Non-invasive and invasive brain stimulation in alcohol use disorders: A critical review of selected human evidence and methodological considerations to guide future research

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Non-invasive and invasive brain stimulation in alcohol use disorders: A critical review of selected human evidence and methodological considerations to guide future research

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ABSTRACT

Introduction: Alcohol use disorder (AUD) ranks among the leading causes of decrements in disability-adjusted life-years. Long-term exposure to alcohol leads to an imbalance of activity between frontal cortical systems and the striatum, thereby enhancing impulsive behaviours and weakening inhibitory control. Alternative therapeutic approaches such as non-invasive and invasive brain stimulation have gained some momentum in the field of addictology by capitalizing on their ability to target specific anatomical structures and correct abnormalities in dysfunctional brain circuits.

Materials and methods: The current review, covers original peer-reviewed published research on the use of brain stimulation methods for the rehabilitation of AUD. A broad and systematic search was carried out on four electronic databases: *NCBI PubMed*, *Web of Science*, *Handbooks* and the *Cochrane Library*. Any original article in English or French language, without restrictions of patient age or gender, article type and publication outlet, were included in the final pool of selected studies.

Results: The outcomes of this systematic review suggest that the dorsolateral prefrontral cortex (DLPFC) is a promising target for treating AUD with high frequency repetitive transcranial magnetic stimulation. Such effect would reduce feelings of craving by enhancing cognitive control and modulating striatal function. Existing literature also supports the notion that changes of DLPFC activity driven by transcranial direct current stimulation, could decrease alcohol craving and consumption. However, to date, no major differences have been found between the efficacy of these two non-invasive brain-stimulation approaches, which require further confirmation. In contrast, beneficial stronger evidence supports an impact of deep brain stimulation reducing craving and improving quality of life in AUD, effects that would be mediated by an impact on the nucleus accumbens, a central structure of the brain's reward circuitry. Overall, neurostimulation shows promise contributing to the treatment of AUD. Nonetheless, progress has been limited by a number of factors such as the low number of controlled randomized trials, small sample sizes, variety of stimulation parameters precluding comparability and incomplete or questionable sham-conditions. Additionally, a lack of data concerning clinical impact on the

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severity of AUD or craving and the short follow up periods precluding and accurate estimation of effect duration after discontinuing the treatment, has also limited the clinical relevance of final outcomes.
Conclusion: Brain stimulation remains a promising approach to contribute to AUD therapy, co-adjuvant of more conventional procedures. However, a stronger therapeutic rational based on solid physio-pathological evidence and accurate estimates of efficacy, are still required to achieve further therapeutic success and expand clinical use.

1. Introduction

Mortality and disease burden in Europe and USA have been dramatically impacted for centuries by alcohol use disorder (AUD), a heterogeneous chronic relapsing condition, caused by a complex interaction of genetic, neurobiological, psychological, and environmental factors [1]. AUD ranks among the leading causes of decrements in disability-adjusted life-years (DALYs) and is the third most prevalent cause of preventable death in the USA [2]. Despite efficacy of benzodiazepines in initial stages of alcohol retreat interventions, long-term sobriety is considerably more challenging to achieve and only ~25% of patients remain abstinent 6 months after withdrawal [3].

Most of psychoactive substances such as tobacco, cocaine, methamphetamine and alcohol are acutely rewarding due to their common action on the dopamine-related meso-cortico-limbic reward circuit: the ventral tegmental area (VTA), the nucleus accumbens (NAc), the amygdala in interaction with the hippocampus and the prefrontal cortex (PFC) [4]. Imaging studies have demonstrated strong links between substance use disorders and dopamine-related dysfunction in cortico-striatal circuitry. Repeated drug use is associated to behavioral reinforcement subtended by neuroplasticity and neural adaptation phenomena in the reward pathway, with increasingly dwindling drug rewarding effects. This generates a habit-driven compulsive use, recruitment of stress neural pathways, with emotional dysregulation and altered prefrontal activity particularly in the dorsolateral prefrontal (DLPFC) and the orbitofrontal cortex (OFC) [5]. Decreased DLPFC activity impairs executive function [6,7] and cognitive performance. In sum, long term exposure to alcohol use leads to an imbalance of activity between cortical frontal systems and the striatum, thereby enhancing impulsive behaviours while also weakening inhibitory control [8].

