STUDY PROTOCOL

Open Access

Efficacy of repetitive transcranial magnetic stimulation (rTMS) for reducing consumption in patients with alcohol use disorders (ALCOSTIM): study protocol for a randomized controlled trial



Benjamin Petit^{1,2*}, Agnès Soudry-Faure³, Ludovic Jeanjean^{4,5}, Jack Foucher^{4,5}, Laurence Lalanne^{6,7,8}, Maud Carpentier⁹, Lysiane Jonval³, Coralie Allard^{1,9}, Mathilde Ravier¹, Amine Ben Mohamed⁹, Vincent Meille¹ and Benoit Trojak^{1,2,10}

Abstract

Background: The number of people with an alcohol use disorder (AUD) was recently estimated to be 63.5 million worldwide. The global burden of disease and injury attributable to alcohol is considerable: about 3 million deaths, namely one in 20, were caused by alcohol in 2015. At the same time, AUD remains seriously undertreated. In this context, alternative or adjunctive therapies such as brain stimulation could play an important role. The early results of studies using repetitive transcranial magnetic stimulation (rTMS) suggest that stimulations delivered to the dorsolateral prefrontal cortex significantly reduce cravings and improve decision-making processes in various addictive disorders. We therefore hypothesize that rTMS could lead to a decrease in alcohol consumption in patients with AUD.

Methods/design: We report the protocol of a randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy of rTMS on alcohol reduction in individuals diagnosed with AUD. The study will be conducted in 2 centers in France. Altogether, 144 subjects older than 18 years and diagnosed with AUD will be randomized to receive 5 consecutive twice-daily sessions of either active or sham rTMS (10 Hz over the right DLPFC, 2000 pulses per day). The main outcomes of the study will be changes in alcohol consumption within the 4 weeks after the rTMS sessions. Secondary outcome measures will include changes in alcohol consumption within the 24 weeks, alcohol cravings, clinical and biological improvements, effects on mood and quality of life, and cognitive and safety assessments, and, for smokers, an assessment of the effects of rTMS on tobacco consumption.

²UFR des Sciences de Santé, Université de Bourgogne, Dijon, France Full list of author information is available at the end of the article



^{*} Correspondence: benjamin.petit@chu-dijon.fr

¹Department of Addictology, University Hospital of Dijon, 14 rue Paul Gaffarel, B.P. 77908, 21079 Dijon Cedex, France

Petit et al. Trials (2022) 23:33 Page 2 of 10

Discussion: Several studies have observed a beneficial effect of rTMS on substance use disorders by reducing craving, impulsivity, and risk-taking behavior and suggest that rTMS may be a promising treatment in addiction. However, to date, no studies have included sufficiently large samples and sufficient follow-up to confirm this hypothesis. The results from this large randomized controlled trial will give a better overview of the therapeutic potential of rTMS in AUD.

Trial registration: ClinicalTrials.gov NCT04773691. Registered on 26 February 2021 https://clinicaltrials.gov/ct2/show/NCT04773691?term=trojak&draw=2&rank=5.

Keywords: Addiction, Alcohol use disorder, Reduction, Repetitive magnetic transcranial stimulation, Non-invasive brain stimulation

Background

Alcohol use disorder (AUD) is considered a major public health problem in Western societies [1]. In 2015, the number of people suffering from an alcohol use disorder was estimated at 63.5 million, namely 843 per 100,000 people, which represents 8.6% of men and 1.7% of women [2, 3]. The global burden of disease and injury attributable to alcohol is considerable: in 2016, about 3 million deaths (approximately 1/20) worldwide were caused by alcohol [4]. In the EU in 2015, alcohol was responsible for 108 deaths per 100,000 people [2]. Because alcohol is implicated in more than 60 diseases (i.e., vascular, endocrine, and neurological diseases, cancer, etc.), and many non-fatal injuries early in life, the disabilityadjusted life years (DALYs) are even higher: in 2016, 5.1% of all DALYs, i.e. 132.6 million DALYs, were caused by alcohol (men: 106.5 million; women: 26.1 million) [2, 4].

At the same time, alcohol use disorders remain seriously undertreated. There is a large treatment gap, given that only around 20% of people in Europe and the USA with a diagnosed AUD actually receive any treatment [5–8]. One of the main reasons is that these patients are not ready to stop drinking and thus are not attracted to the abstinence goals anticipated by the current psychosocial and pharmacological treatments [9]. New treatment strategies that aim to reduce alcohol consumption could make it much easier for patients to ask for help. Thus, new treatments supporting this strategy are required to improve the care of patients suffering from AUD.

In this context, alternative or adjunctive therapies such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), two non-invasive brain stimulation techniques, may play a prominent role. They focally modulate the neuronal excitability of superficial brain regions, and even deeper structures thanks to brain connectivity [10]. Indeed, neuroimaging studies have identified changes in the prefrontal regions of patients diagnosed with addictive disorders, in particular in the dorsolateral prefrontal cortex (DLPFC) [11]. These

brain changes were associated with cravings, manifested by an intense desire or urge to consume a drug, and with impaired inhibitory control [10, 12, 13]. Overall, the early results of studies using rTMS and tDCS applied to the DLPFC found a significantly reduced craving levels in various addictive disorders (tobacco, alcohol, marijuana, and methamphetamines) [14-18]. These results were consolidated by a metaanalysis that included 17 studies [11]. In this metaanalysis, random-effects analysis revealed a pooled standardized effect size (Hedge's g) of 0.476, indicating a medium effect size favoring active stimulation over sham stimulation in the reduction of craving. No significant differences were found between the two brain stimulation techniques, even though their mechanisms of action are somewhat different [11, 19]. Regarding rTMS more specifically, a more recent systematic review, including 26 articles and 748 patients, showed significant reductions in cravings and substance use [20].

Even though these results are encouraging, the vast majority of these studies had small sample sizes and only short-term follow-up. In addition, there was considerable heterogeneity in terms of sample population, study design, and outcome measurements. A majority of these studies focused on clinical symptoms such as cravings instead of assessing more global and pertinent therapeutic effects such as reduced consumption or ability to maintain abstinence, which are the ultimate therapeutic goals for individuals with substance-related and addictive disorders.

We therefore propose to evaluate, for the first time and using a randomized controlled trial (RCT) involving a large sample, the clinical benefits of rTMS in patients with AUD who wish to reduce their alcohol consumption.

Aims

Our hypothesis is that rTMS, which induces changes in the neuronal activity of the DLFPC that decrease cravings, can lead to a decrease in alcohol consumption in patients suffering from AUD. Petit et al. Trials (2022) 23:33 Page 3 of 10

Thus, the principal objective of this study is to evaluate, in non-abstinent patients with AUD, the efficacy of 1 week of rTMS (5 consecutive twice-daily sessions) versus placebo in reducing alcohol consumption within the 4 weeks following the treatment. In addition, we will repeat the alcohol consumption measurements periodically during 24 weeks of follow-up.

