one positive and the other negative) of 5x5cm 2 dimensions, direct electrical currents are passed through the skull (Miranda, Lomarev et al. 2006, Datta, Bansal et al. 2009, Edwards, Cortes et al. 2013). The electrical charge moves in the opposite direction as the current moves to the cathodal pole from the anodal pole. Thus, while the soma of particular cells is directed toward depolarization, apical dendrites in proximity to the anodal pole are typically assumed as moving towards hyperpolarization. Hyperpolarized and depolarized cell compartments may be reversed when cells receive impact from the cathodal pole during cathodal stimulation (see Figure 1). Recordings on the intracellular level demonstrate that direct stimulation that does not exceed 0.3mV leads to a shift in the membrane potential within pyramidal neurons (Bikson, Inoue et al. 2004, Radman, Ramos et al. 2009). Thus, based on the polarity of the stimulation, the resting membrane potential of the cell may shift towards a relatively increased positive/negative charge, which thereby gives rise to or decreases the potential of spontaneous neural firing to occur (Wagner, Valero-Cabre et al. 2007).

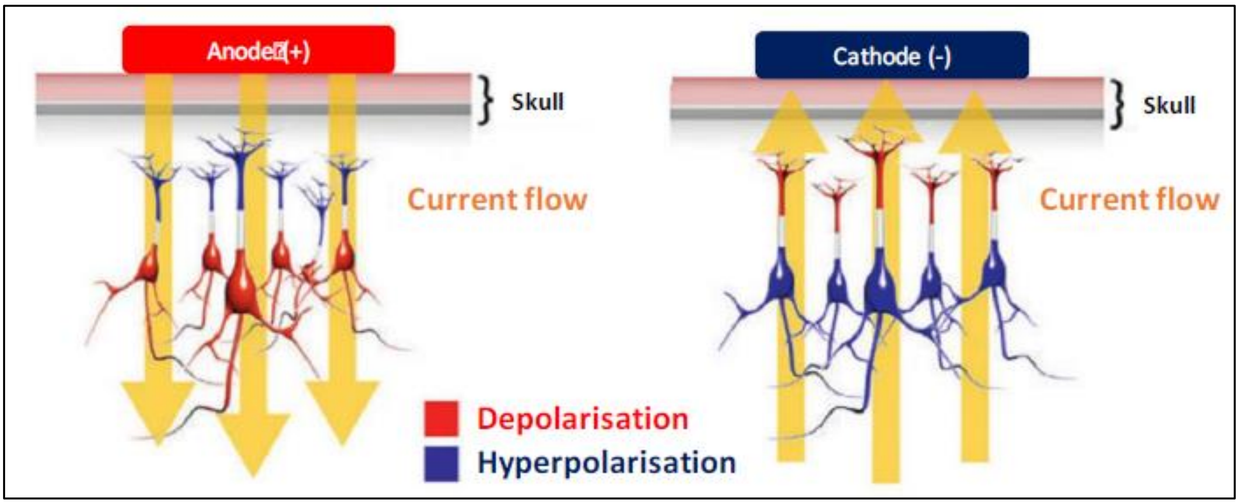


Figure 1.Action mechanisms of tDCS in the cortex beyond the anode and cathode. Adapted from (Moreno-Duarte, Gebodh et al. 2014)

Dose parameters of tDCS – non-linear relations and variability

Current intensity (Nitsche and Paulus 2000), size of the electrode (Wagner, Valero-Cabre et al. 2007), period of stimulation (Nitsche and Paulus 2001, Nitsche, Cohen et al. 2008), the frequency of treatment sessions (Nitsche and Paulus 2000, Nitsche and Paulus 2001, Nitsche, Liebetanz et al. 2003), intervals between sessions (Monte-Silva et al., 2013) and the electrode montage generally compose the stimulation parameters which tend to interact with one another and impact the consequences in addition to the duration of post-stimulation effects.

According to the computational models, even small displacements of 1cm for the electronic placement may influence the peak electric field and its distribution in the brain (Woods, Bryant et al. 2015). Ironside, O’Shea et al. (2016) demonstrated that tDCS that employed anodal-F3 and cathodal-F4 (rather than anodal-F3 and cathodal-Fp2) corresponded with decreased vigilance for threatening stimuli across subjects that presented with typical health conditions.

As it governs the volume of current that reaches the tissue of the brain, the relative distance between the cathode and the anode, the intensity of the electric field within the ROI, and the pattern of current flow are paramount factors (Weaver, Williams et al. 1976, Miranda, Lomarev et al. 2006, Datta, Baker et al. 2011, Bai, Dokos et al. 2014, Galletta, Cancelli et al. 2015). Thus, it follows that the mode of action and stresses for comparable electrode montages across research and positioning systems that are standardized are significantly impacted by the prevision of electrode positioning (Seibt, Brunoni et al. 2015).

Regardless, the multiple changes in the response patterns may also be observed even when all stimulation parameters are constant and the electrode montage is standardized (Strube, Bunse et al. 2016). Such variations may emerge from alterations in the anatomy of the skull, brain, or structural/functional associations (Datta, Baker et al. 2011, Rosso, Valabregue et al. 2014). For instance, consider how the electric current may not effectively peak in the presence of a particular electrode due to subjective anatomical variances that impact current-density clustering (Datta, Bansal et al. 2009, Dmochowski, Datta et al. 2011, Dmochowski, Datta et al. 2013, Bai, Dokos et al. 2014).

In conclusion, dose-response associations may not necessarily present as linear within the space of the parameter and the direction of the effects unambiguously differs across studies and individuals – this may be due to the changes induced by divergent stimulation parameters or even actual variability due to distinct intra-individual response patterns or anatomical differences.

Transcranial electrical stimulation in tinnitus

While general trends of research in the domain of tinnitus primarily target the left auditory cortex (temporal/temporoparietal cortical areas) for the purpose of their study, certain researchers have explored the dorsolateral prefrontal cortex (dlPFC) in isolation as well as from the approach of multisite stimulation to address the condition itself - tinnitus, which supposedly considers both these focuses of research to be key to its origin (Shekhawat, Sundram et al. 2016).

Extant studies that employ neuroimaging as a technique have identified an over-activation for the left auditory cortex among patients that suffer from tinnitus – thus, tinnitus regards the auditory cortex as a typical target for stimulation (Arnold, Bartenstein et al. 1996, Lockwood, Salvi et al. 1998).

According to a study carried out by Garin and associates using a Visual Analogue Scale (VAS), it was found that the intensity of tinnitus was significantly decreased by administering one twenty-minute session of 1 mA anodal tDCS (Garin, Gilain et al. 2011). While the most effective stimulation parameter for a single session was shown to be a 2 mA anodal tDCS for twenty minutes with a specific focus on the left auditory cortex (Shekhawat, Stinear et al. 2013). In 2016, Forogh, Mirshaki et al. (2016) failed to discover significant effects upon applying the same for 5 sessions among patients suffering from tinnitus as evaluated by the Clinical Global Improvement measure, tinnitus loudness VAS, tinnitus related-distress VAS, and the tinnitus handicap inventory.

Studies extend beyond the adoption of conventional tDCS to explore the possible benefits that High-Definition tDCS (HD-tDCS) may have for interventions targeting the elimination or treatment of tinnitus; this includes advancements in the spatial accuracy of the technique by replacing the two large-pad electrodes with small gel-based ones that optimally regulate the flow of the current to the target (Datta, Bansal et al. 2009, Dmochowski, Datta et al. 2011, Villamar, Volz et al. 2013, Heimrath, Breitling et al. 2015, Shekhawat, Sundram et al. 2016).

HD-tDCS makes use of a 4 × 1 ring of electrodes to target brain regions such that a central ring electrode is positioned over the cortical ROI, circumscribed by a four-electrode ring configuration (Villamar, Volz et al. 2013).

A study that used 4 x 1 HD-tDCS to assess the impact of stimulation location (left auditory cortex vs. dlPFC), duration of the stimulation (10 min vs. 20 min), and intensity of stimulation (center anode 1 mA vs. 2 mA) on the variables of tinnitus loudness and annoyance, concluded that while a higher intensity of 2mA proved relatively more effective in addition to a longer duration of 20 minutes, either location was equally effective for dealing with the variables (Shekhawat, Sundram et al. 2016).

As previously mentioned, the dlPFC has also been considered a common target for stimulation, investigated to address transient tinnitus. As the prefrontal cortex is widely known to support the integration of the sensory and emotional aspects of the tinnitus, it is regarded as an important factor for the origin of tinnitus as well as a vital component of the tinnitus distress network (Jastreboff 1990, Kleinjung, Eichhammer et al. 2008, Vanneste, Plazier et al. 2010).

Furthermore, studies in the domain of electrophysiology indicate tinnitus as a consequence of the dysfunctional top-down inhibitory mechanisms which are identified in the prefrontal lobe (Norena, Cransac et al. 1999). This suggests that in addition to affecting the perception of tinnitus, the prefrontal cortex also efficiently switches the signal on or off (Rauschecker, Leaver et al. 2010, Frank, Schecklmann et al. 2012), thereby affecting the distress and intensity of the condition.

Several studies that focus on tinnitus have investigated bifrontal tDCS, wherein the anode is placed over the right dlPFC with the cathode over the left one(Vanneste, Plazier et al. 2010, Vanneste and De Ridder 2011, De Ridder and Vanneste 2012). In 2010, Vanneste, Plazier et al. (2010) carried out a clinical study with 478 patients that suffer from tinnitus to discover that among 29.9% of the patients, tinnitus perception was modulated by a single twenty-minute session of 1.5 mA tDCS with a right anode and left cathode. For these patients, a significant decline was found in the intensity and distress associated with the tinnitus (Vanneste, Plazier et al. 2010).

In support, a subsequent study was carried out, wherein a resting-state electroencephalography (EEG) was employed before and after the tDCS session to identify the mechanism that aids in the suppression of tinnitus – this mechanism was found to be the bifrontal tDCS, which modulates the pregenual anterior cingulate cortex (pgACC), the parahippocampal area, and the right primary auditory cortex in spontaneous brain activity at resting-state (Vanneste and De Ridder 2011).

As per another study conducted by the same researchers, one session of bifrontal tDCS resulted in a relatively larger decrease in the intensity and distress of tinnitus, as opposed to EEG-driven tDCS (De Ridder and Vanneste 2012). Thus, continual and intermittent sessions of bifrontal tDCS were investigated as a potential treatment intervention by several scholars (De Ridder and Vanneste 2012, Faber, Vanneste et al. 2012, Frank, Schecklmann et al. 2012).

One of these groups of researchers noted that six thirty-minute sessions of 1.5 mA tDCS (right anode and left cathode) minimally impacted loudness and annoyance (Frank, Schecklmann et al. 2012). On the other hand, Faber, Vanneste et al. (2012) upon performing six sessions of tDCS for the left and right anodal dlPFC, found that both active conditions, regardless of the anodal position, succeeded in decreasing the annoyance associated with tinnitus, but not its intensity.

Several studies have currently been focusing on the stimulation of the auditory cortex and the dlPFC among tinnitus patients in various ways. For instance, one such study targeted both the regions simultaneously by positioning the cathode over the auditory cortex and the anode over the prefrontal cortex for five sessions (Pal, Maire et al. 2015). Nevertheless, the setup used in the study did not result in any beneficial improvements in the context of tinnitus (Pal, Maire et al. 2015).

Many other studies note the improvement of results following multiple repetitive sessions of tDCS with the minimum being five sessions. As the anode electrode was placed over the left dlPFC instead of the right, it appears that a lateralization effect occurred, thereby inducing highly notable effects (Fregni, Boggio et al. 2006, Fregni, Boggio et al. 2006, Boggio, Zaghi et al. 2009).

The abovementioned studies which assessed the behavioral effect of tDCS over dlPFC on tinnitus loudness and/or annoyance could demonstrate that interfering with neuronal activity in this area results in alleviating the symptom. However, they do not provide information about which neuronal alterations are associated with symptom-alleviation. Such information can be obtained by performing neuroimaging before and after the tDCS. The identification of tDCS-induced neuronal alterations associated with distress reduction is essential for developing treatments.

Another missing part in above-mentioned studies is activating relevant network termed as functional targeting. Given that excitability changes induced by tDCS are subthreshold, i.e., requires some amount of pre-existing activity within neurons or neural networks to exert a measurable behavioral and neurophysiological effect, inclusion of a goal-directed task to behaviorally activate relevant network while tDCS is applied will boost the neuromodulation effect (Nitsche, Koschack et al. 2012, Brunoni, Zanao et al. 2014, Möbius, Lacomblé et al. 2017, Vergallito, Riva et al. 2018, Abend, Sar-el et al. 2019).

Considering all above-mentioned missing parts, we conducted a study wherein repeated sessions of HD-tDCS over left dlPFC concurrent with positive emotion induction (PEI) technique were utilized to maximize the efficacy of stimulation and help for down-regulation of tinnitus negative valence. Further details are explained in the next chapter.

Chapter 2: Introduction

Tinnitus is CAAP of sourceless sound (Ghodratitoostani, Zana et al. 2016). Several studies have reported that auditory phantom perception affects 30% of the general population worldwide (Mills, Albert et al. 1986, Heller 2003). It remains unclear why only 17% of the affected subjects experience bothersome when perceiving tinnitus (Axelsson and Ringdahl 1989). Several cognitive and behavioral theoretical models have attempted to unravel the impact of psychological factors and associated mechanisms in triggering or mitigating tinnitus distress (Jastreboff 1990, Hallam, McKenna et al. 2004, Zenner and Zalaman 2004, Andersson and McKenna 2006, Zenner, Pfister et al. 2006, McKenna, Handscomb et al. 2014, Ghodratitoostani, CB Delbem et al. 2016, Ghodratitoostani, Zana et al. 2016).

Hallam, McKenna et al. (2004) proposed that failure in habituation to tinnitus causes increased awareness because of negative appraisal and emotional significance. Subsequently, classical conditioning was proposed as the principal mechanism behind the aversive emotional states of tinnitus (Jastreboff 1990).

Later, Zenner, Pfister et al. (2006) proposed that tinnitus sensitization develops when perceiving sound is classified as noxious, fear-inducing, unpredictable, and might cause sense of deficiency in coping, and helplessness(Zenner and Zalaman 2004, Zenner, Pfister et al. 2006). McKenna, Handscomb et al. (2014), in their study, documented that cognitive misinterpretation of the tinnitus results in distress and physiological arousal, leading to distorted perception from sensory input (McKenna, Handscomb et al. 2014).

Recently, Ghodratitoostani, Zana et al. (2016) proposed the NfTM and highlighted that the CAAP of tinnitus is essential for causing bothersome. NfTM classifies patients with tinnitus into two stages: A)"Neutral stage": perceiving tinnitus without distress reaction and B)"Clinical distress stage": experiencing distress reaction because of the corresponding negative valence when the tinnitus perceives (Ghodratitoostani, CB Delbem et al. 2016, Ghodratitoostani, Zana et al. 2016). Valence represents emotional states varying along a continuum from positive to negative feelings with a neutral midpoint (Bradley and Lang 1994).

Tinnitus-related valence progressively becomes negative through the ECL mechanism wherein repeated pairing of neutral tinnitus (Conditioned Stimulus) with similar or different negative stimuli (Unconditioned Stimuli) develops negative valence (De Houwer, Thomas et al. 2001, Ghodratitoostani, Zana et al. 2016). On the other hand, negative appraisals such as "The noise makes my life unbearable”, “it will drive me crazy" or "it will overwhelm me" (Handscomb, Hall et al. 2017) intermittently reinforce the cognitive value of tinnitus. Appraisal and ECL mechanisms respectively fuel tinnitus-related cognitive and emotional value leading to preferential attention allocation to the sound and prolonged tinnitus perception (Ghodratitoostani, Zana et al. 2016).

Contrarily, NfTM assumes that the CAAP of tinnitus concurrent with positive emotion induction (Uhrig, Trautmann et al. 2016) might reduce negative valence resulting in lower chance of attention allocation to the sound together with a lower level of distress (Ghodratitoostani, Zana et al. 2016). In practice, specific emotional states can be induced by appropriate and controlled stimuli such as picture, sound, film, text, and virtual reality (Marchewka, Żurawski et al. 2014, Riegel, Żurawski et al. 2016). Positive emotion induction would be further discussed in the method.

NfTM also postulates that continuous evaluation of tinnitus valence, comparing this valence with that of other sensory and auditory inputs, and monitoring persistent perception occurs in the prefrontal cortex (Ghodratitoostani, Zana et al. 2016).

More specifically, dlPFC is believed to be associated with auditory attention (Breit, Schulz et al. 2004), processing of emotional information (Herrington, Mohanty et al. 2005), attentional processing of emotional information (Steele and Lawrie 2004, Jacob, Brück et al. 2014), and cognitive-emotional valuation particularly during down-regulation of negative emotional conditions (Davidson, Putnam et al. 2000). Furthermore, according to the brain asymmetry model in emotional processing, the left hemisphere prevails over positive emotions; whereas the right hemisphere dominates negative ones (Herrington, Mohanty et al. 2005, Alves, Fukusima et al. 2008).

In line with the Valence Theory within the side-lateralized activity, Vanderhasselt, De Raedt et al. (2013) proposed that the anodal tDCS of left-dlPFC increases neural activity in the left hemisphere and leads to preferential cognitive control for positive information (Vanderhasselt, De Raedt et al. 2013). NIBS on the left-dlPFC of healthy individuals unveiled modulatory effects on emotional processing. The patients perceived adverse stimuli less negative (Peña-Gómez, Vidal-Pineiro et al. 2011), enhanced processing of positive stimuli, weakened perception and attention toward negative stimuli, and increased positive information retrieval (Balconi and Ferrari 2013). In contrast, NIBS over right dlPFC showed more identification and attention to negative stimuli and less cognitive control upon negative stimuli, though no effect on mood change was expressed, see (Mondino, Thiffault et al. 2015) review.

