Repetitive Transcranial Magnetic Stimulation as a Treatment Option for Smoking Cessation

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Objectives

This study aims to investigate whether repetitive transcranial magnetic (rTMS) stimulation over the left dorsolateral prefrontal cortex (DLPFC) decreases craving and increases quitting success from smoking in tobacco smokers who wish to quit. This project will also examine whether presentation of provocative visual cues during brain stimulation may produce improved results in reducing craving of smoking as compared to brain stimulation alone.

Introduction

The World Health Organisation (WHO) suggests that smoking is responsible for approximately six million deaths each year[1]. Smokers are at greater risk for heart and blood vessel diseases[2,3]. In addition, smoking causes strokes and coronary heart disease which are the leading causes of death in the United States[2,3]. Additionally, individuals smoking less than 5 cigarettes per day could be affected by early signs of cardiovascular diseases[2,3]. Lung diseases caused by smoking include emphysema and chronic bronchitis[2,3]. Further, smoking causes different types of cancer such as lung, bladder, oesophagus, liver, pancreas and stomach cancer[2,3]. Individuals who quit smoking sharply, cut their cardiovascular risk after one year and decrease the risk of a heart attack[3]. Within 2-5 years of quitting, the risk of stroke may reduce to about the same for non-smokers[3]. Smoking cessation decreases the risk for cancers of the mouth, throat, oesophagus, and bladder drop by half within 5 years[3]. Ten years after smoking cessation, the risk for lung cancer drops by half[3]. Due to these and other health risks which were shown to be directly linked to smoking, a global target was announced aiming to reduce the current prevalence of tobacco use in individuals aged 15 and above, by 30%. In Cyprus, the estimated rate of smoking reached 31% in 2005, making it one of the countries with the highest rates in tobacco consumption. While many smokers desire to quit smoking, only 4-7% of them succeed in quitting smoking without supportive treatment[5].

Several studies have proposed different therapies for quitting smoking. Such therapies include counselling therapies[6,7,8] and pharmaceutical treatments with the use of products such as the nicotine replacement therapy bupropion (Zyban) and varenicline (Chantix)[9,10,11,12,13,14]. However, the majority of those attempting to quit smoking are most likely to relapse, as success of such methods is deemed modest. Due to the failure of the current licensed therapies offered for smoking cessation to sustain the initial effect and the fact that patients present high chances of relapse, there is a need to identify new therapeutic approaches. It is essential that such approaches should be related to physiological brain processes, with the aim of understanding, and therefore implementing therapies that are successful beyond immediate behavioural change. Such therapies should ideally directly target brain networks associated with nicotine craving and addiction such as cognitive control and reward processing brain regions.

Tobacco addiction has been linked with the mesolimbic dopaminergic system since the early 90s' in studies that tried to elucidate the role of tobacco addiction in vitro[31]. Later studies indicated that brain stress systems play a critical role in tobacco addiction. Smoking as well as smoking cessation affect the regulation of the HPA axis. On one hand, smoking leads to increased release of cortisol and adrenocorticotropic hormone, (a hormone which is produced in the frontal, anterior and pituitary gland of the brain), as well as upregulation and desensitization of nicotinic acetylcholine receptors (nAChRs). It is suggested that the excessive number of responsive nAChRs may contribute to cigarettes' craving and relapse[31]. However, it is important to note that the effects of nicotine in the brain at the molecular level differ from the effects that amphetamines and cocaine

addictions have, and it is vital to understand such differences which may contribute in their better understanding and in potential therapies. At the cellular and system level, tobacco addiction is highly associated with excessive dopamine projections and overflow specifically in structures of the nucleus accumbens, namely the core and the median shell[32].