Moreover, we will assess the effects of rTMS on mood, cognitive behavior, and quality of life. In participants who have AUD combined with tobacco use disorder (TUD), the effect of rTMS on tobacco craving and consumption will be explored.

Methods/design

Overview

This is a multicenter, randomized, placebo-controlled, double-blind, parallel-group superiority study comparing 5 consecutive twice-daily sessions of active rTMS versus sham rTMS, with an allocation ratio in the trial of 1:1 (Fig. 1). The study is to be carried out in two French addictology departments (Dijon and Strasbourg), where patients with AUD are treated, and aims to recruit 144 patients with AUD over the course of 2 years. These departments provide consultation to a large number of patients, particularly for alcohol use disorder, among whom the study participants will be recruited. In

addition, a communication via the social networks of the main center and through the local press is planned.

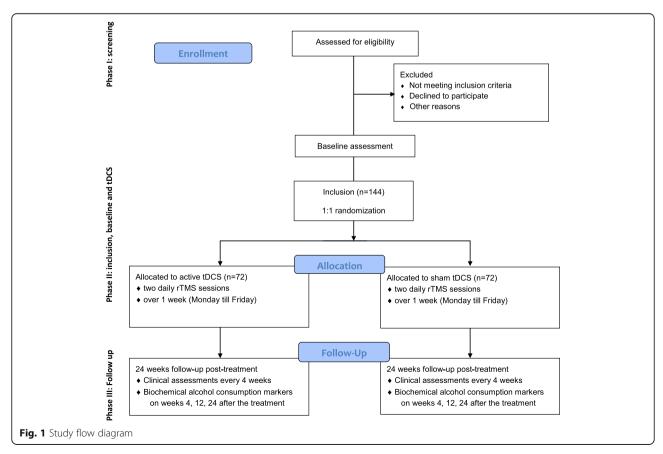
The study protocol was approved by an independent ethics committee (Committee for the Protection of Persons, West V) on 28 June 2020 under the number 2019-A03047-50 and by the French national agency for the safety of medical products and devices (*Agence National de Sécurité des Médicaments et des Produits de Santé*). After providing participants with a complete description of the study, written informed consent will be obtained from each participant.

Each revision will again be submitted to the ANSM and the ethics committee for approval. It will then be the subject of a complete re-editing of the protocol.

The SPIRIT reporting guidelines were applied before submitting this manuscript [21]. The SPIRIT checklist is reported in Fig. 2.

Inclusion criteria

Patients eligible to be enrolled in this trial: (1) males and females over 18 years of age, (2) meeting the criteria for mild to severe AUD as defined in the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) [12], (3) wishing to reduce their alcohol consumption, (4) and having experienced at least one prior attempt to achieve abstinence (unsuccessful or relapse).