Herrington, Mohanty et al. (2005) observed that pleasant words triggered higher activity on the left side dlPFC than on the right one. Furthermore, EEG and fMRI studies illustrated that high levels of baseline activity on the left PFC had brightened the prospects of suppressing negative emotions (Jackson, Burghy et al. 2000, Weissman and Hirsch 2000, Ochsner, Bunge et al. 2002, Jackson, Mueller et al. 2003). Moreover, the down-regulation of negative emotional processing by tDCS have shown that anodal, but not cathodal, stimulation exerts an effect on emotional regulation (Nitsche and Paulus 2000, Fregni, Boggio et al. 2005, Lang, Siebner et al. 2005).

Accordingly, NfTM proposed that modulatory effect of anodal-tDCS over left dlPFC reinforces positive emotion processing, which in turn, helps for down-regulation of tinnitus-related negative valence. Up-regulation (increasing) and down-regulation (decreasing) of positive and negative emotions helps for modification of the emotional experiences and play a crucial role in psychological well-being (Gross, Richards, & John, 2006). In contrast, inefficient emotional regulation is key to development and maintenance of several psychopathological disorders (Sheppes, Suri et al. 2015), such as depression (Hansenne, Nélis et al. 2014, Visted, Vøllestad et al. 2018) and anxiety disorders (Cisler and Olatunji 2012).

Using tDCS for down-regulation of tinnitus-related negative valence (Ghodratitoostani, Zana et al. 2016) depends on the effect of electrical stimulation on the active brain networks, that reinforce or decline the excitability underneath the anode or cathode, respectively (Rahman, Reato et al. 2013). tDCS specificity generally depends on functional and anatomical targeting mechanisms. Targeting refers to subthreshold modulatory-effects on particular functionally-active brain regions regarding stimulation (anodal or cathodal) montages.

Functional targeting in tDCS applications may occur through preferentially modulating an ongoing function on an active brain network (Jackson, Rahman et al. 2016). Functional targeting may also occur due to applied bias to different synaptic inputs (Bikson and Rahman 2013). Anatomical targeting is the focal neuromodulation on specific brain regions by delivering the desired electrical dose achieved only by regulating the tDCS parameters (Peterchev, Wagner et al. 2012). HD-tDCS employs multielectrode montages to improve the anatomical targeting by enhancing the focality of current flow.

Anatomical and functional targeting on the brain is required to boost the neuromodulation effect (Bikson and Rahman 2013). In the current study, similar to our previous work (Ghodratitoostani, Gonzatto Jr et al. 2022) we used an atlas-based head-model for anatomical targeting and PEI technique for functional targeting to provoke positive emotional processing of left dlPFC, all with the purpose of down-regulating tinnitus negative valence.

Accordingly, we hypothesized that ten consecutive sessions of HD-tDCS over left dlPFC concurrent with PEI results in down-regulation of tinnitus negative valence at the neural network level as measured with rsfMRI data.

Secondarily, we hypothesized that induced functional connectivity changes following HD-tDCS concurrent with PEI reduces tinnitus distress as assessed by Tinnitus Handicap Inventory (Schmidt, Teixeira et al. 2006).

Chapter 3: Methods

Inclusion/exclusion criteria

Patients with constant bilateral subjective tinnitus within clinical distress stage with THI score ≥ 18 (Carpenter-Thompson, Schmidt et al. 2015), not taking medication during the intervention time were included. On the other hand, patients who reported pulsatile or unilateral tinnitus, chronic headaches, Meniere disease, otosclerosis, brain tumors, and current use of medications for depression or anxiety were excluded.

Subjects

Throughout 2017 and 2018, we recruited forty-six (n=46) tinnitus patients (among those who were referred to the Specialized Center of Otorhinolaryngology and Speech Therapy, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, University of São Paulo, Brazil) to participate in our Phase I study which was an observational randomized crossover double-blind three-session study including (1) PEI (2) PEI with HD-tDCS (20 min, 2 mA with 30s RAM Up/Down) and (3) PEI with sham (30s Ramp up followed by 30s Ramp Down in the start and stop time of sham application). Preliminary results of phase I study showed that the session of HD-tDCS combined with PEI was more effective since the patients rated their tinnitus loudness lower during and after this session (Ghodratitoostani, Vazirikangolya et al. 2019, Ghodratitoostani, Gonzatto Jr et al. 2022). Accordingly, for the Phase II of the study, we applied **ten** consecutive sessions of simultaneous HD-tDCS and PEI to examine if accumulative effect of this intervention can down-regulate tinnitus negative valence. This study was approved by the Ethics Committee for Analysis of Research Projects, Specialized Center of Otorhinolaryngology and Speech Therapy, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, University of São Paulo, Brazil (HCRP No 55716616.1.1001.5440).

Of those forty-six patients recruited in Phase I, twenty patients showed willingness and gave written informed consent for participating in Phase II which was conducted in August and September of 2018. Considering inclusion criteria for Phase II, we did not include the data of five patients in the analysis although they received the intervention. Three patients could not complete the imaging, hence, the sample size reached twelve (Table 1. Excluded Patients).

To complete the required data, we called the patients and scheduled for data collection in March 2020 but due to COVID pandemic we had to cancel it out and wait to get back to normal. Given that the first deadline for the Ph.D. defense was July 2021 and even after a six-month extension, patient recruitment for research purposes was not permitted; the thesis was wrapped up with all in-hand cases. Twelve tinnitus patients (7 females, mean age = 51.25 ±12.90 years, range 27-67) who had tinnitus for an average of 9 years (SD = 5.16 years, range 1-17 years) participated in Phase II. Nine patients completed the full ten sessions. Two cases attended nine, and one case attended eight intervention sessions.

Number of Cases	Reason for exclusion
1	No MR-Pre
1	No MR-Post
1	Unilateral Tinnitus
4	Non-bothersome Tinnitus THI score lower than 18
1	Poor image quality due to inhomogeneity in the magnetic field

Table 1. Excluded Patients

Audiological profile

Before and after each experiment-session, a trained audiologist determined hearing threshold level using pure tone audiometry (PTA) examination. Frequencies ranging from 250 Hz to 8 kHz were presented to each ear with 1 dB step-size until the threshold of detection was reached. An averaged hearing threshold of each tested frequency was calculated over both ears. Loudness matching was identified by adjusting the intensity of presented sound to match with tinnitus loudness. The level of sound was gradually increased by 1 dB step-size from hearing threshold (Table 2). Loudness discomfort level, minimal masking level, and tinnitus pitch were also determined but are the subject of another study and will not be discussed here.

Behavioral profile

Before each experiment-session, patients completed the Portuguese versions of Tinnitus Handicap Inventory-THI (Schmidt, Teixeira et al. 2006), 6-item version of the State-Trait Anxiety Inventory-STAI (Fioravanti-Bastos, Cheniaux et al. 2011), and Hospital Anxiety and Depression Scale-HADS (Pais-Ribeiro, Silva et al. 2007). At the very beginning of our work, we were using Major Depression Inventory-MDI (Parcias, Rosario et al. 2011) including for three patients of the current study who have no HADS record (Table 2). For anxiety measurement, we only reported state-anxiety scores obtained from STAI which measures anxiety symptoms in the current moment in contrast to the trait-anxiety which measures a generalized predisposition to be anxious. Scores obtained from the above-mentioned questionnaires are reported in Table 2 belonging to the first and the last session of the experiment.

ID	**Sex**	**Age**	**Tinnitus Duration (years)**	**THI**		**State-Anxiety scores-STAI**		**Depression scores-HADS**		**LMT dB HL**		**PTA (dB HL)**	**Auditory Status**
				1st session	last session	1st session	last session	1st session	last session	Loudness Pre 1st session	Loudness Post last session		
2	M	67	11	42	20	43.33	46.67	12^{*}	5^{*}	66	60	58.75	Moderately Severe
13	M	57	14	28	26	33.33	30	7	4	46	55	34.06	Mild
15	M	55	12	74	50	60	50	10	9	64	67	35.63	Mild
21	M	41	9	44	50	43.33	30	5^{*}	7^{*}	69	62	42.5	Mild
22	M	41	5	62	76	26.67	33.33	15^{*}	14^{*}	57	43	23.75	Normal
23	F	27	17	60	52	33.33	40	6	5	55	50	54.7	Moderate
25	F	35	6	56	34	46.67	46.67	1	3	52	53	38.13	Mild
29	F	65	6	28	24	53.33	50	4	2	55	33	32.5	Mild
30	F	55	2	54	32	30	26.67	5	2	49	41	16.9	Normal
36	F	47	15	78	24	56.67	26.67	8	1	51	50	21.56	Normal
37	F	63	1	94	86	80	53.33	13	9	34	33	25.94	Normal
47	F	62	12	72	46	56.67	40	12	9	50	26	30	Mild
mean	7F	51.25	9	57.7	43.3	46.94	39.45			54	47.75	34.53	n/a
SD	5M	12.90	5	20.09	21.03	15.33	9.83			9.53	12.76	12.7	n/a
***P*-value**				0.0182		0.056		-		0.0491			

Table 2.Patients Characteristics

THI: tinnitus handicap inventory, STAI: state-trait anxiety inventory, HADS, hospital anxiety depression scale, MDI: major depression inventory, LMT: loudness match test, PTA: pure-tone average, which is an averaged hearing threshold of tested frequencies over both ears. n/a: not applicable. (*) represents depression scores obtained from MDI. Due to discrepancy in the applied measures, mean and standard deviation were not calculated for depression scores.

In the following, different modules of the study are explained.

High-Definition Transcranial Direct Current Stimulation

A battery-driven current source 1x1 DC-Stimulator (Soterix Medical, NY, USA) and a 4x1 distributor (Soterix Medical, NY, USA) were administered to deliver 2 mA, HD-tDCS for 20 min with a 30 s ramp up and 30 s ramp down. High-definition gel-based electrodes were used to increase anatomical focality in comparison to conventional electrode pads (Nitsche, Doemkes et al. 2007). According to the head model (Figure 3) designed for anodal stimulation of the left-dlPFC and also the international 10–10 EEG system (Figure 2) (Jurcak, Tsuzuki et al. 2007), the center electrode was placed on F3 with a 2 mA current set. The four cathode-electrodes were placed over F1, F5, AF3, and FC3 with approximately 3.5 cm distance away from the anode (Figure 2). Such stimulation electrodes were mounted on a 256-channel EEG-Net.

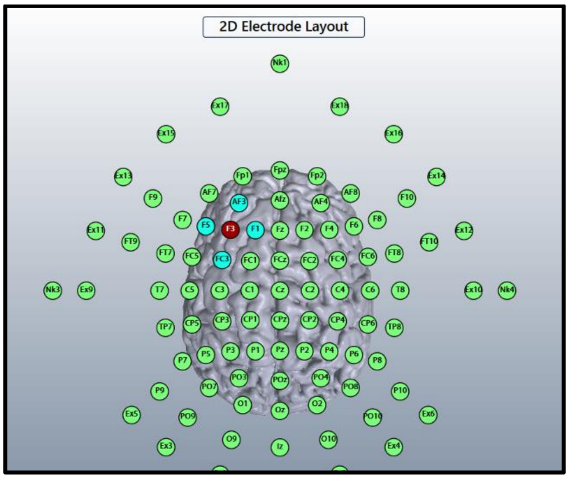


Figure 2.Electrodes’ Layout, EEG 10-10 System over Left-dlPFC

Five electrodes were mounted on left dlPFC as following: Anode (*F3*) as center and cathodes (*F*1, *AF*3, *FC*3, and *F*5) symmetrically surrounded *F3*.

Head Model For HD-tDCS

The brain anatomy (different folding patterns in the cortex, the volume of cerebrospinal fluid, and skull thickness) can considerably influence the current distribution within the head between the electrodes. This variability in current flow among subjects needs personalized head models to ensure anatomical focality in transcranial stimulation (Thomas, Ghodratitoostani et al. 2019). In the current study, HD-Targets software (Soterix Medical Inc., New York, USA) was employed to find the optimal electrode placement for the anodal stimulation of the left-dlPFC (Figure 3).

A previously developed finite element model (Figure 3) was adapted to analyze the effect of HD-tDCS electrode montage on the cortical current flow (Datta 2012). Head modelling and simulation of electrical current distribution were totally conducted by Soterix Medical Company in collaboration with our project. Further details can be found here (Ghodratitoostani, Gonzatto Jr et al. 2022).

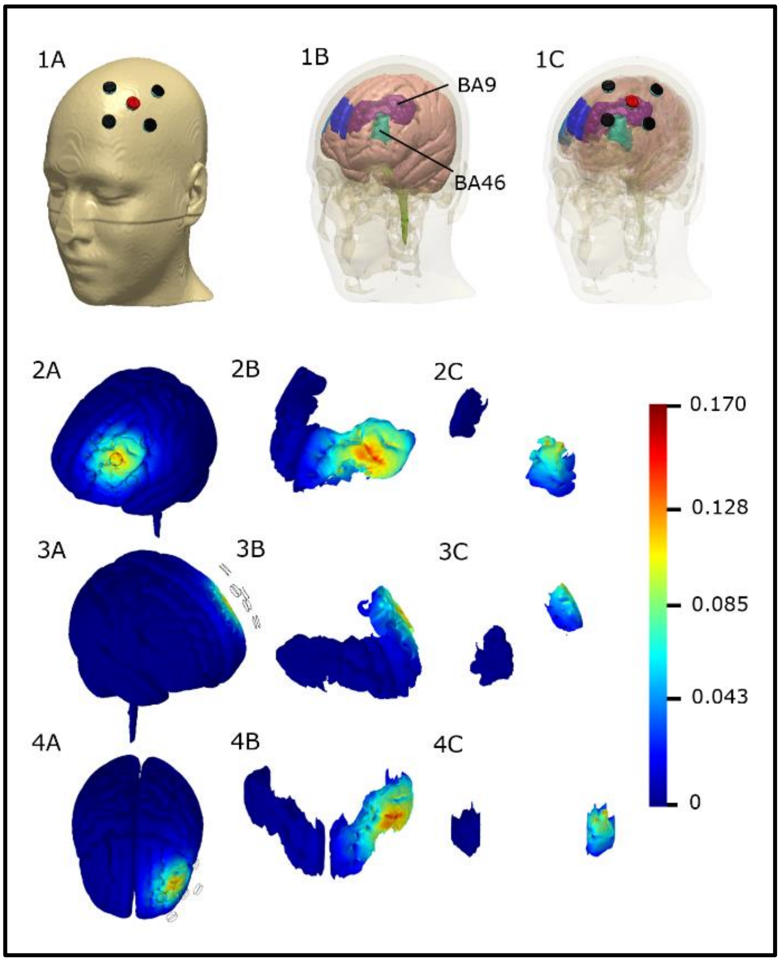


Figure 3.Finite Element Model

Figure 3. Finite element model of the HD-tDCS Montage based on the representative MNI 152 template, Top row: Electrode Montage considered with anode depicted in red and the cathodes depicted in black (left). The underlying brain tissue mask with the individual Brodmann areas regions is depicted in the middle: left BA 9 (purple), left BA 46 (light green), right BA 9 (blue), and right BA 46 (light blue). The HD-tDCS montage in relation to the underlying gray matter and BA masks are shown on the right. Rows 2-4: Induced electric field magnitude plots (left side,

right side, and top views). We plotted the whole brain in the first column, BA 9 in the middle, and BA 46 in the right.

Positive Emotion Induction

In practice, specific emotional states can be induced by appropriate and controlled stimuli such as picture, sound, film, text, and virtual reality (Marchewka, Żurawski et al. 2014, Riegel, Żurawski et al. 2016). One of the most commonly applied and accepted stimuli for emotion induction is the use of pictures (Uhrig, Trautmann et al. 2016). Nencki Affective Picture System (NAPS) is a database of standardized pictures for studying emotion and attention (Marchewka, Żurawski et al. 2014). It provides a detailed list of normative ratings in three dimensions of valence, arousal, and dominance elicited by each picture. It enables researchers to select stimuli triggering a specific range of emotions for their experiments (Marchewka, Żurawski et al. 2014). In the rating of the NAPS dataset, valence points to the positive versus negative emotional state, whereas arousal points to the strength of emotional arousal or excitement (Citron, Gray et al. 2014). The pictures had already been rated using a modified 9-point Likert scale of Self-Assessment Manikin scale for arousal-ratio (Ar): 1 = unaroused/calm, 9 = aroused/excited; for Valence-ratio (Vr): 1 = unhappy/annoyed, 9 = happy/satisfied (Riegel, Moslehi et al. 2017). We employed a set of validated positive emotion-inducing pictures from the NAPS dataset to induce positive emotion simultaneously presented with HD-tDCS over left dlPFC to reduce the tinnitus negative valence. Pictures were aligned at a fixed location at the center of the screen in 1600x1200 pixels. We presented neutral pictures ($4 < Vr < 6$ and $Ar < 6$) included in resting-state blocks and positive pictures ($Vr > 6$) included in visual stimulation blocks developed in Superlab Software. The blocks contained 20 pictures, each one presented for 5s, followed by a 500 ms cue (+). Every single block ended with Tinnitus Loudness Question (TLQ). The total time duration of each block presentation was two minutes (Figure 4).

The resting-state blocks were constructed with neutral pictures that were randomized between sessions and between patients but were presented in the same order within-session. Neutral pictures were selected for evaluating baseline neural activity, which is not elicited by a task. So, the resting-state block was displayed four times to provide a reference and cover all possible repeated measures of rs brain activity that might be affected by previous tasks. According to the Arousal-Biased Competition (ABC) theory, arousal enhances emotional stimuli processing, but impairs neutral stimuli (Mather and Sutherland 2011, Lee, Itti et al. 2012, Sutherland and Mather 2012, Lee, Sakaki et al. 2014, Singh and Sunny 2017). Given that the ABC theory supports biased salient processing, we placed high-arousal-valence pictures (fixed picture presentation) before high-valence pictures (positive picture presentation) per visual stimulation block (Figure 5.).