Over the last ten years, neuroscience has advanced in a level that has allowed researchers to implement methods for diagnosis and treatment of various disorders on brain system level. Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive safe treatment option for a variety of neuropsychiatric disorders which has received FDA approval for Depression[15] and Obsessive Compulsive Disorder[16]. Neuromodulation interventions with the use of TMS also appear as a promising approach in treating addictions[29]. The effect of TMS would ideally be to affect brain circuits by inducing neuroadaptations in the cortico-mesolimbic dopamine system, and in the glutamatergic corticolimbic circuitry where dopamine projections are entrenched[19,20,21]. A review on nine studies focussing on addictions (tobacco, alcohol, cocaine and methamphetamine) investigated outcomes of TMS treatment. Most of the studies applied high frequency (5-20 Hz) rTMS over the left DLPFC. While the underlying mechanism was poorly understood, it was suggested that it may involve dopamine and glutamate function in the cortico-mesolimbic brain circuits and modulation of neuronal activity that mediate cognitive process related to addiction. In this review, support of craving was suggested for nicotine, and in some participants, significant reduced cigarettes consumption was observed. However, changes in craving were not always consistent with decreased smoking[30].

A study by Amiaz and colleagues in 2009, suggested that applying TMS on the left DLPFC at high frequency, could offer an innovative treatment option for tobacco dependency[22]. The intervention included ten daily sessions over the left DLPFC, 20 trains per day at 100% of motor threshold. Each train consisted of 50 pulses at 10 hz with an inter-train interval of 15 seconds. Amiaz investigated the presentation of smoking cues on cigarette consumption, dependence and cravings. A series of 14 pictures were presented to the subjects immediately before the administration of the TMS. Cigarette consumption was measured subjectively through self-report. Craving levels were assessed with the visual analogue scale prior and following the presentation of the visual cues every day. Active TMS was found to significantly reduce both cigarette consumption and nicotine dependence compared to sham stimulation. Additionally, it has been suggested that if rTMS is delivered to the left dorsolateral prefrontal cortex, it could affect decision making which corresponds to addiction and craving[18]. On high frequency at 10 hz (24 trains, 5s per train, 25s inner train-interval 1200 pulses with 11.6 minutes, 90% MT) rTMS stimulation of the DLPFC, Jürgen Pripfl[33] and colleagues demonstrated in 14 healthy smokers on cue-induced nicotine craving and resting-state EEG that the rTMS stimulation had an effect on reducing nicotine craving in short term abstinent smokers, with changes in delta activity. This study has supported the idea that stimulation induce effects are mediated by the dopaminergic brain reward system making it a potentially promising treatment for smoking cessation. The DLPFC of addicted individuals has been associated with the experience of craving[23,24,25], induced by substance-related cues for nicotine[26,27,28]. For instance Brody and colleagues (2002) found activation in the DLPFC in “heavy smokers” when exposed to cigarette-related cues compared with non-smokers. Xingbao Li[35] has suggested that even one session of high-frequency rTMS (10 Hz) on the left DLPFC can significantly reduce subjective craving induced by smoking cues in nicotine-dependent participants. Further, an fMRI study has suggested that expectancy of smoking following the brain

scan, induced activation in areas that usually correspond to arousal, attention and cognitive control while in participants where smoking was not allowed after the brain scan, such activation was non-existent in response to smoking cues[26]. It is therefore important that craving induced cues are present; however most studies use such cues prior to the task or treatment. Further, there is no systematic study comparing a condition of rTMS without an external craving cue, versus a condition of rTMS in combination with a smoking craving cue at the time of treatment. So, it would be interesting to investigate whether craving induced cues during rTMS treatment could produce similar results to studies that used a smoking craving cue prior to treatment, comparing it with rTMS at rest, without a smoking craving cue, where treatment will not be dependent to the smoking cue. Finally, across studies on smoking cessation, it has been reported that researchers have used breath carbon monoxide (CO) cut-off values ranging from 4 to 10 ppm to define abstinence in cigarette-smoking cessation. It has been furtherly demonstrated by Murray Jarvik[34] that there is a negative correlation between blood nicotine levels and craving for cigarettes while carbon monoxide has shown to correlate significantly with nicotine blood levels.