Petit et al. Trials (2022) 23:33 Page 4 of 10

	Administrative information	_	Reporting Earn	Fage and line Number — Beauer Ernel applicable	İ
	Title	-	Oncomptive trib identifying the study design, population, interventiens, and, if applicable, trial according	Page 1 to c e)	
	Trial registration	<u>stin</u>	Trial identifier and registry name. If not pet registreed, name of introduct registry.	Page 21 Line 430	
	Ped regulation slate set Period remin	<u>m</u>	All laws how the Variet Budit-Dryonlation Trial Registration 2013 let. Date and version identifier	Page Miline 200 Page Miline dill	
	Funding Mules and responsibilities	11 11	Source and spec of financial, material, and other septent. Permit, stifflations, and takes of protocol.	Page 30-line 433 Page 11-line 9	
	Robert and responsibilities. some Budorahip	-	contributors	Page 20 inn 612] [Page 20 inn 612] [Page 20 inn 610	
	Rules and responsibilities spensor contact information	222	Huma and contact information for the still spensor	Page 20 Cite 483	
	Bales, and enquerabilities sporter and funder	-	Rate of shally operate and funders, if any invokaly dought collection, monogenest, snolysis, and interpretation of data; enting of the report, and the doction to salemit the roots for publication, including whether they all how all male.	Page 20 Line 611	
	finite, and responsibilities possitions	-	pools of year any transactions. Comparation, rules, and expandabilities of the coordinating control, their important sustance explanation remains, data management team, and other individuals or groups consistently toda, if applicable pair law 32 a for data promoting committee.	Page 14 Line WII	
	Introduction Background and sprovate	nia.		Fage 3 Line RQ Fage 5 Line 3350	
		Γ	Once 'géor of research question and justification the wedertaking the trial, including currency of relevant studies (published and usual/stude) seasoning lensifies and harms for each progression.		
	Resignational records: choice of companions	-	Implementation for shadow of compansions	Fage 20-Line 24T)	
	Orderives Did device	-	Specific alsoches ar hypothesis	Page S Line 334 Page S Line 325	
		Ī	Consciption of individual including type of hid log, pendid proce, orstoom, factories, single group, distantion sette, and harmound jag, suportanty, equivalence, non-infriently.	Page 40 inc 305	
	Methodic Farticipans, int	sovento	reproperty.	Page 8.Line 200	
			As an amount of the control of the c		
	Eligibility order in	222	Inductor and exhator siteria for portograns, if applicable, eligibility of tools for study control and inductions who will perform the interestition (eg.	Page 6 Line 200	
	Interventions description		pergoon, psychotherapidal briderversions for each group with sufficient detail or allow replication, inducing how and when they will be advantaged.	Page 1 Line 201	
	interventions; modifications.			Page 5 Une 225	
	Interventions adversar-	-	Other is fair discretinating or modifying alterated triceventions for a gime trial perhapsed by, drug door change in reponded harms, perforques, preparat, or improving, I exceeding discretal graduates to improve adversions to improvention.	Page 5 Une 200	
			Onetagios to improve adherence to intervention prolocols, and any presidents for moritaining adherence (eg., drug tables nature, laboratory (edis)		
	interventions concentrations (universe)	### ##2	Relevant concomitant canc and incomentions that are permitted or prohibited during the trial	Page 3 (inc)79 Page 31 (inc)74	
		Ī	of parameters presented and program follows; usuallars, and other automate, analysing the specific nelseus resemit viriable (e.g., specific bleed present), analysis metric (e.g., charge than classifier, final visual, the size-and, methodol approprion (e.g. metian, proportion), and lines pixel for evolvalulamen. Explanation of the chinder (elsented proportion) and according to the control of the chinder (elsented proportion) containers in charge manuscript publishmes in charge manuscript.		
	Participant timeline			Figure 2	
		Γ	(missing any number and welfours), excessment, and wishs for puricipants. A submissiful diagram & highly recommended bee		
	Sample size	<u>m</u>	Figure 1 Statement wunder of portoquents recoded to achieve storty objectives and how it was colored to the statement, including climate and distribute accomplishes supporting any sample size.	Page 13 Une 209	
			citablioni		
	Nonsimot Mehalu Jaigment elli	est mervent	Orangies for advising adoptive participant enablemed Schools English stage Stage fore (for controlled trials)	Page 6 Line (S)	
	Miscation sequence granulism	F200	Method of generating the allocation sequence (e.g., computer generated random numbers), and list of any factors for stratification, its reduce	Page 20 Line 200)	
			Motified of generating the allocation sequence by, computer generated random numbers, ancibia of any hobis for instationate in such and produced for substitutions assumes, details of any planned software legic booking disability provided in a systemate discusser that provided in systemate discussers that substitution to those sub-oranit participants or supply-intervalence.		
	Miscator-considered medianism	F200	hthickness of implaneating the allocation sequence (ag, certical foliationary, sequentially number of, spages, could enveloped, docutting, any value to conced the sequence until any value to conced the sequence until	Page 20 Line 20(1)	
	Massier	L		Page (64-ine 261)	
	Minday Shaday	<u> </u>	Who will generate the allocation sequence, who will enrich participants, and who will settle perforperts to interventiens. Who will be blooded after sequencer; to	Page 2004 200)	
		-	Who will be blood also assignment to bromvertions (e.g. this participants, core precisions, cubcame associate, data analyzia), and how of blooked, circumstances under which unblinding	Page 20.00 200) Page 11.1nc 271)	
	Minding (making) emergency underdrag Methods toda calks/dos,	- Mariago	If blooked, circumskerces under which unblinding to permissible, and procedure for revealing a perhipset's allocated intervention during the trial meet, and people's		
	Method total catedion, Esta collection plan	1111	Para list aumanant anticultraturol saturne, beadins, and other trial data, inducing any related processor to promise data made.	Page II Line 2N	
			house, and suspense There has assumement and individuously and underson, bearines, according to the East, individuously and bearines, according to the East, individuously and		
	No. of the last of	L	y slability and radidity, if lenours, finite once on where data callection forms can be bound, if not in the protection. The protection of the protection and	Page 9 Line 200	
	Bata-solection plans returnion	<u> 1100</u>	Plans to promote participant intention and complete following, including list of any outcome size to be collected for participants who discontinues or deplays from intervention protocols.	Page Vord 202	
	Виз-походител:		discriminate is occase non-monorate possoos. Manie for discrimina, calonia, cascuma, and obcogo, anduring any revised processor to promote desi- quiatio jug, discriminate processor to promote desi- quiatio jug, discriminate province desirio di data managementi, peccadures can be found, ill'not in	Page 34 Line 253	
		L			
	Mathitics subseries	220	Stabilisative Book for analysing primary and perombery customes. Before more to whose other selects of the statistical analysis plan can be found, from in the assessed.	Page 13 Con X73	
	tonico admini andro	200	Most in the protect Methods for any additional analysis (eg. subgroup and adjusted analysis)	Fage 23 Con XX2	
	Mathiton analysis population and missing data	222	Codenicion of analysis population relating to proteopinen-advanceur (eg. se-sendemine) analysis), and any statistical methods to també entening data (eg. meltigle imputation).	Page 13 Con X75	
	Methods Municipality Esta manifolisty formal	lan-		Page 14 Line 2011	
	Eats municiping formal specifican	allia.	Comprolition of data monitoring sometimes (IRME), commany of as too and reporting structure, sustained of absolute is is independent interesting to the control superior and comproling structure; and reporting to the control superior interesting to the release as where families about it is called to the control and before it from the proposation. Alternation (e.g., or explanation of why a OSAC is not	to age on hill the	
	Earla manifesting Interior 2005/81		Constraint any interim analyses and stepping quicking, including who will have access to Cheo- arosim-results and make the final decision to semimost the data.	Page 33 Line 345	
	Kerm.	_	Destrook the total Plans for coloring, anamong, reporting, and processing processor, and processing processor, and	Page 11 Line 201	
	india.	L	and the second of the second second second and the second	Page Miline Wil	
	Miles and Miles	Ľ	Programsy and presentents for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.	t age according to	
	sance and dissentation Smouth of the approval	ш	Plans for senting-research relates committee (antitudos el number transit (MEC) (ME) approved	Fage 19 Geo (30)	
	Protectal amountments	#20 #	Plans for summarised by Imperiand produced modifications log, changes to eligibility critaria, sudament, analysis (as referred product) (eg.	Page 6 Line 363	
	Consent or sessor.	-	registies, journals, regulature)	Page 8 Unit 236	
	Comunica analysis	1200	potential rid participants or authorised participants, and how-joint see XS Additional servent provisions for collection and	Fage 8 Line 227	
	Control or pagests on citizsy studies Confrontality	_	Additional senant provision for selfention and use of porticipant data and biological spectrums in ancillary shados, if applicable. New personal information about parametal and	Plage 34 Line 206	
			Have personal information about parantial and annulled participants will be sollented, visued, and maintained in order to protect confidentiality before, closing, and after the trial		
	beduration of interests	#	financial and other competing interests for principal inemtigations for the reward trial and 60% shoty life.	Page 29 Unic 423	
	Esta acoma	122	Business of sale-will have assess to the final brid corpor, and displaces of contracted approximate that limit each assess for investigation.	Page 24 Line 2023 Page 25 Line 425	
	enothers and post trial	100	Provisions, if any, for ancillary and post in informs, and for compression to those arise suffer horns, from that gardicoption.	Page 5 Une 225) Page 9 Une 227	
	Disamination polary I risk results	****	Plans for immedipolers and queries is communicate trial sould stockfolests. Feelbure professionals, the public, and ellers relevant groups by, ve outlistics, reporting in	Page 16 Line 200	
		L	chinest prospility, via cubication, reporting in results shallows, or other data sharing. prospensed to scholing any publication.		
	transmitter policy selection	222	contritions Authorating stiglishing paraleless; and any intended task of preferoismal writers.	Page 34 Crist 283	
	Stannington policy repredictible research	200	Plans, if any, for granting public accounts the full protection participant level date are, and national code.	Page 34 Geo 20(2) (Page 18 See 200)	
	Appendices Informet consent materials		Middle consent from and other related elecumentation given to participants and authorised corruption	to Appendix)	
	Balagical specimens	-	authorized contegence Plans for softenion, belonatory multisation, and pronge of foliogopal specimens for generic or	Page 12 Line 208	
	l	l	Plans for softenium, followedney modulation, and atorogo of foliological specimens for generic or molecular analysis in formarment initiated for folioses are in anothery mudes, if applicable the property of the property of the property of the property of property of prop		
Fig. 2 SPIRIT figure					