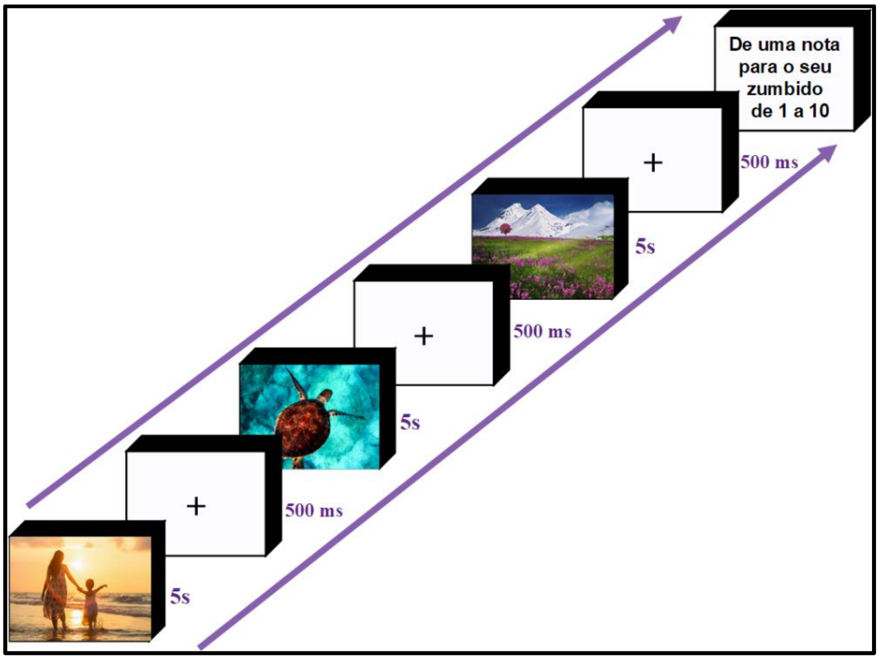


Figure 4.The sequence of picture presentation

Figure 4: The sequence of picture presentation. During the experiment, eighty neutral pictures and two-hundred positive pictures were displayed. Each picture was presented for 5 *s* with a cue of 500 *ms* in between. The PEI was concurrent with anodal stimulation over left dlPFC. Throughout the picture presentation, every two minutes we asked TLQ “Scale your tinnitus

loudness from 1-10”, to keep the patients consciously attended to the perception of their tinnitus and ascertaining ECL procedure. The total time duration of the picture presentation was almost 28 *min*.

Acquisition Procedure

Magnetic resonance images were collected on a 3T system (Achieva X-series, Philips Medical Systems, Best, Netherlands) with a 32-channel head coil at Hospital das Clínicas, Ribeirão Preto, São Paulo, Brazil. Functional images were acquired using EPI sequence with the following parameters: 200 volumes, 29 slices in ascending order without gaps, 4-mm slice thickness, voxel size = 3 × 3 mm, field of view = 240 × 240 mm, TR/TE = 2000/30 ms. The silent sequence was designed by setting to maximal (level 5) ‘‘soft-tone’’ parameter offered by the MRI equipment, which decreases the gradient slew rate, leading to lower coil vibration levels (Rondinoni, Amaro Jr et al. 2013). Structural images were acquired in the SAGITTAL plane with a 1 mm isotropic voxel 3D T1-weighted MPRAGE sequence. Phase and magnitude data stored. The sequence had following parameters: 3.2/7.0/8 (TE/TR/Flip angle); slice thickness = 1mm and matrix = 240×240, allowing isotropic voxel of 1.0×1.0×1.0 mm, field of view (FOV), 240 (FH) × 240 (AP) × 170 (RL) mm^3, SENSE,2. Subjects were instructed to stay alert and remain still while willingly keeping their eyes open or closed. We used cushions between the earmuffs and the head coil to minimize the head movements. In order to assure that the MRI scanner noise has not masked the tinnitus sound, we occasionally asked patients to raise their thumb if they were still perceiving tinnitus throughout the scanning. This imaging acquisition was conducted before and after the intervention (Figure 5).

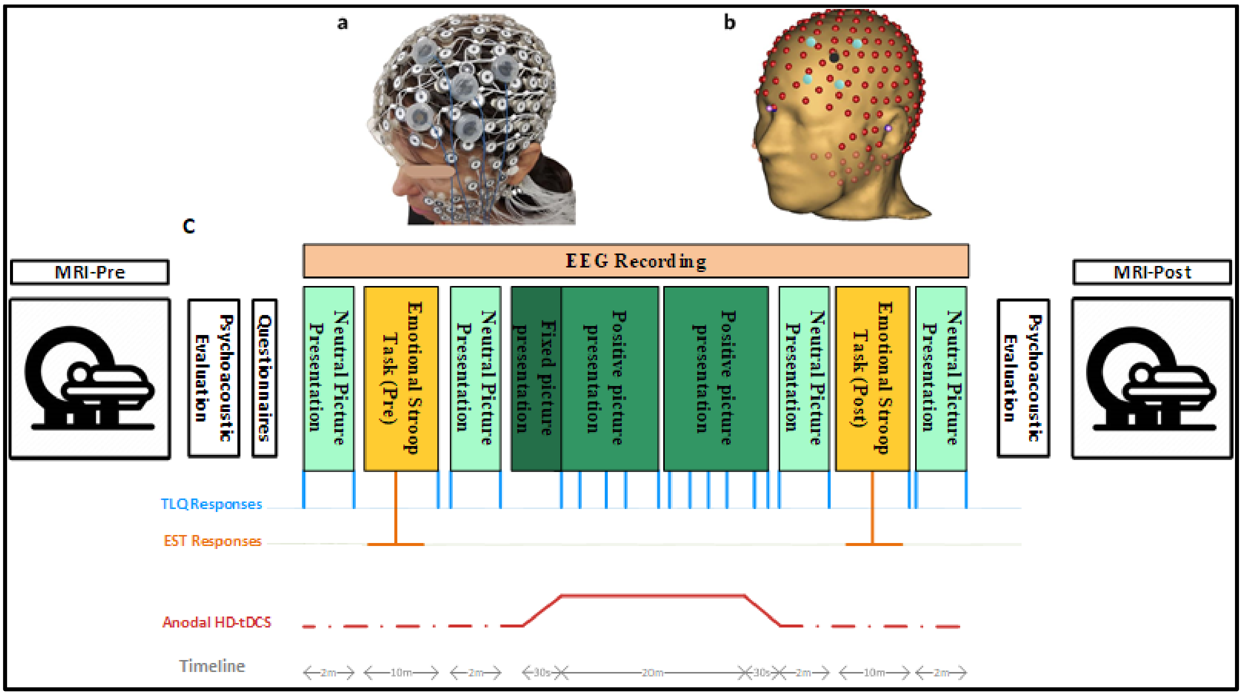


Figure 5.Schematic of the Protocol

Figure 5. Schematic of the protocol: **a)** Realistic Montage for 256-channel HydroCel Geodesic Sensor Net, and the left-dlPFC as the ROI mounted on the EGI-NET. **b)** Co-registered 256-channel EEG, and HD-tDCS Montage on left-dlPFC based on the MR-Driven head model. The stimulation electrodes located in electrode holders were placed near the EEG channels. The electrode holder for the anode is shown in black and that for the cathode is shown in blue. The electrode holders are filled with conductive gel. **c)** Schemas of the protocol. Before each experiment session, the patients filled in the questionnaires. Before and after the experiment sessions but not MR sessions, psychoacoustic parameters of tinnitus were recruited. During the experiment, two sets of pictures were presented with different Valence-ratio (Vr) and arousal-ratio (Ar) rates selected from the NAPS dataset. Neutral pictures (4 <Vr< 6 and Ar< 6) were included in four resting-state blocks and the positive pictures (Vr> 6) in 2x5 consecutive visual stimulation blocks. Each visual stimulation block initiates with four pictures (Vr> 6 and Ar> 6) followed by sixteen pictures (Vr> 6) randomly selected with no replacement from a one-hundred-positive-picture set. Generally, every single block contained 20 pictures each presented for 5*s*

followed by a cue (+) of 500*ms*. The blocks were randomized between sessions and between patients but presented in the same order within session. The total duration of each block presentation was two minutes. The TLQ “Scale your tinnitus loudness from 1-10” was displayed 21 times, and presented in the following order: before-after each resting-state block (containing neutral pictures) and visual stimulation block (containing positive pictures), and after each Emotional Stroop task (EST). Throughout the experiment, the responses of TLQ and EST in blue and orange lines, respectively, as well as EEG signals were all recorded via Superlab software (Cedrus Corporation, San Pedro, CA, USA). The total duration of the experiment ranged between 40 and 45 min with regard to the reaction time of patients in EST and responding to TLQ.

Among different modules explained in the protocol (Figure 5), the focus of our analysis is on rsfMRI data for the rest of the thesis.

MR Data Preprocessing

Using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), structural images were first realigned with the anterior commissure as a reference point for the origin. Then, reorientation was conducted in two steps 1) between structural image and MNI template, and 2) between structural and functional images. We utilized MATLAB toolbox CONN v.20.b (Whitfield-Gabrieli and Nieto-Castanon 2012, Nieto-Castanon 2020) for preprocessing, denoising, and analyzing fMRI data. The CONN's default pipeline for preprocessing was used as follows. The functional images were realigned and unwarped; translated by centering to (0,0,0) coordinates; slice time corrected; scrubbed with ART-based identification for outlier scans [intermediate scrubbing settings, with a global-signal Z-value difference threshold of 5 and a subject differential-motion threshold of 0.9 mm]; segmented into GM, WM, and CSF and normalized to the Montreal Neurological Institute (MNI) template; and spatially smoothed using a 6-mm Gaussian kernel. Structural images were translated by centering to (0,0,0) coordinates, segmented into GM, WM, and CSF, and normalized to the MNI template. Subsequently, CONN's default denoising pipeline was performed to remove nuisance variables, including signal within WM and CSF masks, head motion parameters with first-order temporal derivatives, outliers detected during ART, and linear trends. Finally, a temporal band-pass filter (0.008–0.09 Hz) was applied.

Processing/Functional data analysis

In order to examine if repeated sessions of HD-tDCS over left dlPFC concurrent with PEI can down-regulate tinnitus negative valence at the neural network level, we selected dlPFC and amygdala as seeds of interest considering clinical distress stage of NfTM (Ghodratitoostani, Zana et al. 2016). dlPFC as a key node in fronto-parietal network takes part in allocating top-down attentional resources (Fassbender, Simoes-Franklin et al. 2006) toward highly valued stimuli (Ghodratitoostani, Zana et al. 2016). We further tested more seeds due to their differential activity and/or functional connectivity resulting from tinnitus distress (De Ridder, Vanneste et al. 2011, Golm, Schmidt-Samoa et al. 2013, Schmidt, Akrofi et al. 2013, Shahsavarani, Schmidt et al. 2021). These includes bilateral primary auditory cortices for auditory network (AN), medial PFC and posterior cingulate cortex for DMN as well as four seed ROIs belonging to DAN. The latter seeds were grouped into bilateral posterior intraparietal sulci for DAN1, and bilateral frontal eye fields for DAN2, in similar fashion to the study conducted by (Schmidt, Akrofi et al. 2013). Coordinates for the above-mentioned seeds were the same as those used in Shahsavarani, Schmidt et al. (2021) study. Seeds were generated in the MarsBar toolbox (Brett, Anton et al. 2002) using 6-mm radius spheres centered at the MNI coordinates listed in Table 3.

Network	Seeds	MNI coordinates		
		x	y	z
Emotion Processing	Right Amygdala	18	-7	-17
	Left Amygdala	-17	-2	-24
Fronto-Parietal Network (FPN)	Right dorsolateral prefrontal cortex	41	38	30
	Left dorsolateral prefrontal cortex	-43	33	28
Cingulo-opercular network (CON)	Right anterior insula	47	14	0
	Left anterior insula	-44	13	1
Auditory Network (AN)	Right primary auditory cortex	41	-27	6
	Left primary auditory cortex	-55	-22	9
Dorsal Attention Network 1 (DAN-1)	Right posterior intraparietal sulcus	26	-62	53
	Left posterior intraparietal sulcus	-23	-70	46
Dorsal Attention Network 2 (DAN-2)	Right frontal eye field	27	-11	54
	Left frontal eye field	-25	-11	54
Default Mode Network (DMN)	Medial prefrontal cortex	8	59	19
	Posterior cingulate cortex	-2	-50	25

Table 3.Seed regions and MNI coordinates used to generate resting-state networks

We performed CONN's default seed-to-voxel functional connectivity analysis using a weighted general linear model to estimate the bivariate correlation. For each subject, the average time course of the BOLD signal was extracted from the seed and used as the regressor of interest in the FC analysis.

The correlation coefficients between the time series of the seed region and every other voxel across the brain were computed generating a subject-specific FC map and transformed into a z-score through a Fisher’s r-to-z transformation to improve the normality of the correlation coefficients. These Fisher-transformed subject-specific FC maps were then entered into the second-level group analysis using paired sample t-tests to explore rsFC alterations at specific seeds between pre and post conditions (specifying Post > Pre as between-conditions contrast).

Seeds were tested both unilaterally and bilaterally (Table 4). For the latter analysis, connectivity of the two seed regions in each network were averaged together to produce a single representation of the network, similar to the method employed by (Schmidt, Akrofi et al. 2013).

Results were significant if they survived at p <0.001 uncorrected thresholds together with family-wise error (FWE) corrected threshold of p <0.05 at cluster level, with a cluster extent of 27 voxels. The resulting rsFC maps provided at the group-level was exported into xjview (http://www.alivelearn.net/xjview) for visualization purposes. Information shown in Table 5 and Table 6 were also provided by xjview.

Single-subject Fisher-transformed correlation coefficient values (connectivity values) were extracted from Conn and imported into R-Studio (Team 2021) for creating boxplots and scatterplots. Pearson's correlation analysis was further conducted to test possible relationship between changes in FC values and THI.

Chapter 4: Results

Effects on Neural Correlates: Resting-State Functional Connectivity

In order to examine rsFC alterations following ten consecutive sessions of HD-tDCS over left dlPFC concurrent with PEI, we compared rsfMRI scans obtained before (Pre) and after (Post) the intervention. We analyzed pre-determined seeds, meant to reflect the connectivity with bilateral Amygdala, FPN, CON, AN, DAN1, DAN2, and DMN. Table 4 lists all tested seeds and those with significant effect for post>pre between-condition contrast. Using paired sample t-tests, it was revealed that the intervention significantly reduced rsFC between attention and emotion processing regions at post-intervention when compared with pre-intervention (Table 5). Figure 6 illustrates rsFC maps for regions of significance resulting from Post>Pre contrast. Regions are superimposed on SPM single-subject T1 template. Anatomical locations determined using automated anatomical labeling atlas version.3 embedded in xjview toolbox (http://www.alivelearn.net/xjview). Blue color represents negative correlations and center of crosshairs shows the voxel with the peak intensity.

Network	Seeds	Unilaterally	Bilaterally
Emotion Processing	Right Amygdala	-	Left SPL
	Left Amygdala	Right SPL	
Fronto-parietal Network (FPN)	Right dorsolateral prefrontal cortex	-	Bilateral pgACC
	Left dorsolateral prefrontal cortex	Bilateral pgACC	
Salience Network Cingulo-opercular Network (CON)	Right anterior insula	-	-
	Left anterior insula	-	
Auditory Network (AN)	Right primary auditory cortex	-	-
	Left primary auditory cortex	-	
Dorsal Attention Network 1 (DAN-1)	Right posterior intraparietal sulcus	-	-
	Left posterior intraparietal sulcus	-	
Dorsal Attention Network 2 (DAN-2)	Right frontal eye field	-	-
	Left frontal eye field	-	

Default Mode Network (DMN)	Medial prefrontal cortex	-	-
	Posterior cingulate cortex	-	

Table 4. All tested seeds (unilaterally and bilaterally) and those with significant effect for post>pre contrast

Resting-state FC alterations

Resting-state FC with bilateral amygdala from pre-intervention to the post-intervention decreased in a cluster overlapping the posterior part of left superior parietal lobule (SPL). Unilaterally, left amygdala showed decreased rsFC with posterior part of right SPL at post when compared with pre-intervention (Table 5 and Figure 6 a-d).

Moreover, the between-condition comparison revealed a pattern of reduced rsFC between bilateral dlPFC and bilateral pregenual anterior cingulate cortex (pgACC) from pre to the post-intervention (Table 5 and Figure 6 e-h). Unilaterally, left dlPFC showed decreased rsFC with right superior pgACC and left pgACC at post-intervention when compared with pre-intervention (Table 5 and Figure 6 i-l).

There were no changes in connectivity of other seeds at the established threshold for significance. Although setting the voxel-level significance at uncorrected $p < 0.01$ while maintaining FWE corrected $p < 0.05$ at the cluster level, we observed decreased rsFC between DAN1 and one cluster centered at (MNI coordinate: 26, 6, -14) overlapping with right-sided putamen, subcallosal area, and fronto-orbital cortex at post-intervention when compared with pre-intervention. Same observation was found using right posterior intraparietal sulcus as the seed of interest, this time the suprathreshold voxel was located at (MNI coordinate:12, 22, -12).

On the other hand, right primary auditory cortex showed increased rsFC with post central gyrus and supplementary motor cortex at post-intervention after reducing the voxel height threshold. With the same liberal voxel height threshold, no clusters emerged for the rest of the seeds.