On the bases of previous research findings, in this study, we are going to compare tobacco cravings between three groups (two experimental and one control) of tobacco smokers that wish to quit smoking, after a five-day treatment of five 3-minute theta burst repetitive transcranial magnetic stimulation which will be applied over the left DLPFC. We hypothesize that:
(A) The two experimental groups (group A that will receive real rTMS, four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, while watching a smoking video as a cue for craving, and group B group that will receive real rTMS, four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, with no presentation of the smoking video as a cue for craving, but presentation of a neutral video) will present lower craving scores in relation to their baseline measures,
(B) The two experimental groups, (groups A and B) will present lower craving scores in relation to the placebo group (group C will receive sham rTMS four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, while watching a smoking video as a cue for craving) after the end of rTMS treatment,
(C) We investigate the difference between the presentation or absence of visual cue among the two experimental groups (group A and B that will both receive real rTMS, with the difference that group B will not be presented a smoking video as cue for craving) as to whether presentation or absence of stimuli influences outcome of craving scores.

Method

Participants

Recruitment of participants will be done through public advertisements of the study, as participants belong in the healthy population. Individuals who agree to participate in this study will be volunteers. The minimum number of participants required was determined by an a priori power analysis where at least a sample size of 100 participants was suggested. (*Measures that suggested this sample size were determined by the mixed model, a small to medium effect size (0.4), at an alpha level of probability of 0.05).
Inclusion criteria of participants will be: (a) to be native speakers of the Greek language, (b) to be over the age of 18, (c) to be tobacco dependent users that wish to quit smoking.

Exclusion criteria of participants will be: (a) individuals with metallic parts inside or near the skull, (b) dependency of any other substances apart from nicotine and caffeine.
For the purposes of this study, participants will be formed into three groups. The groups will be as described below:

(A) An experimental group of 34 participants that satisfy all criteria for inclusion. This group will receive real rTMS, four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, while watching a smoking video as a cue for craving;
(B) An experimental group of 34 participants that satisfy all criteria for inclusion. This group will receive real rTMS, four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, with no presentation of the smoking video as a cue for craving, but a neutral video;
(C) A control group of 34 participants that satisfy all criteria for inclusion. This group will receive sham rTMS four sessions per day of intermitted theta burst, for three minutes per session, for five consecutive days, while watching a smoking video as a cue for craving.

Design

This is a randomized, double-blind, sham-controlled study.

Procedure

Prior to the study

After advertisement of the study, potential participants will be able to contact the researcher via contact details that will be given on the advertisement. The researcher will then perform a screening interview (either by phone or email correspondence) regarding the eligibility of participants. The questions will include demographics and contact details: a) telephone number, b) email address, c) sex, d) education and occupation, e) age; and the screening will involve questions regarding eligibility: f) "how many cigarettes do you smoke per day?", g) "for how long have you been a smoker?", h) **"**has there been any period in your life that you managed to quit smoking; if yes for how long and how did you manage to do it?", i) "are you dependant on any other substances e.g. alcohol/drugs/benzodiazepines apart from caffeine and nicotine". These questions will be asked in Greek. If individuals meet the criteria and wish to continue, the researcher will arrange with participants details regarding their visit to the site.

At the research site

Participants will arrive at the Cyprus rTMS Centre, will receive all the required information about their participation, and if agreed, they will sign the consent form and will be led to the testing room. Participants will then complete three questionnaires on a PC, prior to the beginning of the experiment. The questionnaires are all described in Materials section and they are attached in the Appendix. All participants will undergo a breath carbon monoxide (CO) measure prior to each TMS session of each day with the use of a smokerlyzer. Further information about its use is described in the section below.