Exclusion criteria

Patients will be excluded if they have, at the inclusion visit, any of the following: (1) breath-alcohol concentration (BAC) > 0 mg per liter of exhaled air; (2) less than 6 heavy drinking days (HDD) in the previous 4 weeks (defined as more than 60 g of pure alcohol in men and 40 g in women consumed in 1 day) [1]; (3) average alcohol consumption below the medium risk level according to World health Organization (WHO) in the previous 4 weeks ($\leq 40 \text{ g/day for men}$; $\leq 20 \text{ g/day for women}$) [22]; (4) more than 3 days of abstinence prior to inclusion; (5) a revised Clinical Institute Withdrawal Assessment (CIWA) for Alcohol score ≥ 10 (indicating the need for medication-supported detoxification); (6) concomitant treatment with disulfiram, acamprosate, topiramate, baclofene, naltrexone, or nalmefene; (7) a history of predelirium tremens and delirium tremens; (8) DSM-5 substance use disorder other than alcohol or tobacco use disorder; (9) acute psychiatric disorders that have required hospitalization and/or immediate adjustment of psychotropic medications; (10) severe major depression, as defined by 17-item Hamilton Depression scale $(HAM-D) \ge 24$ [23]; (11) recent change in psychotropic medication (< 1 month); (12) severe chronic psychiatric disorders including schizophrenia, paranoia, and bipolar disorder types I and II; (13) advanced liver, kidney, cardiac, or pulmonary disease or other acute serious or unstable medical conditions that would compromise a patient's participation in the study according to the physician's judgment; (14) contra-indications to rTMS: personal history of convulsive seizures, cerebral vascular accident, pacemaker, neurosurgical clips, carotid or aortic clips, heart valves, hearing aid, ventricular bypass valve, sutures with wires or staples, foreign objects in the eye, shrapnel, other prosthesis, or intracranial ferromagnetic material; (15) women who are pregnant or lactating; (16) women of childbearing potential with a positive urine β-human chorionic gonadotrophin pregnancy test at inclusion; (17) concurrent participation in another trial, employees of the investigator or trial site, and patients protected by law; (18) persons who are not covered by national health insurance; (19) patients, in the opinion of the investigation, not able to complete the TimeLine Follow-Back (TLFB) and to record their daily alcohol consumption in a diary (derived from the TLFB) during the 3 months of the study; and (20) patients who refused to sign the consent form and "safety agreement".

The "safety agreement" is a paper contract which expressly mentions that if a participant comes to the hospital for a visit or a rTMS session using his/her own car and has a BAC > 0.25 mg/l of exhaled air (which prohibits a person from driving a car in France), he/she will accept to give his/her car keys to the medical staff and authorize the staff to call a member of his/her family or Petit et al. Trials (2022) 23:33 Page 5 of 10

a friend to take the patient home if he/she is unable to use public transport.

Study process

The study will have three phases (Fig. 1):

- 1) During the first phase, subjects will be screened using the inclusion and exclusion criteria. Each subject will be given information regarding the implementation of the study and the objectives of the research.
- 2) The second phase will correspond to both the inclusion of participants and the period of rTMS sessions. This phase will always begin on Monday with 5 steps: (1) participants will be evaluated for study eligibility based on the inclusion and exclusion criteria; (2) after receiving the study information (including information concerning biological samples collected for biomarker assessment) again, they will have to sign the informed consent form (including the completion of the biological samples) and the "safety agreement" after ascertaining that participants have a zero alcohol blood level using breath alcohol concentration, collected by the investigators; (3) a clinical (including TLFB) and biological baseline assessment will be performed (visit 1); (4) included participants will be randomized to active or placebo rTMS; and (5) the first rTMS session will be delivered.

Then, daily sessions will be performed during the following days up to Friday, delivered by a trained operator. Since the treatment lasts only 5 consecutive days, no criteria were defined for discontinuing or modifying allocated intervention. In consideration of these elements, no other specific strategy to improve adherence to the protocol or its monitoring has been planned. The second phase will end by a clinical assessment (visit 2) once the last rTMS session has been delivered.

3) The third phase will be a 6-month follow-up phase without treatment. A clinical assessment will be performed every 4 weeks, and biochemical markers of alcohol consumption will be measured at 1, 3, and 6 months after the end of the stimulation. To promote participant retention and complete follow-up, we will use phone call to reschedule visits if they have been missed, or by default made them by phone.

The management of the patients at the end of the study will depend on the therapeutic results: it will be proposed to follow the reduction strategy in cases of efficacy, or to change the therapeutic goal through abstinence if alcohol consumption has worsened. In addition, no compensation is planned for to those who suffer harm from trial participation.

Interventions

Patients will receive two consecutive 10 Hz rTMS sessions per day over the right DLPFC on 5 consecutive days. One rTMS session will consist of twenty trains of

50 pulses with an intensity of 110% of the resting motor threshold, separated by 19 intertrains of 30 s (1000 pulses per session). The two daily rTMS sessions will be separated by an interval of 15 min. This scheme of 2 sessions per day with a free interval of 15 min was successfully tested in a study on the treatment of depression [24]. In sum, each patient will receive 2000 pulses per day, and so 10,000 pulses at the end of the week of treatment.

The comparator will be sham rTMS. A placebocontrolled design was chosen as it is easy to apply with rTMS (placebo coil) and because placebo is a gold standard for randomized controlled trial. Moreover, the main aim of this study is not to compare rTMS to reference treatment, but to provide evidence of its efficacy.

We will use a Medtronic MagPro X100 Stimulator (MagVenture) with two types of coils: an MCF-B65 butterfly type coil with external liquid cooling unit (maximum magnetic field on the coil surface of 2.5 teslas) and a MCF-P-B65 sham coil with a magnetic field attenuation of more than 80%. After the randomization, following the arm to which the patient will be assigned (active stimulation or placebo), the operator will install the corresponding coil before the patient enters the room. During the stimulations, the investigators will not have access to stimulation room, only the operators will be able to attend the sessions, to preserve double-blinding.

Randomization

Randomization will be performed the day of inclusion, online, using the secure CleanWebTM system by the investigator after identification though a personal password after a final check of the eligibility criteria (website https://chu-dijon.tentelemed.com). Patients will be randomly assigned to one of the two groups in a 1:1 ratio to one of two arms: rTMS active or rTMS placebo. The allocation algorithm, which relies on a minimization approach, is established by the study statistician (Unité de Soutien Méthodologique à la Recherche, USMR, Hospital University of Dijon) before the start of the trial. This allocation is stratified on center and sex. Investigators and patients will be blinded to the treatment assignment. A comprehensive document describing the randomization procedure will be kept in a confidential manner at the USMR.