Network	Seeds	Region	BA	Cluster Size	Peak MNI coordinates			Peak Intensity	Cluster-level p FWE-corrected
					x	y	z		
Emotion Processing	Bilateral Amygdala	L SPL		113	-32	-76	36	-6.80	0.004 *
	Left Amygdala	R SPL		79	38	-68	28	-6.58	0.038
Fronto-Parietal Network	Bilateral dlPFC	L pgACC	10/32	206	-14	36	16	-7.03	0.00008 **
		R pgACC	32	107	16	38	12	-5.80	0.0086 *
	Left dlPFC	R Sup. pgACC	32	145	6	36	12	-7.41	0.00084 **
		L pgACC	10	113	-16	50	4	-6.87	0.0045 *

Table 5.Regions of significance for Post>Pre contrast

Statistical threshold was set at $p < 0.05$ FWE corrected for multiple comparisons. Anatomical locations determined using automated anatomical labeling atlas v.3 embedded in xjview (http://www.alivelearn.net/xjview). ** represents higher significance level. SPL: superior parietal lobule, pgACC: pregenual anterior cingulate cortex, Sup: superior, L: left, R: right.

For anatomical labeling of superior parietal lobule as the suprathreshold voxel showing reduced rsFC with amygdala, two additional neuroimaging experts with more than 15 years of experience were consulted.

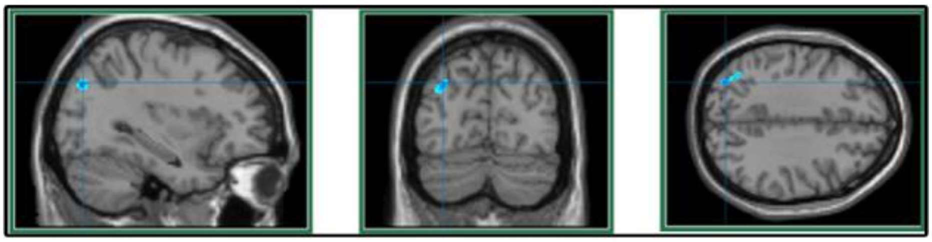
We also reported the MNI coordinate and its associated region for center of gravity of significant clusters (Table 6). Center of gravity indicates the center of an activation cluster consisting of a defined number of voxels (Mintun, Fox et al. 1989). Using this parameter allows for identification of the cluster geometry and how it is spatially distributed, for instance, from right-to-left or anterior-to-posterior (Fesl, Braun et al. 2008).

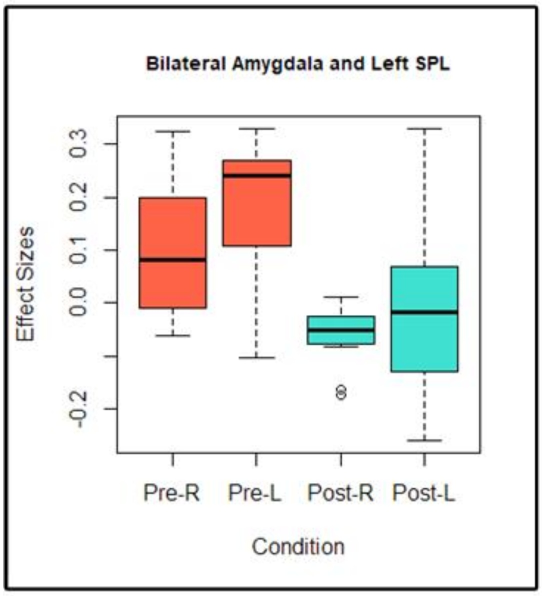
Network	Seeds	Cluster Size	Peak MNI coordinate			Region	CoG* MNI coordinate			Region
			x	**y**	**z**		**x**	**y**	**z**	
Emotion Processing	Bilateral Amygdala	113	-32	-76	36	L SPL	-36	-71	33	L Parietal Lobe
	Left Amygdala	79	38	-68	28	R SPL	39	-70	28	R posterior MTG
Fronto-Parietal Network	Bilateral dlPFC	107	16	38	12	Limbic Lobe-R pgACC	17	45	7	R MFG-ACC
		206	-14	36	16	Limbic Lobe-L pgACC	-15	46	8	L MFG-BA 10
	Left dlPFC	145	6	36	12	Limbic-R Superior pgACC	7	44	8	R preACC-BA32
		113	-16	50	4	L pgACC	-13	50	7	L Superior MFG

Table 6.Center of gravity corresponding to each region of significance for Post>Pre contrast

* CoG: Center of Gravity. SPL: superior parietal lobule, MTG: middle temporal gyrus, pgACC: pregenual anterior cingulate cortex, MFG: medial frontal gyrus. Anatomical locations determined using automated anatomical labeling atlas v.3 embedded in xjview (http://www.alivelearn.net/xjview)

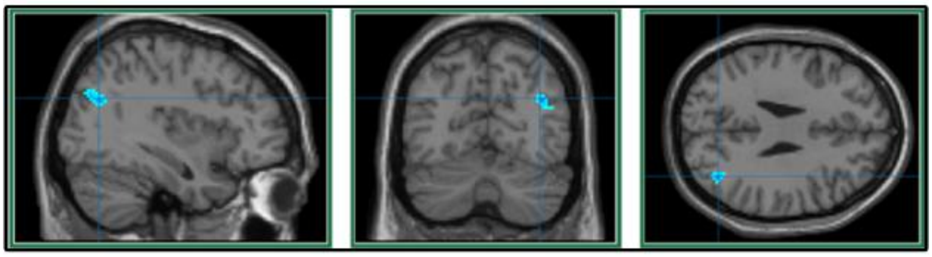
Figure 6.rsFC maps resulting from Post>Pre Contrast and boxplots of the effect size

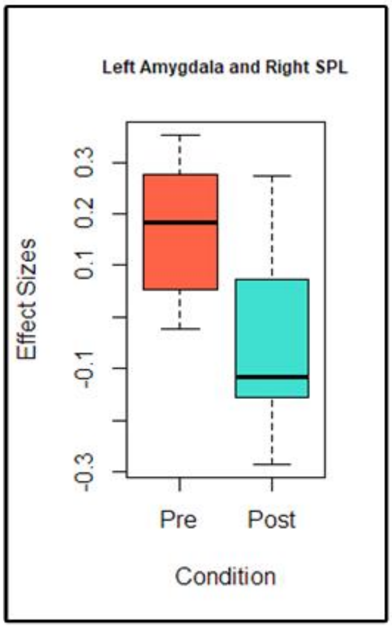




a) Left SPL showed reduced rsFC with bilateral amygdala at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

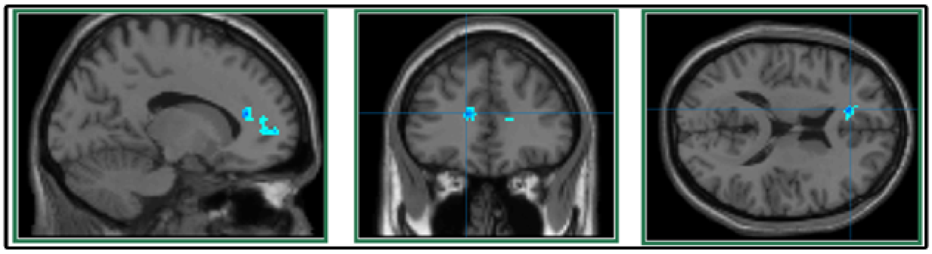
b) Distribution of connectivity values between bilateral amygdala and left SPL comparing pre and post conditions. The boxplot shows reduction in connectivity values at post-session.

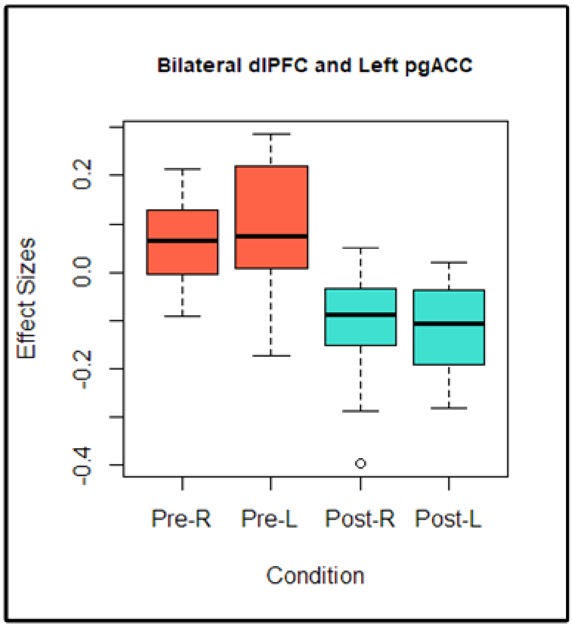




c) Right SPL showed reduced rsFC with left amygdala at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

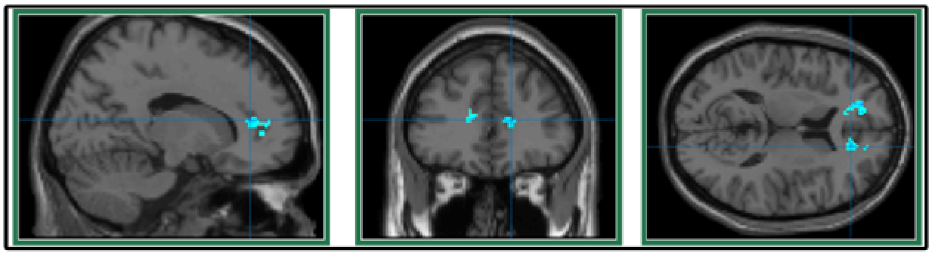
d) Distribution of connectivity values between left amygdala and right SPL comparing pre and post conditions. The boxplot shows reduction in connectivity values at post-session.

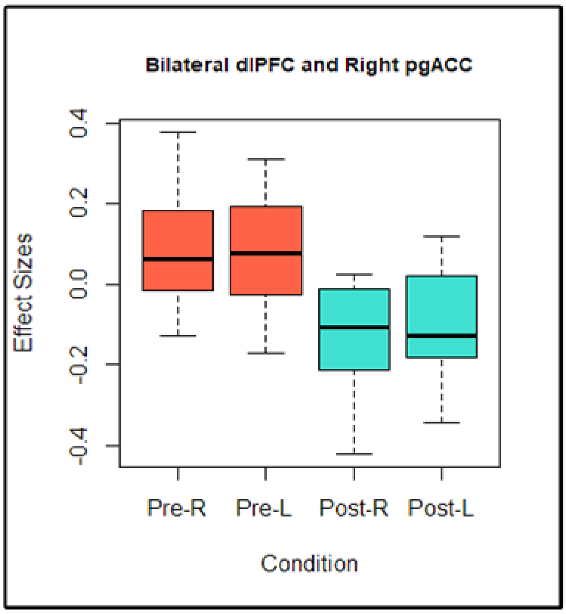




e) Left pgACC showed reduced rsFC with bilateral dlPFC at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

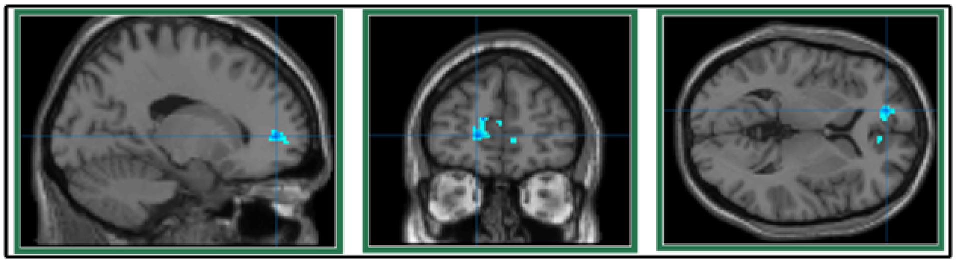
f) Distribution of connectivity values between bilateral dlPFC and left pgACC comparing pre and post conditions. The boxplot shows reductions in connectivity values at post-session.

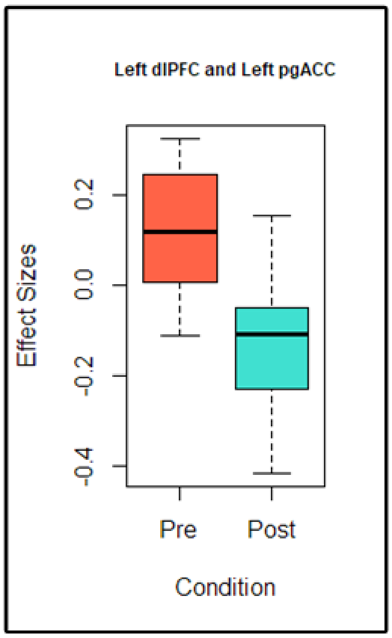




g) Right pgACC showed reduced rsFC with bilateral dlPFC at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

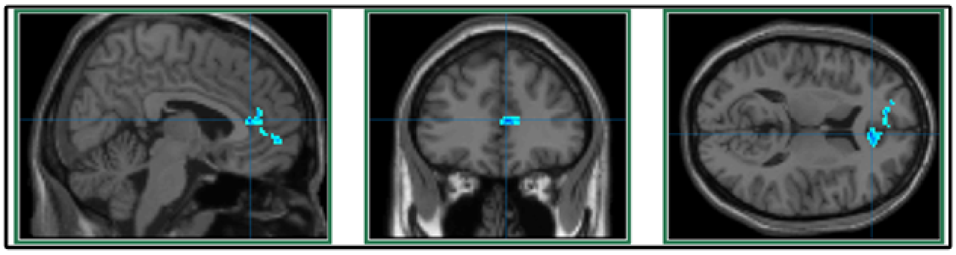
h) Distribution of connectivity values between bilateral dlPFC and right pgACC comparing pre and post conditions. The boxplot shows reductions in connectivity values at post-session.

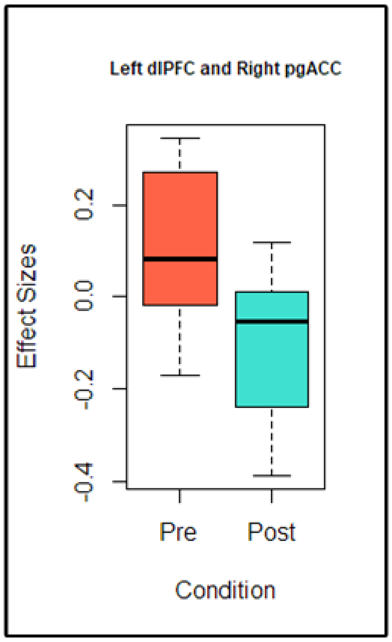




i) Left pgACC showed reduced rsFC with left dlPFC at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

j) Distribution of connectivity values between left dlPFC and left pgACC comparing pre and post conditions. The boxplot shows reductions in connectivity values at post-session.





k) Right pgACC showed reduced rsFC with left dlPFC at post-session. The statistical threshold was set at uncorrected $p < 0.001$ at the whole brain level, and FWE corrected $p < 0.05$ at the cluster level.

l) Distribution of connectivity values between left dlPFC and right pgACC comparing pre and post conditions. The boxplot shows reductions in connectivity values at post-session.

Figure 6: SPL: superior parietal lobule, pgACC: pregenual anterior cingulate cortex, dlPFC: dorsolateral prefrontal cortex, Statistical threshold was set at $p < 0.05$ FWE corrected for multiple comparisons. The background anatomical image is single-subject T1 image available at SPM canonical.

Effects on Behavioral Correlates: Tinnitus Handicap Inventory

Using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp), paired t-tests analysis showed that THI scores were significantly lower at the post-intervention compared to pre-intervention [t (11) = 2.77, $p = 0.0182$]. Table 7 shows the mean and standard deviations of THI scores at each session. Th boxplots in Figure 7 illustrate the distribution of THI scores at pre and post conditions. As it shows a reduction in THI scores at post-intervention is observed when compared with pre-intervention.

	Session	
	Pre-Intervention	Post-Intervention
Mean	57.67	43.33
SD	20.09	21.03

Table 7.Statistics of THI scores at pre- and post-intervention

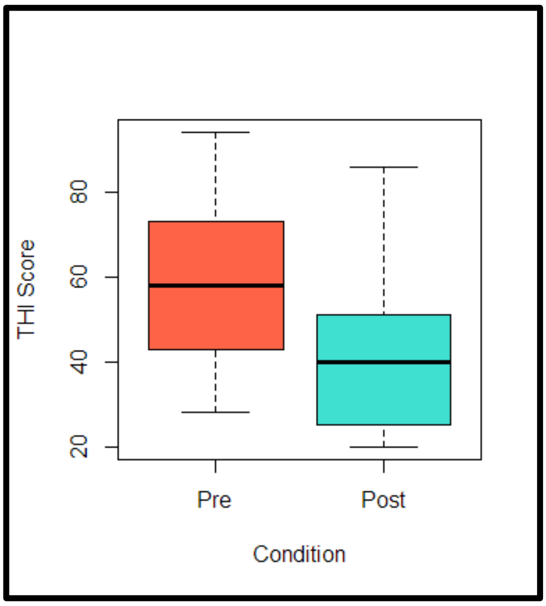


Figure 7.Boxplot for THI Scores Pre vs Post

Effects on FC-THI relationship

Pearson's correlation analysis was conducted to examine if there is any relationship between changes in FC values and changes in THI scores. Results showed no significant correlation ($p<0.05$) in the values of both variables neither at pre nor at post conditions, suggesting that the mechanism behind FC-THI relationship has not been affected by the intervention.

To visualize the treatment effect, we plotted FC values against THI scores observed at both pre- and post-conditions. As shown in Figure 8 and previously reported, an apparent reduction in specific FC values and THI scores is observed at post-intervention (blue lines) relative to pre-intervention (red lines). Visually inspecting, one might notice that there is no relationship between FC values and THI scores neither at pre- nor at post-conditions, as was observed after correlation analysis. All in all, the intervention has affected the variables independently with no apparent common underlying mechanism (Figure 8)

Figure 8. Comparison of FC values and THI scores between pre and post conditions

Points in the plots refer to subject-specific observations for FC values and THI scores before (red) and after (blue) the intervention. Observations belonging to the same condition (pre or post) were connected, creating a line to facilitate the comparison. In all plots, the placement of the blue points below the red points and roughly under the score of 50, respectively indicates lower FC values and THI scores obtained at post-intervention. Note: for bilateral seeds representing a network, we separately plotted FC values belonging to the left and the right hemisphere.