The researcher will then take the appropriate head measures using the 10-20 system and then will place a cap on the participant's head. The participant will sit on the TMS chair and the researcher will place the (real/sham) TMS coil on the participant's left DLPFC and start the session. While participants will be receiving TMS, they will be presented with a smoking video as a cue for craving, throughout each TMS session (except for one group that they will not be presented with a cue craving video, but with a neutral video). There are two available videos, and those will be presented in a randomised manner for each participant. After each session, participants will have a forty-five minute break and then return for the next TMS session. Once done with all five days of TMS therapy, they will be again assessed with the three questionnaires.

To protect personal data and for conditions to be double-blind (participants will not know whether they receive real or sham TMS and researcher will not know whether they administer real or sham TMS), participants will be pseudo-anonymised on an excel database and will be assigned in a randomised manner to each defined group. Demographic and personal data of participants will be confidential only to the researchers involved in the study and will be protected and handled according to the Data Protection Act 2018 and the ICH Good Clinical Practice for data protection. Recorded data of participants will include: demographic details, data of self-report questionnaires at baseline and follow up measures, and CO breath levels.

Following TMS treatment

Following the end of the rTMS treatment, participants will be contacted again to complete the three questionnaires. This will be done at one week, one month and six months post-TMS treatment.

Materials

Questionnaires

The tools used in this study are three questionnaires:
- The Fagerstrom Test of Nicotine Dependence (in Greek),
- The Factor Structure of Tobacco Craving-Short Form (will be adjusted to Greek),
- The Perceived Stress Scale (in Greek).

These questionnaires will be administered to each participant prior to the first day of TMS treatment, after the last day of TMS treatment, after one week, after one month, and after six months. Participants will complete the questionnaires on a 14" laptop at baseline and first follow up, and then online during the remaining follow ups. The aim of the questionnaires will be to test for nicotine dependence, levels of craving, and screening for anxiety levels of participants at different time points. Those data will then be used for within and between participants' analyses. Further, participants will be asked through a visual analogue scale ranked from 1-100 "How much do you want to smoke right now?", prior and after each TMS session, as previously used by Revital Amiaz in similar methodology studies, to assess cue-induced craving of participants.

Smokerlyzer

Smokerlyzer is a non-invasive tool that measures the amount of CO on a smoker's breath and establishes smoking status biochemically. It will be used prior to each TMS session every day for each participant and its measures will be later used for analyses purposes.

Craving Videos

Two videos will be used during the TMS sessions, presented in a randomized manner. The first video is a smoking video which lasts for three minutes and its purpose is to be a cue for inducing craving. The other video used will be a neutral video, illustrating daily tasks that do not involve smoking. This video will be used as a control video.

TMS Protocol

This study will attempt to use accelerated theta burst stimulation of TMS, and specifically the 3-minute FDA-approved protocol for depression. rTMS will be applied to each participant for a period of five consecutive days. Each day will consist of four sessions of the 3-minute theta-burst stimulation with a 45-minute gap (which is the optimal gap) between sessions. The protocol includes 2 seconds of stimulation on the left dorsolateral prefrontal cortex which is followed by an 8 second pause. There will be 600 pulses in total for each 3-minute session. The site of stimulation will be the left DLPFC. It will be measured by using the 10-20 system, it will be determined by the Beam F3 software and it will be at 100% of the motor threshold.

Planned Analysis

The data will be analysed in SPSS. Analyses of hypotheses will be carried out with a mixed model (repeated measures within and between factors). Within factors will be determined from the craving scores in the baseline and follow ups from the three questionnaires, and CO measures. Between factors will be determined by the three experimental groups. Analyses will be adjusted for sex, age and visual stimuli.

Expected outcomes & Benefits of the study

Few studies have examined smoking cessation through a TMS treatment. Further, there is a question as to whether exposure to behavioural cues before or during TMS treatment may influence craving outcomes, which may improve our understanding in the mechanisms that influence successful outcome, while using induced plasticity methods. While we expect that experimental groups will have significantly decreased craving scores compared to control group, generally this study will aid in our understanding regarding potential options for smoking cessation and possibly for other addictions with similar physiological mechanisms.

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