Emergency unblinding will be performed in an emergency situation when the status of the brain stimulation (real or placebo) must be known to the investigator in order to provide appropriate medical treatment.

Outcomes

In the "Guideline on the development of medicinal products for the treatment of alcohol dependence" for alcohol Petit et al. Trials (2022) 23:33 Page 6 of 10

reduction strategies, the European Medicines Agency (EMA) recommend using a co-primary efficacy outcome, change from baseline in total alcohol consumption (TAC) per month, and reduction in number of HDD [1]. Thus, our principal effective criteria on alcohol reduction will be both the change in TAC from baseline to week 4, defined as mean daily alcohol consumption over 28 days (in g/day), and the number of HDD. Baseline will be defined as alcohol consumption during the 28 days before randomization using the *alcohol Timeline Followback* (TLFB) method, a validated method that retrospectively obtains estimates of daily drinking using a calendar [25, 26]. During follow-up, patients will be asked to report their alcohol consumption on a daily basis.

The secondary evaluation criteria will be the change from baseline to the end of the rTMS sessions, and then for each 4-week period after the treatment up to week 24 in:

- TAC (g/day) and number of HDD
- Proportion of subjects with a significant categorical shift in World Health Organization (WHO) risk levels of drinking: low risk (H≤40 g/d; F≤20 g/d), medium risk (H≤60 g/d; F≤40 g/d), high risk (H≤100 g/d; F≤60 g/d, and very high risk (H>100 g/d; F>60 g/d) [22]
- Proportion of subjects with a 50%, 70%, and 90% reduction in alcohol consumption as well as the proportion of patients who potentially achieve abstinence
- Level of alcohol dependence severity (alcohol dependence scale)
- Craving/urge to drink assessment (visual analogue scale, obsessive compulsive drinking scale)
- Clinical global impression-severity and improvement
- Scores for depression scales (HAM-D—17 items)
- Quality of Life (short form health survey—12 items)

Other secondary evaluation criteria will include the change from baseline at week 4, week 12, and week 24 after the treatment, in:

- Biochemical alcohol consumption markers (gamma glutamyl transferase, mean corpuscular volume, aspartate aminotransferase, alanine aminotransferase, and carbohydrate deficient transferrin)
- Cognitive assessment (Montreal cognitive assessment)
- Number of cigarettes smoked/day and craving for tobacco (visual analogue scale, tobacco craving questionnaire) for smokers.

Number of patients with adverse events will be determined at the time of each visit.

No genetic or molecular analysis is planned.

Sample size calculation

The sample size was calculated using PASS software (version 11, Kayesville, UT, USA) [27]. As the primary efficacy outcome, the EMA recommend using both TAC and the number of HDD [1]. Besides, any reduction in total alcohol consumption of at least 10 g/day for patients with alcohol use disorders will reduce the annual and lifetime risk of alcohol-related death [28].

In this context, the sample size calculation based on an expected difference between the treatment groups of $15\,\mathrm{g/day}$ in total alcohol consumption or $3\,\mathrm{days}$ per month, with a standard deviation for the TAC of $30\,\mathrm{g/day}$ and with an autocorrelation of 0.3 to 0.7 between observations in the same subject, between 82 and 122 patients, would be required.

Considering a significance level of 1.25% (co-primary outcome) and a power of 80%, and with the hypothesis of a premature withdrawal or a non-initiation of treatment (acute repeated alcoholism) for 20% of individuals, 144 patients (72 per group) should be included to meet the objectives of the study.

Statistical analysis

All randomized participants will be analyzed regardless of the treatment allocated (intention to treat analyses (ITT)) and after excluding patients with deviation from the protocol (per-protocol analyses (PP)).

The main analysis will be carried out with the intention to treat population. The co-primary outcome of change from baseline in TAC and reduction in the number of HDD at 4 weeks after treatment and its association with rTMS will be analyzed under the intention-to-treat principle using a mixed model for repeated measures.

The baseline and demographic characteristics of the two groups (active rTMS vs sham rTMS) will be described in terms of numbers and percentages and quantitative variables in means and standard deviations, or medians and interquartile intervals. The comparability of the two groups at baseline will be evaluated using the chi-squared test or Fisher's test for qualitative variables, and Student's T test or the Wilcoxon-Mann-Whitney test for continuous variables. Then, a mixed model repeated measures will be conducted to estimate the effect of treatment on TAC first, and HDD second. Observed cases will be considered random effects, and site, sex, time, and treatment as fixed effects. We will use multiple imputation techniques to compensate for potential bias introduced by missing endpoint data [29].

Petit et al. Trials (2022) 23:33 Page 7 of 10

For the primary outcome, per-protocol analysis will also be conducted among participants who have completed baseline and endpoint assessments. The secondary outcome measurements will be analyzed with similar models to those used for the co-primary, continuous variables and logistic regression for dichotomized outcomes.

No interim analysis is planned.

All tests will be one-sided. The primary results will be examined at a significance level of 0.0125 (co-primary outcome). For secondary outcomes, the threshold for significance will be fixed at 0.025. All analyses will be performed using SAS version 9.4 (SAS Institute Inc) by the team of statisticians of the Unité de Soutien Méthodologique, Direction of Clinical Research, University Hospital of Dijon, France. Statistical code will not be made public.

Data management (data entry, coding, security and storage) and statistical evaluation will be carried out by the Clinical Research Department of the Dijon University Hospital, which is a service which is independent of the care units where the patients will be treated. As this is a very low risk trial for patients, French legislation does not require the creation and monitoring of a data monitoring committee. In consequence, no auditing of trial conduct was planned.

Only the patient's anonymous code is reported in the case report form (CRF). This is comprised of the patient's initials (first letter of the family name and the first name), the number of the center, and the number corresponding to the position in the list of inclusions.

Results

The results will first be posted on the registration page of clinicaltrials.gov.

Then, we will communicate the results through oral communications, posters, and scientific publications. No publication restrictions are planned. To be considered an author, a person must (Vancouver rules):

- Make substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
- and to the drafting the work or revising it critically for important intellectual content;
- and to the final approval of the version to be published;
- and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Discussion

In recent years, rTMS was transformed from an emerging experimentation to a useful modern tool for the

treatment of various neurologic and psychiatric disorders [30]. Some studies report beneficial effects for treating patients with substance-related and addictive disorders because it has beneficial effects on craving reduction and other cognitive dysfunctions that may underlie addictive disorders, with rTMS targeting the DLPFC [13, 16, 31–36]. Among the existing studies, only three have focused on patients treated for AUD, and these studies used an abstinence-based strategy. They found interesting results in terms of craving reduction, modulation of decision-making processes, and improvements in quality of life, and one of them observed a reduction in alcohol relapses [13, 34, 35]. However, none considered an approach based on reducing alcohol consumption even though a number of benefits can be expected, such as a reduction in alcohol-related damage and better acceptability of the therapeutic goal [9]. This strategy could be even more attractive given that treatment time is short (i.e., a few days of brain stimulation) and rTMS is known to be safe [37–39].