Chapter 5: Discussion

When tinnitus is perceived, patients in clinical stage experience distress because of the corresponding negative valence (Ghodratitoostani, CB Delbem et al. 2016, Ghodratitoostani, Zana et al. 2016). In light of the NfTM predictions and transcranial electrical stimulation application, we paired CAAP of tinnitus with presentation of positively-valenced pictures concurrent with anodal HD-tDCS over left dlPFC aiming at reducing tinnitus negative valence. We delivered the intervention for ten consecutive sessions and collected the rsfMRI scans as well as tinnitus handicap inventory before and after the intervention.

Neural Correlate

A general picture of the results is a reduction in rsFC between attention and emotion processing regions suggesting that the brain is calming down following repeated sessions of HD-tDCS over left dlPFC concurrent with PEI.

Amygdala-SPL

The primary regions of the limbic network are the amygdala, parahippocampus, and insula, which altogether function for the processing of emotion (Stein, Wiedholz et al. 2007, Robinson, Laird et al. 2010). The SPL, the frontal eye fields, the inferior precentral sulcus, and the middle temporal cortex develop the dorsal attention network (Brissenden, Levin et al. 2016, Dixon, Andrews-Hanna et al. 2017, Dumais, Chernyak et al. 2018) which primarily regulates externally oriented attention, including the goal-directed top-down process (Rohr, Vinette et al. 2017). More specifically, the posterior part of the SPL (where we found in our study) is engaged in selective attention; accordingly, a subset of information is selected for preferential processing (Behrmann, Geng et al. 2004).

In our study, the observed reduction in rsFC between the amygdala and SPL at post-intervention might reflect that the amygdala assigns lower emotional value to the sound accompanied by lowered biased attention.

The results of several studies have shown increased involvement of dorsal attention network in tinnitus patients compared with healthy controls (Hu, Lyu et al. 2021) and hearing loss patients (Schmidt, Akrofi et al. 2013).

In Schmidt, Akrofi et al. (2013) study, the analysis of the DAN revealed increased connectivity between frontal eye fields and right parahippocampus suggesting an interaction between attention and emotion networks in tinnitus patients when compared with hearing loss controls. Hu, Lyu et al. (2021) study compared tinnitus patients with healthy controls and found enhanced connectivity of the left superior parietal gyrus with several brain regions, including the left inferior parietal gyrus, the left superior marginal gyrus, and the right superior frontal gyrus (Hu, Lyu et al. 2021). The study by Mantini, Perrucci et al. (2007) also revealed increased activity in the superior parietal gyrus during the resting state possibly indicating that the attention system in tinnitus patients is more active at rest than that in the control group. Considering findings above, our observation of lowered SPL-amygdala FC at post-intervention highlights the beneficial effect of our intervention.

As mentioned earlier, the posterior part of the SPL plays a role in selective attention or biased attention processing (Behrmann, Geng et al. 2004). A number of studies have reported the beneficial effect of anodal tDCS over left dlPFC in reducing the attentional bias.

In a sample of depressed individuals, Brunoni, Zanao et al. (2014) revealed that a single-session of anodal tDCS over left DLPFC decreased attentional interference of negative and positive information in an emotional Stroop task. Compiling tDCS with neuroimaging, Ironside, Browning et al. (2019) indicated that tDCS over left dlPFC reduced attention bias to threat and diminished amygdala threat reactivity relative to sham stimulation, in line with dlPFC function in down-regulating amygdala reacting to the treat (Ironside, Browning et al. 2019). Using an eye-tracked video stress task, Chen, Basanovic et al. (2017) reported reduced attention bias to negative content following tDCS of left dlPFC. They also found that the effect of tDCS on emotional reaction to negative information mediates with attention bias (Chen, Basanovic et al. 2017). However, there still studies with the absence of effect on attention bias following dlPFC stimulation (Clarke, Van Bockstaele et al. 2020) which may have emerged due to confounding factors and differences in their methodologies and study design. In this context, the results of EST can provide further support if attention bias has reduced at post-intervention (Williams, Mathews et al. 1996).

dlPFC-pgACC

The rostral or pregenual region of the ACC (pgACC-BA 24/32) is distinctively referred to as the 'affective division' of ACC (Vogt, Nimchinsky et al. 1995, Bush, Luu et al. 2000) which is a core part of the neural circuitry of valuation (Amemori and Graybiel 2012, Bartra, McGuire et al. 2013, Clithero and Rangel 2014) implicated in continuous representation of affective value, also implicated in emotional processing (Vogt, Nimchinsky et al. 1995, Vogt, Derbyshire et al. 1996, Vogt 2009), mediation of emotional arousal (Critchley, Elliott et al. 2000, Critchley, Mathias et al. 2001, Critchley, Melmed et al. 2002), and evaluation of emotional salience in concert with amygdala and other limbic regions (Bush, Luu et al. 2000). As a marker of salience, emotional arousal determines the allocation of brain resources and heightens sensitivity to the environmental cues (Lane, Reiman et al. 1998, Lane, Chua et al. 1999, Niedenthal and Kitayama 2013).

The perceived affective or arousing value of stimuli can evoke greater recruitment of cognitive resources and more selective focusing through top-down influences mediated by, for example, frontoparietal and thalamic systems (Armony and Ledoux 1999, Mesulam 1999). Frontoparietal attentional systems might receive direct inputs from regions involved in ascertaining the motivational significance of stimuli, such as, through reciprocal connections with anterior and posterior cingulate cortices, basal forebrain nuclei (Posner and Petersen 1990, Maddock 1999, Mesulam 1999), or orbitofrontal areas (Rolls 1996, Armony and Dolan 2002). Inputs from these regions might in turn, affect the response to emotional stimuli (Vuilleumier, Armony et al. 2003).

Relevant to our study, reduced rsFC between dlPFC (as a node of FPN) and pgACC might indicate that tinnitus is less emotionally significant at post-intervention coupled with less allocation of attentional resources to it. Effect of dlPFC stimulation over distant areas like pgACC might be due to the reciprocal anatomical connections between these two regions (Pandya, Van Hoesen et al. 1981, Vogt and Pandya 1987, Yukie and Shibata 2009).

In line with our findings, the participation of pgACC in tinnitus distress has been identified in several EEG and fMRI tinnitus studies (Schlee, Hartmann et al. 2009, De Ridder, Vanneste et al. 2011, Vanneste and De Ridder 2011, Golm, Schmidt-Samoa et al. 2013, Song, Vanneste et al. 2015, Song, Vanneste et al. 2015).

In Vanneste and De Ridder (2011) study, before and after the bifrontal tDCS with the anode over right and cathode over left dlPFC, a resting-state EEG was utilized to identify the mechanism that aids in the suppression of tinnitus loudness and distress. They observed changes in resting-state spontaneous neuronal activity of the pregenual ACC, the parahippocampal area, and the right primary auditory cortex at post-tDCS which was associated with transient suppression of tinnitus distress and loudness (Vanneste and De Ridder 2011).

In a task fMRI study, Golm, Schmidt-Samoa et al. (2013) administered emotional sentences to examine the differences in emotional processing between highly and low distressed tinnitus patients. They identified greater activity in perigenual ACC, dlPFC, medial PFC, insula, anterior midcingulate cortex, dlPFC, superior, and middle frontal gyrus among highly-distressed tinnitus patients. Moreover, activity in the regions mentioned above was positively correlated with tinnitus-related distress (Golm, Schmidt-Samoa et al. 2013).

In our study, the CoG of the cluster showing reduced rsFC with dlPFC was in the bilateral medial frontal gyrus. Support for the contribution of the medial frontal gyrus in tinnitus distress comes from previous studies (De Ridder, Vanneste et al. 2011, Golm, Schmidt-Samoa et al. 2013). In the same study mentioned above, Golm, Schmidt-Samoa et al. (2013), reported higher activation in the right medial frontal gyrus among highly-distressed tinnitus patients compared to low-distressed ones. This higher activation was positively correlated with tinnitus distress suggesting that this region is part of the distress network and can be an ideal stimulation site for mitigating tinnitus distress (Golm, Schmidt-Samoa et al. 2013). Accordingly, reduced engagement of the medial frontal gyrus in our study might indicate a lower level of distress experienced at post-intervention.

Similar to our findings, the role of dlPFC in valence attribution to emotional experiences has been reported in different studies wherein anodal tDCS of left dlPFC reduced negative emotional processing (Boggio, Zaghi et al. 2009, Peña-Gómez, Vidal-Pineiro et al. 2011). In Peña-Gómez, Vidal-Pineiro et al. (2011) study, 1 mA anodal tDCS over the left DLPFC lessened the perceived intensity of emotional valence for negative stimuli but not for positive or neutral stimuli when compared with sham condition (Peña-Gómez, Vidal-Pineiro et al. 2011). Another study found that 2 mA anodal tDCS over the left DLPFC reduced the perception of unpleasantness and personal discomfort in response to images depicting human suffering (Boggio, Zaghi et al. 2009). More recently, Clarke, Van Bockstaele et al. (2020) study provided evidence that left dlPFC tDCS decreased negative emotional reactivity to the aversive content exhibited in the video viewing task. Similarly, Rêgo, Lapenta et al. (2015) indicated attenuated elevations in negative valence and emotional arousal ratings in response to viewing painful situations following left dlPFC tDCS compared to right dlPFC tDCS and sham tDCS conditions.

Conversely, in some cases, the favorable effects of tDCS are relatively small or difficult to replicate (Tremblay, Lepage et al. 2014). The main reason for such discrepancy in the tDCS results is essentially different stimulation parameters applied across studies (Dedoncker, Brunoni et al. 2016).

Behavioral Correlate

Comparing THI scores before and after the intervention, we found that the scores were significantly lowered at post-intervention relative to pre-intervention. This is most probably resulting from the reduction in the engagement of attention and emotion processing regions reflecting the decreased burden of the tinnitus.

Favorable results of dlPFC tDCS on the psychological aspect of tinnitus have been widely reported, although widely varying dose parameters across these studies limits concluding. For instance, using THI as the primary endpoint, Frank, Schecklmann et al. (2012) noted that six thirty-minute sessions of 1.5 mA tDCS (right anode and left cathode) minimally impacted loudness and annoyance (Frank, Schecklmann et al. 2012). With similar electrode arrangement and intensity, Vanneste, Plazier et al. (2010) carried out a clinical study recruiting 478 patients who suffer from tinnitus and reported that a single twenty-minute tDCS session modulated tinnitus perception among 29.9% of the patients. A significant decline was found in the intensity and distress of these patients when assessed with VAS (Vanneste, Plazier et al. 2010). On the other hand, in a cross-over sham-controlled study, Faber, Vanneste et al. (2012) performed six sessions of anodal tDCS for the left or right dlPFC with a cathode electrode over contralateral dlPFC. Results of VAS found that both active conditions, regardless of the anodal position, succeeded in decreasing the annoyance associated with tinnitus but not its intensity(Faber, Vanneste et al. 2012). However, above-mentioned studies lack for functional targeting and identification of neural alterations associated with symptom-alleviation which should be taken into account in future studies.

Neurofunctional tinnitus Model

In agreement with NfTM, our results corroborated the role of the ECL mechanism in developing tinnitus valence. NfTM proposed that for tinnitus patients within the clinical distress stage, CAAP of tinnitus has been repeatedly paired with negative unconditioned stimuli resulting in the generation of tinnitus negative valence. Based on this postulation, in the current study, we used the ECL mechanism to reduce the previously-shaped negative valence by pairing CAAP of tinnitus with PEI and HD-tDCS over the left dlPFC. The observed reduction in rsFC with attention and emotion processing regions and THI scores at post-intervention highlighted the contribution of the ECL mechanism in changing the valence. Such promising results provoke the development of treatments based on the ECL mechanism to reduce the negative valence of tinnitus when paired with positively valenced and high arousal stimuli such as pictures and films (Uhrig, Trautmann et al. 2016). These stimuli can be presented in a game-like design, app-based format, or via goggles of virtual reality to provide a cost-effective home-based individualized treatment.

Our results both at the neural and the behavioral levels are in accordance with NfTM predictions, i.e., the weaker cognitive-emotional value of the sound lowers the chance of attention allocation and the experienced distress level (Ghodratitoostani, Zana et al. 2016). Observing the same trend of reduced rsFC between DAN1 and right subcallosal/OFC at a more liberal threshold adds further support to NfTM predictions. This model, however, did not take into account the involvement of parietal attention processing regions. Therefore, we propose to explain the differences in attention-emotion interactions between patients with neutral and clinical distress tinnitus while incorporating the parietal attention-processing regions in the model.

Given that the general picture of our results is the interaction between attention and emotion processing regions, one possible explanation for the respective interaction could be via the framework of the salience network. The salience network is responsible for mediating attention to relevant external stimuli and operating in terms of the associated processing of cognition and emotion (Menon and Uddin 2010, Elton and Gao 2014). However, after the intervention, we did not observe any changes in the rsFC of the anterior insula as one of the main nodes of the salience network. It is suggested that future studies examine if the anterior insula and dorsal anterior cingulate cortex, representing the salience network, indicate any differential functional coupling in tinnitus patients within the clinical distress stage. A further justification for considering the salience network relates to the correlation between stimulus valence and the salience network (Anders, Lotze et al. 2004, Viinikainen, Kätsyri et al. 2012). If this correlation was verified for tinnitus, NfTM needs to be revised accordingly.

NfTM proposes how different brain regions interact resulting in tinnitus distress. Our observation of alterations in the amygdala, ACC, and lateral PFC at post-intervention confirmed their contribution to tinnitus distress as proposed by NfTM. More specifically, the finding that the pregenual part of ACC plays a role in tinnitus distress added further detail to the anatomical structure of NfTM. Although our findings provided some support for NfTM, further investigations are still required for the model validation.

Conclusion

The current study aimed to examine if repeated sessions of HD-tDCS over left dlPFC concurrent with PEI can down-regulate the tinnitus negative valence both at the neural network and behavioral level. Results indicated attenuated rsFC between attention and emotion processing regions at post-intervention when compared with pre-intervention. Generally, the brain has calmed down after receiving the intervention. To illustrate, we observed that reducing the negative valence of tinnitus could lessen the chance of attention allocation to the sound with a lower level of distress, as was predicted based on NfTM. However, we still do not know the exact underlying mechanisms which led to the lower rsFC between attention and emotion processing regions; this might derive from improvement in the function of cognitive control regions (Husain 2016) to which we were unable to find a track. Alternatively, the current findings might stem from the participation of some hub regions mediating cognitive-emotional processes resulting in emotion regulation and controlling behavior (Pessoa 2014). Collectively, future investigations in light of NfTM are required to better understand the root causes of these beneficial effects.

Limitations and Future Directions

The first limitation of the current study was the small sample size that hampers inferences on the general population; therefore, the results are only experimental; however, they are still reliable because they passed multiple comparison corrections. Next, the tinnitus duration and hearing threshold level were heterogeneous across our patients which affects rsFC (Schmidt, Akrofi et al. 2013, Carpenter-Thompson, Schmidt et al. 2015). In future studies, the relevance of depression-anxiety scores representing the general distress with THI scores representing tinnitus-related distress can be investigated in correlation with changes in local FC values. In our study, the discrepancy in the utilized depression measures limited afore-mentioned investigation. A further limitation of our study is the absence of a sham-controlled group and follow-up measurements. Moreover, our work lacks individualized head models for anatomical targeting considering cross-subject heterogeneity in the location of the dlPFC.

Another critical issue is the fact that stimulation of a given area produces widespread modulation of brain activity and connectivity, which can simultaneously affect multiple cognitive functions (Dedoncker, Brunoni et al. 2016). This can lead to a fundamental problem of interpretation since the observed tDCS-induced after-effect could be due to the interaction of several parallel cognitive effects. Future studies can include an additional active stimulation site besides dlPFC to test if similar results would be replicated to provide a more precise idea for interpreting the results. In addition, effective connectivity is highly suggested since it gives information about the direction and causality of the connectivity (Friston, Frith et al. 1993) and thereupon attains an improved vision of the flow of signals through the regions and networks. All the above-mentioned suggestions should be taken into account in future studies.

References

Abend, R., R. Sar-el, T. Gonen, I. Jalon, S. Vaisvaser, Y. Bar-Haim and T. Hendler (2019). "Modulating Emotional Experience Using Electrical Stimulation of the Medial-Prefrontal Cortex: A Preliminary tDCS-fMRI Study." Neuromodulation: Technology at the Neural Interface **22**(8): 884-893.

Alves, N. T., S. S. Fukusima and J. A. Aznar-Casanova (2008). "Models of brain asymmetry in emotional processing." Psychology & Neuroscience **1**: 63-66.

Amaral, A. A. and D. R. Langers (2015). "Tinnitus-related abnormalities in visual and salience networks during a one-back task with distractors." Hearing Research **326**: 15-29.

Amemori, K.-i. and A. M. Graybiel (2012). "Localized microstimulation of primate pregenual cingulate cortex induces negative decision-making." Nature neuroscience **15**(5): 776-785.

Anders, S., M. Lotze, M. Erb, W. Grodd and N. Birbaumer (2004). "Brain activity underlying emotional valence and arousal: A response-related fMRI study." Human brain mapping **23**(4): 200-209.

Andersson, G. and L. McKenna (2006). "The role of cognition in tinnitus." Acta Oto-Laryngologica **126**(sup556): 39-43.

Armony, J. L. and R. J. Dolan (2002). "Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study." Neuropsychologia **40**(7): 817-826.

Armony, J. L. and J. E. Ledoux (1999). How danger is encoded: towards a systems, cellular, and computational understanding of cognitive-emotional interactions, MIT Press.

Arnold, W., P. Bartenstein, E. Oestreicher, W. Römer and M. Schwaiger (1996). "Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: a PET study with [18F] deoxyglucose." Orl **58**(4): 195-199.

Axelsson, A. and A. Ringdahl (1989). "Tinnitus—a study of its prevalence and characteristics." British journal of audiology **23**(1): 53-62.

Bai, S., S. Dokos, K.-A. Ho and C. Loo (2014). "A computational modelling study of transcranial direct current stimulation montages used in depression." Neuroimage **87**: 332-344.

Balconi, M. and C. Ferrari (2013). "Repeated transcranial magnetic stimulation on dorsolateral prefrontal cortex improves performance in emotional memory retrieval as a function of level of anxiety and stimulus valence." Psychiatry and clinical neurosciences **67**(4): 210-218.

Bartra, O., J. T. McGuire and J. W. Kable (2013). "The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value." Neuroimage **76**: 412-427.

Beck, A. T., C. Ward, M. Mendelson, J. Mock and J. Erbaugh (1961). "Beck depression inventory (BDI)." Arch Gen Psychiatry **4**(6): 561-571.

Behrmann, M., J. J. Geng and S. Shomstein (2004). "Parietal cortex and attention." Curr Opin Neurobiol **14**(2): 212-217.

Bestmann, S., A. O. de Berker and J. Bonaiuto (2015). "Understanding the behavioural consequences of noninvasive brain stimulation." Trends in cognitive sciences **19**(1): 13-20.

Bikson, M., M. Inoue, H. Akiyama, J. K. Deans, J. E. Fox, H. Miyakawa and J. G. Jefferys (2004). "Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro." The Journal of physiology **557**(1): 175-190.

Bikson, M. and A. Rahman (2013). "Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms." Frontiers in human neuroscience **7**: 688.

Bindman, L. J., O. Lippold and J. Redfearn (1962). "Long-lasting changes in the level of the electrical activity of the cerebral cortex produced by polarizing currents." Nature **196**(4854): 584-585.

Bindman, L. J., O. Lippold and J. Redfearn (1963). "Comparison of the effects on electrocortical activity of general body cooling and local cooling of the surface of the brain." Electroencephalography and clinical neurophysiology **15**(2): 238-245.

Birn, R. M., J. B. Diamond, M. A. Smith and P. A. Bandettini (2006). "Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI." Neuroimage **31**(4): 1536-1548.

Biswal, B., F. Zerrin Yetkin, V. M. Haughton and J. S. Hyde (1995). "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI." Magnetic resonance in medicine **34**(4): 537-541.

Boggio, P. S., S. Zaghi and F. Fregni (2009). "Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS)." Neuropsychologia **47**(1): 212-217.

Bradley, M. M. and P. J. Lang (1994). "Measuring emotion: the self-assessment manikin and the semantic differential." Journal of behavior therapy and experimental psychiatry **25**(1): 49-59.

Breit, S., J. B. Schulz and A.-L. Benabid (2004). "Deep brain stimulation." Cell and tissue research **318**(1): 275-288.

Brett, M., J.-L. Anton, R. Valabregue and J.-B. Poline (2002). Region of interest analysis using an SPM toolbox. 8th international conference on functional mapping of the human brain, Sendai.

Brissenden, J. A., E. J. Levin, D. E. Osher, M. A. Halko and D. C. Somers (2016). "Functional evidence for a cerebellar node of the dorsal attention network." Journal of Neuroscience **36**(22): 6083-6096.

Brunoni, A. R., T. A. Zanao, M.-A. Vanderhasselt, L. Valiengo, J. F. de Oliveira, P. S. Boggio, P. A. Lotufo, I. M. Benseñor and F. Fregni (2014). "Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression." Neuromodulation: Technology at the Neural Interface **17**(2): 138-142.

Brunoni, A. R., T. A. Zanao, M. A. Vanderhasselt, L. Valiengo, J. F. de Oliveira, P. S. Boggio, P. A. Lotufo, I. M. Benseñor and F. Fregni (2014). "Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression." Neuromodulation: Technology at the Neural Interface **17**(2): 138-142.

Burton, H., A. Wineland, M. Bhattacharya, J. Nicklaus, K. S. Garcia and J. F. Piccirillo (2012). "Altered networks in bothersome tinnitus: a functional connectivity study." BMC neuroscience **13**(1): 1-15.

Bush, G., P. Luu and M. I. Posner (2000). "Cognitive and emotional influences in anterior cingulate cortex." Trends in cognitive sciences **4**(6): 215-222.

Buxton, R. B. (2016). "Beyond BOLD correlations: a more quantitative approach for investigating brain networks." Journal of Cerebral Blood Flow & Metabolism **36**(3): 461-462.

Carpenter-Thompson, J. R., S. Schmidt, E. McAuley and F. T. Husain (2015). "Increased frontal response may underlie decreased tinnitus severity." PLoS One **10**(12): e0144419.

Carpenter-Thompson, J. R., S. A. Schmidt and F. T. Husain (2015). "Neural plasticity of mild tinnitus: an fMRI investigation comparing those recently diagnosed with tinnitus to those that had tinnitus for a long period of time." Neural Plasticity **2015**.

Caspary, D. M., L. Ling, J. G. Turner and L. F. Hughes (2008). "Inhibitory neurotransmission, plasticity and aging in the mammalian central auditory system." Journal of Experimental Biology **211**(11): 1781-1791.

Chang, C., J. P. Cunningham and G. H. Glover (2009). "Influence of heart rate on the BOLD signal: the cardiac response function." Neuroimage **44**(3): 857-869.

Chen, N. T., J. Basanovic, L. Notebaert, C. MacLeod and P. J. Clarke (2017). "Attentional bias mediates the effect of neurostimulation on emotional vulnerability." Journal of psychiatric research **93**: 12-19.

Cianfrone, G., D. Pentangelo, F. Cianfrone, F. Mazzei, R. Turchetta, M. Orlando and G. Altissimi (2011). "Pharmacological drugs inducing ototoxicity, vestibular symptoms and tinnitus: a reasoned and updated guide." Eur Rev Med Pharmacol Sci **15**(6): 601-636.

Cisler, J. M. and B. O. Olatunji (2012). "Emotion regulation and anxiety disorders." Current psychiatry reports **14**(3): 182-187.

Citron, F. M., M. A. Gray, H. D. Critchley, B. S. Weekes and E. C. Ferstl (2014). "Emotional valence and arousal affect reading in an interactive way: neuroimaging evidence for an approach-withdrawal framework." Neuropsychologia **56**: 79-89.

Clarke, P. J., B. Van Bockstaele, W. Marinovic, J. A. Howell, M. E. Boyes and L. Notebaert (2020). "The effects of left DLPFC tDCS on emotion regulation, biased attention, and emotional reactivity to negative content." Cognitive, Affective, & Behavioral Neuroscience **20**(6): 1323-1335.

Clithero, J. A. and A. Rangel (2014). "Informatic parcellation of the network involved in the computation of subjective value." Social cognitive and affective neuroscience **9**(9): 1289-1302.

Cole, D. M., S. M. Smith and C. F. Beckmann (2010). "Advances and pitfalls in the analysis and interpretation of resting-state FMRI data." Frontiers in systems neuroscience **4**: 8.

Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nature reviews neuroscience **3**(3): 201-215.

Cordes, D., V. M. Haughton, K. Arfanakis, J. D. Carew, P. A. Turski, C. H. Moritz, M. A. Quigley and M. E. Meyerand (2001). "Frequencies contributing to functional connectivity in the cerebral cortex in “resting-state” data." American journal of neuroradiology **22**(7): 1326-1333.

Creutzfeldt, O. D., G. H. Fromm and H. Kapp (1962). "Influence of transcortical dc currents on cortical neuronal activity." Experimental neurology **5**(6): 436-452.

Critchley, H. D., R. Elliott, C. J. Mathias and R. J. Dolan (2000). "Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study." Journal of Neuroscience **20**(8): 3033-3040.

Critchley, H. D., C. J. Mathias and R. J. Dolan (2001). "Neural activity in the human brain relating to uncertainty and arousal during anticipation." Neuron **29**(2): 537-545.

Critchley, H. D., R. N. Melmed, E. Featherstone, C. J. Mathias and R. J. Dolan (2002). "Volitional control of autonomic arousal: a functional magnetic resonance study." Neuroimage **16**(4): 909-919.

Crönlein, T., B. Langguth, P. Geisler and G. Hajak (2007). "Tinnitus and insomnia." Progress in brain research **166**: 227-233.

Damoiseaux, J. S., S. Rombouts, F. Barkhof, P. Scheltens, C. J. Stam, S. M. Smith and C. F. Beckmann (2006). "Consistent resting-state networks across healthy subjects." Proceedings of the national academy of sciences **103**(37): 13848-13853.

Datta, A. (2012). "Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models." Frontiers in psychiatry **3**: 91.

Datta, A., J. M. Baker, M. Bikson and J. Fridriksson (2011). "Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient." Brain stimulation **4**(3): 169-174.

Datta, A., V. Bansal, J. Diaz, J. Patel, D. Reato and M. Bikson (2009). "Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad." Brain stimulation **2**(4): 201-207. e201.

Davidson, R. J., K. M. Putnam and C. L. Larson (2000). "Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence." science **289**(5479): 591-594.

De Houwer, J., S. Thomas and F. Baeyens (2001). "Association learning of likes and dislikes: A review of 25 years of research on human evaluative conditioning." Psychological bulletin **127**(6): 853.

De Ridder, D. and S. Vanneste (2012). "EEG driven tDCS versus bifrontal tDCS for tinnitus." Frontiers in Psychiatry **3**: 84.

De Ridder, D., S. Vanneste and M. Congedo (2011). "The distressed brain: a group blind source separation analysis on tinnitus." PloS one **6**(10): e24273.

De Ridder, D., S. Vanneste, N. Weisz, A. Londero, W. Schlee, A. B. Elgoyhen and B. Langguth (2014). "An integrative model of auditory phantom perception: tinnitus as a unified percept of interacting separable subnetworks." Neuroscience & Biobehavioral Reviews **44**: 16-32.

Dedoncker, J., A. R. Brunoni, C. Baeken and M.-A. Vanderhasselt (2016). "The effect of the interval-between-sessions on prefrontal transcranial direct current stimulation (tDCS) on cognitive outcomes: a systematic review and meta-analysis." Journal of Neural Transmission **123**(10): 1159-1172.

Dedoncker, J., A. R. Brunoni, C. Baeken and M.-A. Vanderhasselt (2016). "A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters." Brain stimulation **9**(4): 501-517.

Diesch, E., M. Andermann, H. Flor and A. Rupp (2010). "Functional and structural aspects of tinnitus-related enhancement and suppression of auditory cortex activity." Neuroimage **50**(4): 1545-1559.

Dixon, M. L., J. R. Andrews-Hanna, R. N. Spreng, Z. C. Irving, C. Mills, M. Girn and K. Christoff (2017). "Interactions between the default network and dorsal attention network vary across default subsystems, time, and cognitive states." Neuroimage **147**: 632-649.

Dmochowski, J. P., A. Datta, M. Bikson, Y. Su and L. C. Parra (2011). "Optimized multi-electrode stimulation increases focality and intensity at target." Journal of neural engineering **8**(4): 046011.

Dmochowski, J. P., A. Datta, Y. Huang, J. D. Richardson, M. Bikson, J. Fridriksson and L. C. Parra (2013). "Targeted transcranial direct current stimulation for rehabilitation after stroke." Neuroimage **75**: 12-19.

Dobie, R. A. (2003). "Depression and tinnitus." Otolaryngologic Clinics of North America **36**(2): 383-388.

Dosenbach, N. U., D. A. Fair, F. M. Miezin, A. L. Cohen, K. K. Wenger, R. A. Dosenbach, M. D. Fox, A. Z. Snyder, J. L. Vincent and M. E. Raichle (2007). "Distinct brain networks for adaptive and stable task control in humans." Proceedings of the National Academy of Sciences **104**(26): 11073-11078.

Dubljević, V., V. Saigle and E. Racine (2014). "The rising tide of tDCS in the media and academic literature." Neuron **82**(4): 731-736.

Dumais, K. M., S. Chernyak, L. D. Nickerson and A. C. Janes (2018). "Sex differences in default mode and dorsal attention network engagement." PLoS One **13**(6): e0199049.

Edwards, D., M. Cortes, A. Datta, P. Minhas, E. M. Wassermann and M. Bikson (2013). "Physiological and modeling evidence for focal transcranial electrical brain stimulation in humans: a basis for high-definition tDCS." Neuroimage **74**: 266-275.

Eggermont, J. J. (2015). "Tinnitus and neural plasticity (Tonndorf lecture at XIth international tinnitus Seminar, Berlin, 2014)." Hearing research **319**: 1-11.

Eggermont, J. J. and H. Komiya (2000). "Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood." Hearing research **142**(1-2): 89-101.

Eggermont, J. J. and L. E. Roberts (2004). "The neuroscience of tinnitus." Trends in neurosciences **27**(11): 676-682.

Elton, A. and W. Gao (2014). "Divergent task-dependent functional connectivity of executive control and salience networks." Cortex **51**: 56-66.

Faber, M., S. Vanneste, F. Fregni and D. De Ridder (2012). "Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex." Brain stimulation **5**(4): 492-498.

Fabijańska, A., J. Smurzyński, K. Kochanek, G. Bartnik, D. Raj-Koziak and H. Skarżyński (2012). "The influence of high frequency hearing loss on the distortion product otoacoustic emissions in tinnitus subjects with normal hearing threshold (0, 25-8 kHz)." Otolaryngologia Polska= The Polish Otolaryngology **66**(5): 318-321.

Fassbender, C., C. Simoes-Franklin, K. Murphy, R. Hester, J. Meaney, I. Robertson and H. Garavan (2006). "The role of a right fronto-parietal network in cognitive control." Journal of Psychophysiology **20**(4): 286-296.

Fesl, G., B. Braun, S. Rau, M. Wiesmann, M. Ruge, P. Bruhns, J. Linn, T. Stephan, J. Ilmberger and J.-C. Tonn (2008). "Is the center of mass (COM) a reliable parameter for the localization of brain function in fMRI?" European radiology **18**(5): 1031-1037.

Fioravanti-Bastos, A. C. M., E. Cheniaux and J. Landeira-Fernandez (2011). "Development and validation of a short-form version of the Brazilian state-trait anxiety inventory." Psicologia: Reflexão e Crítica **24**: 485-494.

Forogh, B., Z. Mirshaki, G. R. Raissi, A. Shirazi, K. Mansoori and T. Ahadi (2016). "Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial." Neurological Sciences **37**(2): 253-259.

Fox, M. D., M. Corbetta, A. Z. Snyder, J. L. Vincent and M. E. Raichle (2006). "Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems." Proceedings of the National Academy of Sciences **103**(26): 10046-10051.

Fox, M. D., A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen and M. E. Raichle (2005). "The human brain is intrinsically organized into dynamic, anticorrelated functional networks." Proceedings of the National Academy of Sciences **102**(27): 9673-9678.

Fox, M. D., D. Zhang, A. Z. Snyder and M. E. Raichle (2009). "The global signal and observed anticorrelated resting state brain networks." Journal of neurophysiology **101**(6): 3270-3283.

Frank, E., M. Schecklmann, M. Landgrebe, J. Burger, P. Kreuzer, T. B. Poeppl, T. Kleinjung, G. Hajak and B. Langguth (2012). "Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study." Journal of Neurology **259**(2): 327-333.

Fregni, F., P. S. Boggio, M. Nitsche, F. Bermpohl, A. Antal, E. Feredoes, M. A. Marcolin, S. P. Rigonatti, M. T. Silva and W. Paulus (2005). "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory." Experimental brain research **166**(1): 23-30.

Fregni, F., P. S. Boggio, M. A. Nitsche, M. A. Marcolin, S. P. Rigonatti and A. Pascual-Leone (2006). "Treatment of major depression with transcranial direct current stimulation."

Fregni, F., P. S. Boggio, M. A. Nitsche, S. P. Rigonatti and A. Pascual-Leone (2006). Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression, Wiley Subscription Services, Inc., A Wiley Company Hoboken. **23:** 482-484.

Friston, K., C. Frith, P. Liddle and R. Frackowiak (1993). "Functional connectivity: the principal-component analysis of large (PET) data sets." Journal of Cerebral Blood Flow & Metabolism **13**(1): 5-14.

Fritz, J. B., M. Elhilali, S. V. David and S. A. Shamma (2007). "Auditory attention—focusing the searchlight on sound." Current opinion in neurobiology **17**(4): 437-455.

Galletta, E. E., A. Cancelli, C. Cottone, I. Simonelli, F. Tecchio, M. Bikson and P. Marangolo (2015). "Use of computational modeling to inform tDCS electrode montages for the promotion of language recovery in post-stroke aphasia." Brain stimulation **8**(6): 1108-1115.

Garin, P., C. Gilain, J.-P. Van Damme, K. De Fays, J. Jamart, M. Ossemann and Y. Vandermeeren (2011). "Short-and long-lasting tinnitus relief induced by transcranial direct current stimulation." Journal of neurology **258**(11): 1940-1948.

Ghodratitoostani, I., A. CB Delbem, M. Torabi-Nami, B. Makkiabadi, H. Jalilvand and T. Ganz Sanchez (2016). "Theoretical tinnitus multimodality framework: a neurofunctional model." Journal of Advanced Medical Sciences and Applied Technologies **2**(1): 181-189.

Ghodratitoostani, I., O. A. Gonzatto Jr, Z. Vaziri, A. C. Delbem, B. Makkiabadi, A. Datta, C. Thomas, M. A. Hyppolito, A. C. Santos and F. Louzada (2022). "Dose-Response Transcranial Electrical Stimulation Study Design: A Well-Controlled Adaptive Seamless Bayesian Method to Illuminate Negative Valence Role in Tinnitus Perception." Frontiers in Human Neuroscience.