Although the current literature status seems to indicate rTMS may be effective in AUD and other substance use disorders, these conclusions needed to be further explored, mainly because these studies are limited by their small sample sizes, which has resulted in great heterogeneity, even in a well-conducted meta-analysis. Our aim is thus to conduct an RCT with a large sample size in order to investigate whether a treatment strategy using rTMS has the potential to become a promising treatment in AUD. In addition, unlike previous studies, our RCT will provide insight into whether rTMS has long-lasting effects in patients with AUD. We hope that our study will remedy these shortcomings and provide a high level of evidence for the short- and long-term efficacy of modulating DLPFC excitability via rTMS to treat AUD. This trial, which is to date one of the largest RCTs to assess the efficacy of rTMS in substancerelated and addictive disorders, may also contribute to enhancing the efficacy of non-invasive brain stimulation techniques in the comprehensive treatment of addiction.

Trial registration data

Primary registry and trial identifying number	Clinicaltrials.gov NCT04773691		
Date of registration in primary registry	February 26 th , 2021		
Source(s) of monetary or material support	National Hospital Research Program 2014 of the French Ministry of Health		
Primary sponsor	National Hospital Research Program 2014 of the French Ministry of Health		
Secondary sponsor	N/A		
Contact for public queries	Dr Benjamin Petit, M.D., benjamin. petit@chu-dijon.fr		
Contact for scientific queries	Dr Benjamin Petit, M.D., benjamin.		

Petit et al. Trials (2022) 23:33 Page 8 of 10

Trial registration data (Continued)

Trial registration data (Continued) Clinicaltrials.gov Clinicaltrials.gov Primary registry and trial Primary registry and trial identifying number NCT04773691 identifying number NCT04773691 petit@chu-dijon.fr baclofen, naltrexone, and nalmefen (< 1 month) Public title Efficacy of repetitive transcranial magnetic - Patient with a history or presence of stimulation (rTMS) for reducing pre-delirium tremens or delirium tremens consumption in patients with alcohol use - Patient with a substance use disorder disorders (ALCOSTIM): study protocol for a (DSM-5 criteria) with psychoactive randomized controlled trial substances other than tobacco and alcohol. Scientific title Efficacy of repetitive transcranial magnetic stimulation (rTMS) for reducing - Patient with acute psychiatric disorders requiring hospitalization and/or consumption in patients with alcohol use disorders (ALCOSTIM): study protocol for a immediate adjustment of psychotropic medication randomized controlled trial - Patient with severe depression, defined Countries of recruitment France by a score of 24 or more on the Hamilton Depression Scale (HAM-D). Health condition(s) or Alcohol use disorder - Patient who has had a recent change problem(s) studied (< 1 month) in the prescription of Intervention(s) Active rTMS (1,000 pulses per session, 2 psychotropic treatment sessions per day, 5 days) - Patient with severe and/or chronic psychiatric disorders, including Sham rTMS schizophrenia, paranoia and bipolar Key inclusion and exclusion Ages eligible for study: ≥ 18 years disorders type I and II criteria Genders eligible for study: both - Patient with severe heart, kidney, liver Accepts healthy volunteers: no or lung failure or other condition that the doctor believes could compromise the Inclusion criteria: meeting the criteria for patient's participation in the study. mild to severe AUD as defined in the - Patient with a contraindication to the Diagnostic and Statistical Manual of practice of rTMS; personal history of Mental Disorders-5th edition (DSM-5); seizure, pacemaker, neurosurgical clips, wishing to reduce their alcohol consumpcarotid or aortic clips, heart valves, tion; and having experienced at least one hearing aid, ventricular bypass valve, prior attempt to achieve abstinence (unsutures with wires or staples, foreign successful or relapse). bodies in the eye, shrapnel, other Exclusion criteria: prosthesis or cephalic ferromagnetic - person who is not affiliated to or not a material. beneficiary of national health insurance - Patient simultaneously participating in - person subject to a legal protection another therapeutic trial measure (curatorship, guardianship) - Patient employed by the investigator or - person subject to a legal safeguard - Patient who, according to the investigator, is unable to complete a - pregnant, parturient or breastfeeding women consumption diary and follow up visits for - adult unable to express consent 6 months - patient of childbearing age with a - Patient refusing to sign the "safety positive pregnancy test at inclusion contract "* specific to the study patient with an exhaled alcohol level > Study type Interventional 0 mg/l inclusive - patient with heavy alcohol Allocation: randomized intervention consumption < 6 days in the 4 weeks model. Parallel assignment. prior to inclusion (European Medicine Masking: double blind (patient, Agency, 2010; one day with alcohol investigator) consumption of 60 g or more for men Primary purpose: treatment and 40 g for women) - patient with an average alcohol March 2021 Date of first enrolment consumption below the WHO average Target sample size 144 risk level in the 4 weeks prior to inclusion (WHO, 2000, less than or equal to 40 g/ Recruitment status Recruiting day for men and 40 g for women) change in TAC and number of HDD from - patient being abstinent more than 5 Primary outcome(s) days before inclusion baseline to week 4 - patient with a CIWA (Clinical Institute change from baseline to the end of the Key secondary outcomes Withdrawal Evaluation: assessment of the rTMS sessions, and then for multiple severity of alcohol withdrawal) score interim endpoints after the treatment up greater than or equal to 10 at inclusion to week 24: - Patient with concomitant treatment - TAC (g/day) and number of HDD with disulfiram, acamprosate, topiramate, - Proportion of subjects with a significant

Petit et al. Trials (2022) 23:33 Page 9 of 10

Trial registration data (Continued)

Primary registry and trial identifying number

Clinicaltrials.gov NCT04773691

categorical shift in World Health Organization (WHO) risk levels of drinking: low risk (H≤40 g/d; F≤20 g/d), medium risk (H≤60 g/d; F≤40 g/d), high risk (H≤100 g/d; F≤60 g/d, and very high risk (H> 100 g/d; F> 60 g/d) [22]

- Proportion of subjects with a 50%, 70% and 90% reduction in alcohol consumption as well as the proportion of patients who potentially achieve abstinence
- Level of alcohol dependence severity (alcohol dependence scale)
- Craving/urge to drink assessment (visual analogue scale, obsessive compulsive drinking scale)
- Clinical global impression-severity and improvement
- Scores for depression scales (HAM-D 17 items)
- Quality of Life (short form health survey- 12 items)
- Biochemical alcohol consumption markers (gamma glutamyl transferase, mean corpuscular volume, aspartate aminotransferase, alanine aminotransferase and carbohydrate deficient transferrin)
- Cognitive assessment (Montreal cognitive assessment)
- Number of cigarettes smoked/day and craving for tobacco (visual analogue scale, tobacco craving questionnaire) for smokers.