Ghodratitoostani, I., Z. Vazirikangolya, D. Nascimento, M. Colacique, F. Louzada, A. Delbem, C. Barros, A. Oliveira, M. Hyppolito and J. Leite (2019). "Anodal HD-tDCS of left dlPFC together with Positive Emotion Induction Can Modulate Tinnitus Loudness." Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation **12**(2): 470.

Ghodratitoostani, I., Y. Zana, A. C. Delbem, S. S. Sani, H. Ekhtiari and T. G. Sanchez (2016). "Theoretical Tinnitus Framework: A Neurofunctional Model." Front Neurosci **10**: 370.

Ghodratitoostani, I., Y. Zana, A. C. Delbem, S. S. Sani, H. Ekhtiari and T. G. Sanchez (2016). "Theoretical tinnitus framework: a neurofunctional model." Frontiers in neuroscience **10**: 370.

Gimsing, S. (2010). "Vestibular schwannoma: when to look for it?" The Journal of Laryngology & Otology **124**(3): 258-264.

Golm, D., C. Schmidt-Samoa, P. Dechent and B. Kröner-Herwig (2013). "Neural correlates of tinnitus related distress: an fMRI-study." Hearing research **295**: 87-99.

Gu, J. W., C. F. Halpin, E.-C. Nam, R. A. Levine and J. R. Melcher (2010). "Tinnitus, diminished sound-level tolerance, and elevated auditory activity in humans with clinically normal hearing sensitivity." Journal of neurophysiology **104**(6): 3361-3370.

Guitton, M. J., J. Caston, J. Ruel, R. M. Johnson, R. Pujol and J.-L. Puel (2003). "Salicylate induces tinnitus through activation of cochlear NMDA receptors." Journal of Neuroscience **23**(9): 3944-3952.

Hackett, T. A. (2011). "Information flow in the auditory cortical network." Hearing research **271**(1-2): 133-146.

Halford, J. B. and S. D. Anderson (1991). "Anxiety and depression in tinnitus sufferers." Journal of psychosomatic research **35**(4-5): 383-390.

Hallam, R., S. Jakes and R. Hinchcliffe (1988). "Cognitive variables in tinnitus annoyance." British Journal of Clinical Psychology **27**(3): 213-222.

Hallam, R., L. McKenna and L. Shurlock (2004). "Tinnitus impairs cognitive efficiency." International journal of audiology **43**(4): 218-226.

Handscomb, L. E., D. A. Hall, G. W. Shorter and D. J. Hoare (2017). "Positive and negative thinking in tinnitus: factor structure of the tinnitus cognitions questionnaire." Ear and hearing **38**(1): 126.

Handscomb, L. E., D. A. Hall, G. W. Shorter and D. J. Hoare (2017). "Positive and Negative Thinking in Tinnitus: Factor Structure of the Tinnitus Cognitions Questionnaire." Ear and Hearing **38**(1): 126-132.

Hansenne, M., D. Nélis, D. Feyers, E. Salmon and S. Majerus (2014). "Better neuronal efficiency after emotional competences training: An fMRI study." Psychologica Belgica **54**(4): 328.

Heffner, H. E. and I. A. Harrington (2002). "Tinnitus in hamsters following exposure to intense sound." Hearing research **170**(1-2): 83-95.

Heimrath, K., C. Breitling, K. Krauel, H. J. Heinze and T. Zaehle (2015). "Modulation of pre-attentive spectro-temporal feature processing in the human auditory system by HD-t DCS." European Journal of Neuroscience **41**(12): 1580-1586.

Heller, A. J. (2003). "Classification and epidemiology of tinnitus." Otolaryngologic Clinics of North America **36**(2): 239-248.

Henry, J. A., K. C. Dennis and M. A. Schechter (2005). "General review of tinnitus."

Herrington, J. D., A. Mohanty, N. S. Koven, J. E. Fisher, J. L. Stewart, M. T. Banich, A. G. Webb, G. A. Miller and W. Heller (2005). "Emotion-modulated performance and activity in left dorsolateral prefrontal cortex." Emotion **5**(2): 200.

House, J. W. and D. Brackman (1981). Tinnitus: surgical treatment. Ciba foundation symposium.

Howsam, G., A. Sharma, S. Lambden, J. Fitzgerald and P. Prinsley (2005). "Bilateral objective tinnitus secondary to congenital middle-ear myoclonus." The Journal of Laryngology & Otology **119**(6): 489-491.

Hu, H., Y. Lyu, S. Li, Z. Yuan, C. Ye, Z. Han and G. Lin (2021). "Aberrant Resting-State Functional Connectivity of the Dorsal Attention Network in Tinnitus." Neural plasticity **2021**.

Husain, F. T. (2016). "Neural networks of tinnitus in humans: elucidating severity and habituation." Hearing research **334**: 37-48.

Ironside, M., M. Browning, T. L. Ansari, C. J. Harvey, M. N. Sekyi-Djan, S. J. Bishop, C. J. Harmer and J. O'Shea (2019). "Effect of prefrontal cortex stimulation on regulation of amygdala response to threat in individuals with trait anxiety: a randomized clinical trial." JAMA psychiatry **76**(1): 71-78.

Ironside, M., J. O'Shea, P. J. Cowen and C. J. Harmer (2016). "Frontal cortex stimulation reduces vigilance to threat: implications for the treatment of depression and anxiety." Biological psychiatry **79**(10): 823-830.

Jackson, D., C. Burghy, A. Hanna, C. Larson and R. Davidson (2000). Resting frontal and anterior temporal EEG asymmetry predicts ability to regulate negative emotion. Psychophysiology, CAMBRIDGE UNIV PRESS 40 WEST 20TH STREET, NEW YORK, NY 10011-4211 USA.

Jackson, D. C., C. J. Mueller, I. Dolski, K. M. Dalton, J. B. Nitschke, H. L. Urry, M. A. Rosenkranz, C. D. Ryff, B. H. Singer and R. J. Davidson (2003). "Now you feel it, now you don't: Frontal brain electrical asymmetry and individual differences in emotion regulation." Psychological science **14**(6): 612-617.

Jackson, M. P., A. Rahman, B. Lafon, G. Kronberg, D. Ling, L. C. Parra and M. Bikson (2016). "Animal models of transcranial direct current stimulation: methods and mechanisms." Clinical Neurophysiology **127**(11): 3425-3454.

Jacob, H., C. Brück, M. Domin, M. Lotze and D. Wildgruber (2014). "I can't keep your face and voice out of my head: neural correlates of an attentional bias toward nonverbal emotional cues." Cerebral Cortex **24**(6): 1460-1473.

Jastreboff, P. J. (1990). "Phantom auditory perception (tinnitus): mechanisms of generation and perception." Neuroscience research **8**(4): 221-254.

Jastreboff, P. J. and M. M. Jastreboff (2003). "Tinnitus retraining therapy for patients with tinnitus and decreased sound tolerance." Otolaryngologic Clinics of North America **36**(2): 321-336.

Jurcak, V., D. Tsuzuki and I. Dan (2007). "10/20, 10/10, and 10/5 systems revisited: their validity as relative head-surface-based positioning systems." Neuroimage **34**(4): 1600-1611.

Kaltenbach, J. A. (2011). "Tinnitus: models and mechanisms." Hearing research **276**(1-2): 52-60.

Kim, J.-y., Y.-h. Kim, S. Lee, J.-H. Seo, H.-J. Song, J. H. Cho and Y. Chang (2012). "Alteration of functional connectivity in tinnitus brain revealed by resting-state fMRI?: a pilot study." International journal of audiology **51**(5): 413-417.

Kleinjung, T., P. Eichhammer, M. Landgrebe, P. Sand, G. Hajak, T. Steffens, J. Strutz and B. Langguth (2008). "Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: a pilot study." Otolaryngology—Head and Neck Surgery **138**(4): 497-501.

Kwong, K. K., J. W. Belliveau, D. A. Chesler, I. E. Goldberg, R. M. Weisskoff, B. P. Poncelet, D. N. Kennedy, B. E. Hoppel, M. S. Cohen and R. Turner (1992). "Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation." Proceedings of the National Academy of Sciences **89**(12): 5675-5679.

Lane, R. D., P. M. Chua and R. J. Dolan (1999). "Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures." Neuropsychologia **37**(9): 989-997.

Lane, R. D., E. M. Reiman, B. Axelrod, L.-S. Yun, A. Holmes and G. E. Schwartz (1998). "Neural correlates of levels of emotional awareness: Evidence of an interaction between emotion and attention in the anterior cingulate cortex." Journal of cognitive neuroscience **10**(4): 525-535.

Lang, N., H. R. Siebner, N. S. Ward, L. Lee, M. A. Nitsche, W. Paulus, J. C. Rothwell, R. N. Lemon and R. S. Frackowiak (2005). "How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain?" European Journal of Neuroscience **22**(2): 495-504.

Langers, D. R., P. van Dijk, E. S. Schoenmaker and W. H. Backes (2007). "fMRI activation in relation to sound intensity and loudness." Neuroimage **35**(2): 709-718.

Lanting, C., E. De Kleine and P. Van Dijk (2009). "Neural activity underlying tinnitus generation: results from PET and fMRI." Hearing research **255**(1-2): 1-13.

Lanting, C., A. WoźAniak, P. van Dijk and D. R. Langers (2016). Tinnitus-and task-related differences in resting-state networks. Physiology, psychoacoustics and cognition in normal and impaired hearing, Springer, Cham**:** 175-187.

Leaver, A. M., T. K. Turesky, A. Seydell-Greenwald, S. Morgan, H. J. Kim and J. P. Rauschecker (2016). "Intrinsic network activity in tinnitus investigated using functional MRI." Human brain mapping **37**(8): 2717-2735.

Lee, M. H., C. D. Smyser and J. S. Shimony (2013). "Resting-state fMRI: a review of methods and clinical applications." American Journal of neuroradiology **34**(10): 1866-1872.

Lee, T.-H., L. Itti and M. Mather (2012). "Evidence for arousal-biased competition in perceptual learning." Frontiers in psychology **3**: 241.

Lee, T.-H., M. Sakaki, R. Cheng, R. Velasco and M. Mather (2014). "Emotional arousal amplifies the effects of biased competition in the brain." Social cognitive and affective neuroscience **9**(12): 2067-2077.

Lockwood, A. H., R. Salvi, M. Coad, M. Towsley, D. Wack and B. Murphy (1998). "The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity." Neurology **50**(1): 114-120.

Maddock, R. J. (1999). "The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain." Trends in neurosciences **22**(7): 310-316.

Mantini, D., M. G. Perrucci, C. Del Gratta, G. L. Romani and M. Corbetta (2007). "Electrophysiological signatures of resting state networks in the human brain." Proceedings of the National Academy of Sciences **104**(32): 13170-13175.

Marchewka, A., Ł. Żurawski, K. Jednoróg and A. Grabowska (2014). "The Nencki Affective Picture System (NAPS): Introduction to a novel, standardized, wide-range, high-quality, realistic picture database." Behavior research methods **46**(2): 596-610.

Mather, M. and M. R. Sutherland (2011). "Arousal-biased competition in perception and memory." Perspectives on psychological science **6**(2): 114-133.

Maudoux, A., P. Lefebvre, J.-E. Cabay, A. Demertzi, A. Vanhaudenhuyse, S. Laureys and A. Soddu (2012). "Auditory resting-state network connectivity in tinnitus: a functional MRI study." PloS one **7**(5): e36222.

McKenna, L., L. Handscomb, D. J. Hoare and D. A. Hall (2014). "A scientific cognitive-behavioral model of tinnitus: novel conceptualizations of tinnitus distress." Frontiers in Neurology **5**: 196.

Menon, V. and L. Q. Uddin (2010). "Saliency, switching, attention and control: a network model of insula function." Brain structure and function **214**(5): 655-667.

Mesulam, M.-M. (1999). "Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events." Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences **354**(1387): 1325-1346.

Mills, R., D. Albert and C. Brain (1986). "Tinnitus in childhood." Clinical Otolaryngology & Allied Sciences **11**(6): 431-434.

Mintun, M. A., P. T. Fox and M. E. Raichle (1989). "A highly accurate method of localizing regions of neuronal activation in the human brain with positron emission tomography." Journal of Cerebral Blood Flow & Metabolism **9**(1): 96-103.

Miranda, P. C., M. Lomarev and M. Hallett (2006). "Modeling the current distribution during transcranial direct current stimulation." Clinical neurophysiology **117**(7): 1623-1629.

Möbius, M., L. Lacomblé, T. Meyer, D. J. Schutter, T. Gielkens, E. S. Becker, I. Tendolkar and P. van Eijndhoven (2017). "Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction." Social cognitive and affective neuroscience **12**(4): 526-533.

Mondino, M., F. Thiffault and S. Fecteau (2015). "Does non-invasive brain stimulation applied over the dorsolateral prefrontal cortex non-specifically influence mood and emotional processing in healthy individuals?" Frontiers in cellular neuroscience **9**: 399.

Mühlnickel, W., T. Elbert, E. Taub and H. Flor (1998). "Reorganization of auditory cortex in tinnitus." Proceedings of the National Academy of Sciences **95**(17): 10340-10343.

Niedenthal, P. M. and S. Kitayama (2013). The heart's eye: Emotional influences in perception and attention, Academic Press.

Nieto-Castanon, A. (2020). Handbook of functional connectivity Magnetic Resonance Imaging methods in CONN, Hilbert Press.

Nitsche, M. A., L. G. Cohen, E. M. Wassermann, A. Priori, N. Lang, A. Antal, W. Paulus, F. Hummel, P. S. Boggio and F. Fregni (2008). "Transcranial direct current stimulation: state of the art 2008." Brain stimulation **1**(3): 206-223.

Nitsche, M. A., S. Doemkes, T. Karakose, A. Antal, D. Liebetanz, N. Lang, F. Tergau and W. Paulus (2007). "Shaping the effects of transcranial direct current stimulation of the human motor cortex." Journal of neurophysiology **97**(4): 3109-3117.

Nitsche, M. A., J. Koschack, H. Pohlers, S. Hullemann, W. Paulus and S. Happe (2012). "Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans." Frontiers in psychiatry **3**: 58.

Nitsche, M. A., D. Liebetanz, A. Antal, N. Lang, F. Tergau and W. Paulus (2003). "Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects." Supplements to Clinical neurophysiology **56**: 255-276.

Nitsche, M. A. and W. Paulus (2000). "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation." The Journal of physiology **527**(Pt 3): 633.

Nitsche, M. A. and W. Paulus (2001). "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans." Neurology **57**(10): 1899-1901.

Norena, A., H. Cransac and S. Chery-Croze (1999). "Towards an objectification by classification of tinnitus." Clinical Neurophysiology **110**(4): 666-675.

Norena, A. and J. Eggermont (2003). "Changes in spontaneous neural activity immediately after an acoustic trauma: implications for neural correlates of tinnitus." Hearing research **183**(1-2): 137-153.

Norena, A. J., M. Tomita and J. J. Eggermont (2003). "Neural changes in cat auditory cortex after a transient pure-tone trauma." Journal of Neurophysiology **90**(4): 2387-2401.

Ochsner, K. N., S. A. Bunge, J. J. Gross and J. D. Gabrieli (2002). "Rethinking feelings: an FMRI study of the cognitive regulation of emotion." Journal of cognitive neuroscience **14**(8): 1215-1229.

Ogawa, S., T.-M. Lee, A. R. Kay and D. W. Tank (1990). "Brain magnetic resonance imaging with contrast dependent on blood oxygenation." proceedings of the National Academy of Sciences **87**(24): 9868-9872.

Pais-Ribeiro, J., I. Silva, T. Ferreira, A. Martins, R. Meneses and M. Baltar (2007). "Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale." Psychology, health & medicine **12**(2): 225-237.

Pal, N., R. Maire, M. A. Stephan, F. R. Herrmann and D. H. Benninger (2015). "Transcranial direct current stimulation for the treatment of chronic tinnitus: a randomized controlled study." Brain stimulation **8**(6): 1101-1107.

Pandya, D., G. Van Hoesen and M.-M. Mesulam (1981). "Efferent connections of the cingulate gyrus in the rhesus monkey." Experimental brain research **42**(3): 319-330.

Parcias, S., B. P. d. Rosario, T. Sakae, F. Monte, A. C. Guimarães and A. J. Xavier (2011). "Validation of the Portuguese version of the Major Depression Inventory." Jornal Brasileiro de Psiquiatria **60**(3): 164-170.

Passi, S., G. Ralli, E. Capparelli, A. Mammone, D. Scacciatelli and G. Cianfrone (2008). "The THI questionnaire: psychometric data for reliability and validity of the Italian version." International Tinnitus Journal **14**(1): 26.

Peña-Gómez, C., D. Vidal-Pineiro, I. C. Clemente, Á. Pascual-Leone and D. Bartres-Faz (2011). "Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics." PloS one **6**(7): e22812.

Pessoa, L. (2014). "Understanding brain networks and brain organization." Physics of life reviews **11**(3): 400-435.

Peterchev, A. V., T. A. Wagner, P. C. Miranda, M. A. Nitsche, W. Paulus, S. H. Lisanby, A. Pascual-Leone and M. Bikson (2012). "Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices." Brain stimulation **5**(4): 435-453.

Posner, M. I. and S. E. Petersen (1990). "The attention system of the human brain." Annual review of neuroscience **13**(1): 25-42.

Purpura, D. P. and J. G. McMurtry (1965). "Intracellular activities and evoked potential changes during polarization of motor cortex." Journal of neurophysiology **28**(1): 166-185.

Radman, T., R. L. Ramos, J. C. Brumberg and M. Bikson (2009). "Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro." Brain stimulation **2**(4): 215-228. e213.

Rahman, A., D. Reato, M. Arlotti, F. Gasca, A. Datta, L. C. Parra and M. Bikson (2013). "Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects." The Journal of physiology **591**(10): 2563-2578.

Raichle, M. E., A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard and G. L. Shulman (2001). "A default mode of brain function." Proceedings of the National Academy of Sciences **98**(2): 676-682.

Rauschecker, J. P., A. M. Leaver and M. Mühlau (2010). "Tuning out the noise: limbic-auditory interactions in tinnitus." Neuron **66**(6): 819-826.

Rêgo, G. G., O. M. Lapenta, L. M. Marques, T. L. Costa, J. Leite, S. Carvalho, Ó. F. Gonçalves, A. R. Brunoni, F. Fregni and P. S. Boggio (2015). "Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain." Neuroscience letters **594**: 12-16.

Riegel, M., A. Moslehi, J. M. Michałowski, Ł. Żurawski, M. Horvat, M. Wypych, K. Jednoróg and A. Marchewka (2017). "Nencki affective picture system: Cross-cultural study in Europe and Iran." Frontiers in psychology **8**: 274.

Riegel, M., Ł. Żurawski, M. Wierzba, A. Moslehi, Ł. Klocek, M. Horvat, A. Grabowska, J. Michałowski, K. Jednoróg and A. Marchewka (2016). "Characterization of the Nencki Affective Picture System by discrete emotional categories (NAPS BE)." Behavior research methods **48**(2): 600-612.

Roberts, L. E., J. J. Eggermont, D. M. Caspary, S. E. Shore, J. R. Melcher and J. A. Kaltenbach (2010). "Ringing ears: the neuroscience of tinnitus." Journal of Neuroscience **30**(45): 14972-14979.

Roberts, L. E., F. T. Husain and J. J. Eggermont (2013). "Role of attention in the generation and modulation of tinnitus." Neuroscience & Biobehavioral Reviews **37**(8): 1754-1773.

Robinson, J. L., A. R. Laird, D. C. Glahn, W. R. Lovallo and P. T. Fox (2010). "Metaanalytic connectivity modeling: delineating the functional connectivity of the human amygdala." Human brain mapping **31**(2): 173-184.

Rogers, B. P., S. B. Katwal, V. L. Morgan, C. L. Asplund and J. C. Gore (2010). "Functional MRI and multivariate autoregressive models." Magnetic resonance imaging **28**(8): 1058-1065.

Rohr, C. S., S. A. Vinette, K. A. Parsons, I. Y. Cho, D. Dimond, A. Benischek, C. Lebel, D. Dewey and S. Bray (2017). "Functional connectivity of the dorsal attention network predicts selective attention in 4–7 year-old girls." Cerebral Cortex **27**(9): 4350-4360.

Rolls, E. T. (1996). "The orbitofrontal cortex." Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences **351**(1346): 1433-1444.

Rondinoni, C., E. Amaro Jr, F. Cendes, A. Dos Santos and C. Salmon (2013). "Effect of scanner acoustic background noise on strict resting-state fMRI." Brazilian journal of medical and biological research **46**: 359-367.

Rosso, C., R. Valabregue, C. Arbizu, S. Ferrieux, P. Vargas, F. Humbert, Y. Attal, A. Messé, C. Zavanone and S. Meunier (2014). "Connectivity between right inferior frontal gyrus and supplementary motor area predicts after-effects of right frontal cathodal tDCS on picture naming speed." Brain stimulation **7**(1): 122-129.

Sadaghiani, S., G. Hesselmann and A. Kleinschmidt (2009). "Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection." Journal of Neuroscience **29**(42): 13410-13417.

Salvi, R. J., J. Wang and D. Ding (2000). "Auditory plasticity and hyperactivity following cochlear damage." Hearing research **147**(1-2): 261-274.

Schlee, W., T. Hartmann, B. Langguth and N. Weisz (2009). "Abnormal resting-state cortical coupling in chronic tinnitus." BMC neuroscience **10**(1): 1-11.

Schmidt, L. P., V. N. Teixeira, C. Dall Igna, D. Dallagnol and M. M. Smith (2006). "Brazilian Portuguese Language version of the" Tinnitus Handicap Inventory": validity and reproducibility." Revista Brasileira de Otorrinolaringologia **72**(6): 808-810.

Schmidt, S. A., K. Akrofi, J. R. Carpenter-Thompson and F. T. Husain (2013). "Default mode, dorsal attention and auditory resting state networks exhibit differential functional connectivity in tinnitus and hearing loss." PloS one **8**(10): e76488.

Schmidt, S. A., J. Carpenter-Thompson and F. T. Husain (2017). "Connectivity of precuneus to the default mode and dorsal attention networks: a possible invariant marker of long-term tinnitus." NeuroImage: Clinical **16**: 196-204.

Seeley, W. W., V. Menon, A. F. Schatzberg, J. Keller, G. H. Glover, H. Kenna, A. L. Reiss and M. D. Greicius (2007). "Dissociable intrinsic connectivity networks for salience processing and executive control." Journal of Neuroscience **27**(9): 2349-2356.

Seibt, O., A. R. Brunoni, Y. Huang and M. Bikson (2015). "The pursuit of DLPFC: non-neuronavigated methods to target the left dorsolateral pre-frontal cortex with symmetric bicephalic transcranial direct current stimulation (tDCS)." Brain stimulation **8**(3): 590-602.

Seki, S. and J. J. Eggermont (2003). "Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss." Hearing research **180**(1-2): 28-38.

Shahsavarani, S., R. A. Khan and F. T. Husain (2019). "Tinnitus and the brain: a review of functional and anatomical magnetic resonance imaging studies." Perspectives of the ASHA Special Interest Groups **4**(5): 896-909.

Shahsavarani, S., S. A. Schmidt, R. A. Khan, Y. Tai and F. T. Husain (2021). "Salience, emotion, and attention: the neural networks underlying tinnitus distress revealed using music and rest." Brain research **1755**: 147277.

Shekhawat, G. S., C. M. Stinear and G. D. Searchfield (2013). "Transcranial direct current stimulation intensity and duration effects on tinnitus suppression." Neurorehabilitation and neural repair **27**(2): 164-172.

Shekhawat, G. S., F. Sundram, M. Bikson, D. Truong, D. De Ridder, C. M. Stinear, D. Welch and G. D. Searchfield (2016). "Intensity, duration, and location of high-definition transcranial direct current stimulation for tinnitus relief." Neurorehabilitation and neural repair **30**(4): 349-359.

Sheppes, G., G. Suri and J. J. Gross (2015). "Emotion regulation and psychopathology." Annual review of clinical psychology **11**: 379-405.

Singh, D. and M. M. Sunny (2017). "Emotion induced blindness is more sensitive to changes in arousal as compared to valence of the emotional distractor." Frontiers in Psychology **8**: 1381.

Smith, S. M., P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, N. Filippini, K. E. Watkins, R. Toro and A. R. Laird (2009). "Correspondence of the brain's functional architecture during activation and rest." Proceedings of the national academy of sciences **106**(31): 13040-13045.

Song, J.-J., S. Vanneste, W. Schlee, P. Van de Heyning and D. De Ridder (2015). "Onset-related differences in neural substrates of tinnitus-related distress: the anterior cingulate cortex in late-onset tinnitus, and the frontal cortex in early-onset tinnitus." Brain Structure and function **220**(1): 571-584.

Song, J. J., S. Vanneste and D. De Ridder (2015). "Dysfunctional noise cancelling of the rostral anterior cingulate cortex in tinnitus patients." PloS one **10**(4): e0123538.

Sonmez, G., C. C. Basekim, E. Ozturk, A. Gungor and E. Kizilkaya (2007). "Imaging of pulsatile tinnitus: a review of 74 patients." Clinical imaging **31**(2): 102-108.

Steele, J. D. and S. M. Lawrie (2004). "Segregation of cognitive and emotional function in the prefrontal cortex: a stereotactic meta-analysis." Neuroimage **21**(3): 868-875.

Stein, J. L., L. M. Wiedholz, D. S. Bassett, D. R. Weinberger, C. F. Zink, V. S. Mattay and A. Meyer-Lindenberg (2007). "A validated network of effective amygdala connectivity." Neuroimage **36**(3): 736-745.

Stouffer, J. and R. S. Tyler (1990). "Characterization of tinnitus by tinnitus patients." Journal of Speech and Hearing Disorders **55**(3): 439-453.

Strube, W., T. Bunse, M. A. Nitsche, A. Nikolaeva, U. Palm, F. Padberg, P. Falkai and A. Hasan (2016). "Bidirectional variability in motor cortex excitability modulation following 1 mA transcranial direct current stimulation in healthy participants." Physiological reports **4**(15): e12884.

Sutherland, M. R. and M. Mather (2012). "Negative arousal amplifies the effects of saliency in short-term memory." Emotion **12**(6): 1367.

Team, R. (2021). "RStudio: Integrated Development Environment for R, 1.4. 1106." R Studio, PBC: Boston, MA, USA.

Thomas, C., I. Ghodratitoostani, A. C. Delbem, A. Ali and A. Datta (2019). Influence of gender-related differences in transcranial direct current stimulation: A Computational Study. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), IEEE.

Tremblay, S., J.-F. Lepage, A. Latulipe-Loiselle, F. Fregni, A. Pascual-Leone and H. Théoret (2014). "The uncertain outcome of prefrontal tDCS." Brain stimulation **7**(6): 773-783.

Tyler, R. S. and L. J. Baker (1983). "Difficulties experienced by tinnitus sufferers." Journal of Speech and Hearing disorders **48**(2): 150-154.

Uhrig, M. K., N. Trautmann, U. Baumgärtner, R.-D. Treede, F. Henrich, W. Hiller and S. Marschall (2016). "Emotion elicitation: A comparison of pictures and films." Frontiers in psychology **7**: 180.

Van Den Heuvel, M. P. and H. E. H. Pol (2010). "Exploring the brain network: a review on resting-state fMRI functional connectivity." European neuropsychopharmacology **20**(8): 519-534.

Vanderhasselt, M.-A., R. De Raedt, A. R. Brunoni, C. Campanhã, C. Baeken, J. Remue and P. S. Boggio (2013). "tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli." PloS one **8**(5): e62219.

Vanneste, S. and D. De Ridder (2011). "Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity." European Journal of Neuroscience **34**(4): 605-614.

Vanneste, S., M. Plazier, J. Ost, E. van der Loo, P. Van de Heyning and D. De Ridder (2010). "Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study." Experimental brain research **202**(4): 779-785.

Vanneste, S., M. Plazier, E. Van Der Loo, P. Van de Heyning, M. Congedo and D. De Ridder (2010). "The neural correlates of tinnitus-related distress." Neuroimage **52**(2): 470-480.

Vergallito, A., P. Riva, A. Pisoni and L. J. R. Lauro (2018). "Modulation of negative emotions through anodal tDCS over the right ventrolateral prefrontal cortex." Neuropsychologia **119**: 128-135.

Viinikainen, M., J. Kätsyri and M. Sams (2012). "Representation of perceived sound valence in the human brain." Human brain mapping **33**(10): 2295-2305.

Villamar, M. F., M. S. Volz, M. Bikson, A. Datta, A. F. DaSilva and F. Fregni (2013). "Technique and considerations in the use of 4x1 ring high-definition transcranial direct current stimulation (HD-tDCS)." JoVE (Journal of Visualized Experiments)(77): e50309.

Visted, E., J. Vøllestad, M. B. Nielsen and E. Schanche (2018). "Emotion regulation in current and remitted depression: a systematic review and meta-analysis." Frontiers in psychology **9**: 756.

Vogt, B. (2009). Cingulate neurobiology and disease, Oxford University Press.

Vogt, B. A., S. Derbyshire and A. K. Jones (1996). "Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging." European Journal of Neuroscience **8**(7): 1461-1473.

Vogt, B. A., E. A. Nimchinsky, L. J. Vogt and P. R. Hof (1995). "Human cingulate cortex: surface features, flat maps, and cytoarchitecture." Journal of Comparative Neurology **359**(3): 490-506.

Vogt, B. A. and D. N. Pandya (1987). "Cingulate cortex of the rhesus monkey: II. Cortical afferents." Journal of Comparative Neurology **262**(2): 271-289.

Vossel, S., J. J. Geng and G. R. Fink (2014). "Dorsal and ventral attention systems: distinct neural circuits but collaborative roles." The Neuroscientist **20**(2): 150-159.

Vuilleumier, P., J. Armony and R. Dolan (2003). "Reciprocal links between emotion and attention." Human brain function **2**: 419-444.

Wagner, T., A. Valero-Cabre and A. Pascual-Leone (2007). "Noninvasive human brain stimulation." Annu. Rev. Biomed. Eng. **9**: 527-565.

Weaver, L., R. Williams and S. Rush (1976). "Current density in bilateral and unilateral ECT." Biological Psychiatry **11**(3): 303-312.

Weissman, J. L. and B. E. Hirsch (2000). "Imaging of tinnitus: a review." Radiology **216**(2): 342-349.

Whitfield-Gabrieli, S. and A. Nieto-Castanon (2012). "Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks." Brain connectivity **2**(3): 125-141.

Williams, J. M. G., A. Mathews and C. MacLeod (1996). "The emotional Stroop task and psychopathology." Psychological bulletin **120**(1): 3.

Wineland, A. M., H. Burton and J. Piccirillo (2012). "Functional connectivity networks in nonbothersome tinnitus." Otolaryngology--Head and Neck Surgery **147**(5): 900-906.

Woods, A. J., V. Bryant, D. Sacchetti, F. Gervits and R. Hamilton (2015). "Effects of electrode drift in transcranial direct current stimulation." Brain stimulation **8**(3): 515-519.

Yukie, M. and H. Shibata (2009). "Interactions in the monkey." Cingulate neurobiology and disease: 145.

Zenner, H.-P. and I. M. Zalaman (2004). "Cognitive tinnitus sensitization: behavioral and neurophysiological aspects of tinnitus centralization." Acta oto-laryngologica **124**(4): 436-439.

Zenner, H. P., M. Pfister and N. Birbaumer (2006). "Tinnitus sensitization: sensory and psychophysiological aspects of a new pathway of acquired centralization of chronic tinnitus." Otology & Neurotology **27**(8): 1054-1063.

Journal Publications

1. **Vaziri. Z.**, Nami. M., Leite. J.P., Delbem. A. C. B., Hyppolito. M. A., Ghodratitoostani. I. "Conceptual Framework for Insomnia: A Cognitive Model in Practice". (2021). Frontiers in Neuroscience. 15. 781. https://doi.org/10.3389/fnins.2021.628836

2. Iman Ghodratitoostani, Oilson A. Gonzatto Junior, Zahra Vaziri, Alexandre C. Delbem, Bahador Makki Abadi, Abhishek Datta, Chris Thomas, Miguel A. Hyppolito, Antonio C. Santos, Francisco Louzada, João P. Leite. "Dose-response transcranial Electrical Stimulation Study Design: A Well-controlled Adaptive Seamless Bayesian Method to illuminate negative valence role in tinnitus perception". (2022). Frontiers in Human Neuroscience. 10.3389/fnhum.2022.811550

Conferences posters

1. Vaziri Z. S., GhodratiToostani, I., Nami, M., Delbem, A.C.B., Leite, J.P. **"The Contribution of Tinnitus Negative Valence in Sleep-threat Development".** (2018). **11th International Tinnitus Research Initiative (TRI) conference, Germany**, **Regensburg,** March.

2. GhodratiToostani, I., Jalilvand, H., Delbem, A.C.B., Vaziri Z. S., Barros, C.G.C., Hyppolito, M.A. "**Considering Psychoacoustic Parameters Contribution is Sufficient in Predicting Gain Preference"**. (2018). **11th International Tinnitus Research Initiative (TRI) conference, Germany, Regensburg,** March.

3. GhodratiToostani, I., Vaziri Z. S., Nascimento, D.C., Colacique, M., Louzada, F., Delbem, A.C.B., Barros, C.G.C., Oliveira, A.A., Hyppolito, M.A., Leite, J.P. "The Effect of Positive Emotion Induction and HD- tDCS on Tinnitus Loudness Scale". (2018). **11th International Tinnitus Research Initiative (TRI) conference, Germany, Regensburg,** March.

4. Nascimento D., Lozada, F., Ghodratitoostani, I., Vaziri Z. S. "Copula bivariate model: Predictive Analytics on estimation tinnitus psychoacoustic parameters". (2018). **6th Workshop on Probabilistic and Statistical Methods**, Sao Carlos, Brazil.

5. Nascimento, D. C., Ghodrattitoostani, I. Vaziri, Z. S., Colacique, M., Louzada, F., Delbem, A. C. B., Barros, C.G.C., Oliveira, A. A., Hyppolito, M. A., Leite, J. P. "**Statistics Without Borders:**

Overpassing between conscious and brain response". (2018). 3rd Latin American Conference on Statistical Computing, San Jose, USA.

6. Vaziri Z. S., GhodratiToostani, I., Nami, M., Delbem, A.C.B., Leite, J.P. **"The Contribution of Tinnitus Negative Valence in Sleep-threat Development".** (2018). Social and Affective Neuroscience Advanced School**, Sao Paulo, Brazil,** August.

7. **Vaziri**, **Z.S.,** I.G. Toostani, A.C.B. Delbem, M. Nami, J.P Leite. "**Cognitive Model of Tinnitus with Comorbid Insomnia".** (2019). Brain Stimulation Conference. Vancouver, Canada.

8. **Vaziri**, **Z.S.,** I.G. Toostani, A.C.B. Delbem, M. Nami, J.P Leite . Modulation of Tinnitus-Related Emotional Processing and Its Effects on Attentional Bias: A model validation study-TRI 2020.

Here is the link to the Abstract Book of Tinnitus Conference in Regensburg-Germany 2018.

http://2018.tri-conf.org/images/tri-conference/abstract-book-TRI-2018.pdf

Latest FAPESP release film about our project: https://youtu.be/nY7HLOqm4KA