Trial status

Version 1.1; last edited 22/06/2020

Enrolment for this study will begin on March 1, 2021. At the time of submission, we have enrolled the first participant.

Study duration as predicted: 30 months and 1 week

Abbreviations

AUD: Alcohol use disorders; CIWA: Clinical institute withdrawal assessment for alcohol; CRF: Case report form; DALYs: Disability-adjusted life years; DLPF C: Dorsolateral prefrontal cortex; DSM-5: Diagnostic and statistical manual of mental disorders. 5th ed; EMA: European medicines agency; HAM-D: Hamilton depression rating scale; HDD: Heavy drinking days; rTMS: Repetitive transcranial magnetic stimulation; RCT: Randomized controlled trial; TAC: Total alcohol consumption; tDCS: Transcranial direct current stimulation; TLFB: Alcohol timeline followback; TUD: Tobacco use disorder; WHO: World Health Organization

Acknowledgements

The authors are grateful to the French Ministry of Health for a grant from the National Hospital Research Program (PHRC-I 2014), and the University Hospital of Dijon for the support given to the study. The authors would like to thank Suzanne Rankin for her help with proofreading.

Authors' contributions

BT, BP, and VM conceived and designed the study protocol and wrote the manuscript. ASF and LJo participated in the conception of the study, helped

to draft the manuscript, and are responsible for the statistical analyses. MC, ABM, CA, and MR sought ethical approval, participated in the design and the coordination of the study, and ensured financial and all material needs were met. LL, LJe, and JF participated in the review of literature, manuscript writing, and revision. The corresponding author had final responsibility for the decision to submit for publication. The authors read and approved the final manuscript.

Funding

This study is funded by the National Hospital Research Program 2014 of the French Ministry of Health. The sponsor peer-reviewed the protocol. The funders had no other role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by an independent ethics committee (Committee for the Protection of Persons, West V) on 28 June 2020 under the number 2019-A03047-50 and by the French national agency for the safety of medical products and devices (Agence National de Sécurité des Médicaments et des Produits de Santé).

Consent for publication

The results will first be posted on the registration page of clinicaltrials.gov. Then, we will communicate the results through oral communications, posters, and scientific publications. No publication restrictions are planned.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Addictology, University Hospital of Dijon, 14 rue Paul Gaffarel, B.P. 77908, 21079 Dijon Cedex, France. ²UFR des Sciences de Santé, Université de Bourgogne, Dijon, France. ³Unité de Soutien Méthodologique à la Recherche, Délégation à la Recherche et à l'Innovation (DRCI), University Hospital of Dijon, 1 boulevard Jeanne d'Arc BP 77 908, 21 079 Dijon Cedex, France. ⁴UMR CNRS 7357 iCube, FMTS (Fédération de Médecine Translationnelle de Strasbourg), Université de Strasbourg, Strasbourg, France. ⁵Centre de neuroModulation Non-Invasive de Strasbourg – CEMNIS, Hôpitaux Universitaires de Strasbourg, Hôpital Civil, 1 place de l'Hopital, BP426, 67091 Strasbourg Cedex, France. ⁶INSERM 1114, Department of Psychiatry and Addictology, University Hospital of Strasbourg, Fédération de Médecine Translationnelle de Strasbourg (FMTS), 67000 Strasbourg, France. ⁷Department of Psychiatry and Addictology, University Hospital of Strasbourg, Fédération de Médecine Translationnelle de Strasbourg (FMTS), 67000 Strasbourg, France. ⁸Pôle Psychiatrie, Santé Mentale et Addictologie, Clinique de psychiatrie, Hôpitaux Universitaires de Strasbourg, 1 place de l'hôpital, BP 426, F-67091 Strasbourg Cedex, France. $^9\mathrm{D\'el\'egation}$ à la Recherche et à l'Innovation (DRCI), University Hospital of Dijon, 1 boulevard Jeanne d'Arc – BP 77 908, 21079 Dijon Cedex, France. ¹⁰INSERM UMR1093-CAPS, Université Bourgogne Franche-Comté, UFR des Sciences du Sport, Dijon, France.

Received: 20 April 2021 Accepted: 15 December 2021 Published online: 12 January 2022

References

- European Medicines Agency. Guideline on the developpement of medicinal products for the treatment of alcohol dependence. 2010. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_ guideline/2010/03/WC500074898.pdf.
- Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addict Abingdon Engl. 2018;113(10):1905–26. https://doi.org/10.1111/add.14234.

Petit et al. Trials (2022) 23:33 Page 10 of 10

- Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. Lancet Lond Engl. 2019;394(10200):781–92. https://doi.org/10.1016/S0140-6736(19)31775-1.
- World Health Organization, Management of Substance Abuse Team, World Health Organization. Global status report on alcohol and health 2018. 2018.
 Available from: https://www.who.int/publications/i/item/9789241565639.
- Rehm J, Allamani A, Vedova RD, Elekes Z, Jakubczyk A, Landsmane I, et al. General practitioners recognizing alcohol dependence: a large crosssectional study in 6 European countries. Ann Fam Med. 2015;13(1):28–32. https://doi.org/10.1370/afm.1742.
- Rathod SD, Roberts T, Medhin G, Murhar V, Samudre S, Luitel NP, et al.
 Detection and treatment initiation for depression and alcohol use disorders:
 facility-based cross-sectional studies in five low-income and middle-income
 country districts. BMJ Open. 2018;8(10):e023421. https://doi.org/10.1136/
 bmjopen-2018-023421.
- Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. Bull World Health Organ. 2004;82(11):858–66.
- Rehm J, Dawson D, Frick U, Gmel G, Roerecke M, Shield KD, et al. Burden of disease associated with alcohol use disorders in the United States. Alcohol Clin Exp Res. 2014;38(4):1068–77. https://doi.org/10.1111/acer.12331.
- Gastfriend DR, Garbutt JC, Pettinati HM, Forman RF. Reduction in heavy drinking as a treatment outcome in alcohol dependence. J Subst Abuse Treat. 2007;33(1):71–80. https://doi.org/10.1016/j.jsat.2006.09.008.
- Sauvaget A, Trojak B, Bulteau S, Jiménez-Murcia S, Fernández-Aranda F, Wolz I, et al. Transcranial direct current stimulation (tDCS) in behavioral and food addiction: a systematic review of efficacy, technical, and methodological issues. Front Neurosci. 2015;9:349. https://doi.org/10.3389/ fnins.2015.00349.
- Jansen JM, Daams JG, Koeter MWJ, Veltman DJ, van den Brink W, Goudriaan AE. Effects of non-invasive neurostimulation on craving: a meta-analysis. Neurosci Biobehav Rev. 2013;37(10):2472–80. https://doi.org/10.1016/j. neubiorev.2013.07.009.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5. 5 edition. Washington, D.C: American Psychiatric Publishing; 2013. 991 p.
- Klauss J, Penido Pinheiro LC, Silva Merlo BL, Correia Santos G de A, Fregni F, Nitsche MA, et al. A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. Int J Neuropsychopharmacol. 2014;17(11):1793–803. https://doi.org/10.1017/S14 61145714000984.
- Trojak B, Meille V, Achab S, Lalanne L, Poquet H, Ponavoy E, et al. Transcranial magnetic stimulation combined with nicotine replacement therapy for smoking cessation: A Randomized Controlled Trial. Brain Stimulat. 2015;8(6):1168–74. https://doi.org/10.1016/j.brs.2015.06.004.
- Höppner J, Broese T, Wendler L, Berger C, Thome J. Repetitive transcranial magnetic stimulation (rTMS) for treatment of alcohol dependence. World J Biol Psychiatr. 2011;12(sup1):57–62. https://doi.org/10.3109/15622975.2011. 508383
- Shahbabaie A, Golesorkhi M, Zamanian B, Ebrahimpoor M, Keshvari F, Nejati V, et al. State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. Int J Neuropsychopharmacol. 2014; 17(10):1591–8. https://doi.org/10.1017/S1461145714000686.
- Ma T, Sun Y, Ku Y. Effects of Non-invasive Brain Stimulation on Stimulant Craving in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-Analysis. Front Neurosci. 2019;13. Available from: https://www.frontiersin.org/articles/10.3389/fnins.2019.01095/full.
- Kim HJ, Kang N. Bilateral transcranial direct current stimulation attenuated symptoms of alcohol use disorder: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatr. 2020;110160:110160. https://doi. org/10.1016/j.pnpbp.2020.110160.
- 19. Bolden L, Pati S, Szaflarski J. Neurostimulation, neuromodulation, and the treatment of epilepsies. Journal of Epileptology. 2015;23(1):45–59.
- Zhang JJQ, Fong KNK, Ouyang R-G, Siu AMH, Kranz GS. Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis. Addict Abingdon Engl. 2019;114(12):2137–49. https://doi. org/10.1111/add.14753.
- Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ Br Med J Publ Group. 2013;346:e7586.

- World Health Organization. International guide for monitoring alcohol consumption and related harm. World Health Organization. 2000. https://a pps.who.int/iris/handle/10665/66529.
- Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. J Affect Disord. 2013; 150(2):384–8. https://doi.org/10.1016/j.jad.2013.04.028.
- Modirrousta M, Meek BP, Wikstrom SL. Efficacy of twice-daily vs once-daily sessions of repetitive transcranial magnetic stimulation in the treatment of major depressive disorder: a retrospective study. Neuropsychiatr Dis Treat. 2018;14:309–16. https://doi.org/10.2147/NDT.S151841.
- Pedersen ER, Grow J, Duncan S, Neighbors C, Larimer ME. Concurrent validity of an online version of the Timeline Followback assessment. Psychol Addict Behav. 2012;26(3):672–7. https://doi.org/10.1037/a0027945.
- Sobell LC, Sobell MB. TimelineFollow-back: a technique for assessing selfreported ethanol consumption. In: Litten RZ Allen JP Eds Meas Alcohol
- Consum Psychosoc Biol Method. Totowa, NJ: Humana Press; 1992. p. 41–72.

 27. Hintze J. PASS 11. Kaysville, Utah, USA: NCSS, LLC; 2011. Available from: www.ncss.com.
- Rehm J, Zatonksi W, Taylor B, Anderson P. Epidemiology and alcohol policy in Europe. Addict Abingdon Engl. 2011;106(Suppl 1):11–9. https://doi.org/1 0.1111/i.1360-0443.2010.03326.x.
- Schafer JL. Multiple imputation: a primer. Stat Methods Med Res. 1999;8(1): 3–15. https://doi.org/10.1177/096228029900800102.
- Palm U, Reisinger E, Keeser D, Kuo M-F, Pogarell O, Leicht G, et al. Evaluation of Sham Transcranial Direct Current Stimulation for Randomized. Placebo-Controlled Clinical Trials Brain Stimulat. 2013;6(4):690–5. https://doi. org/10.1016/j.brs.2013.01.005.
- Fecteau S, Agosta S, Hone-Blanchet A, Fregni F, Boggio P, Ciraulo D, et al. Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers: A preliminary study. Drug Alcohol Depend. 2014;140:78–84. https://doi.org/10.1016/j.drugalcdep.2014. 03036
- Boggio PS, Liguori P, Sultani N, Rezende L, Fecteau S, Fregni F. Cumulative priming effects of cortical stimulation on smoking cue-induced craving. Neurosci Lett. 2009;463(1):82–6. https://doi.org/10.1016/j.neulet.2009.07.041.
- Fregni F, Orsati F, Pedrosa W, Fecteau S, Tome FAM, Nitsche MA, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. Appetite. 2008;51(1):34–41. https://doi.org/10.1 016/j.appet.2007.09.016.
- da Silva MC, Conti CL, Klauss J, Alves LG, do Nascimento Cavalcante HM, Fregni F, et al. Behavioral effects of transcranial Direct Current Stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. J Physiol-Paris. 2013;107:493–502.
- Boggio PS, Sultani N, Fecteau S, Merabet L, Mecca T, Pascual-Leone A, et al. Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. Drug Alcohol Depend. 2008;92(1-3):55–60. https://doi.org/10.1016/j.drugalcdep.2007.06. 011.
- Boggio PS, Campanhã C, Valasek CA, Fecteau S, Pascual-Leone A, Fregni F. Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. Eur J Neurosci. 2010;31(3):593–7. https://doi.org/10.1111/j.1460-9568.2010.07080.x.
- Higgins ES, George MS. Brain stimulation therapies for clinicians. Washington, DC: American Psychiatric Pub; 2009. 185 p.
- Feil J, Zangen A. Brain stimulation in the study and treatment of addiction. Neurosci Bio Behav Rev. 2010;34(4):559–74. https://doi.org/10.1016/j. neubiorev.2009.11.006.
- Ekhtiari H, Tavakoli H, Addolorato G, Baeken C, Bonci A, Campanella S, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. Neurosci Biobehav Rev. 2019;104:118–40. https://doi.org/10.101 6/j.neubiorev.2019.06.007.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.