Current treatments for drug addiction include behavioral and pharmacological therapies. Such interventions aim to reduce impulsivity by manipulating autonomic responses and strengthen deliberate self-control or memory consolidation and by virtue of such effects, favor relapse prevention. Nonetheless, despite intensive research, the latter have proven of limited efficacy [9,10]. In this context, invasive neuromodulation with deep or intracranial brain stimulation (DBS) or non-invasive brain stimulation (NIBS) via rTMS (repetitive Transcranial Magnetic Stimulation) or tDCS (transcranial Direct Current Stimulation) may allow the selective targeting of anatomical structures and/or dysfunctional brain circuits in addiction patients and the correction of their dysfunctions. The current rational for both, invasive and non-invasive neurostimulation approaches relies on a direct restoration of dopaminergic neurochemistry in the striatum (DBS) either directly or via connectivity effects on cortico-striatal loops (rTMS, tDCS). Additionally, both approaches, but more specifically NIBS, may also operate by modulating cortical dysfunction influencing reward-related cognitive functions or mood (stimulation of the DLPFC), able to reduce craving (inhibition of the OFC) and ultimately increase the periods of alcohol abstinence.

The aim of the current systematic review is to summarize original peer-reviewed studies published in indexed scientific journals addressing the therapeutic role of invasive and non-invasive brain stimulation methods in the field of AUD. On such basis we put forward a series of critical comments to improve future research in this challenging type of socially and clinically sensitive addiction disorders.

2. Materials & methods

We completed a search on three electronic databases: *NCBI PubMed*, the *Web of Science*, *Handbooks* and the *Cochrane Library*. Articles in English and French language were both accepted. The following search terms (MeSH) were used on each database: "*Alcohol*" OR "*Alcoholism*", AND "*Stimulation*" OR "*Transcranial magnetic stimulation*" OR "*Brain stimulation*" OR "*Transcranial Direct Current Stimulation*" OR "*Transcranial electrical stimulation*" OR "*Deep Brain Stimulation*", OR "*Cranial electrical stimulation*" OR "*Craving*", and clusters of the former free terms, combined in multiple search strategies. On *NCBI PubMed*, this search was refined with 'original *article'* and *'human'*. No restrictions on age, gender, article type, publication outlet or date were implemented for the search. Combinations of these different terms were tested in order to compare results. On *Clinical Trial*, the search was carried out with the terms: "*stimulation*" and "*alcohol*". In addition to extracting data available in each of the retrieved articles, reference lists from each retrieved article were thoroughly examined to eventually identify studies missed in our initial search. The last set of searches was completed on July 2020.

3. Results

3.1. Transcranial magnetic stimulation (TMS)

3.1.1. Basic principles and preclinical studies

Transcranial magnetic stimulation was developed 35 years ago and initially used as a diagnostics tool to attest cortico-spinal conductivity and cortical excitability in clinical neurophysiology [31,32]. TMS technology is based on the principle of electromagnetic induction. It uses single, pairs, bursts or long patterns of magnetic pulses to induce electrical currents in the brain via a coil placed on the scalp surface, hence non-invasively. TMS devices are based on large capacitors that charge electricity and deliver through a winding-copper wire coil monophasic/biphasic current pulses of several thousands of Amperes, lasting for ~150/250 μs. According to Faraday's electromagnetic induction principles, high intensity magnetic pulses conveyed by the TMS coil penetrate through the scalp inducing a current on underlying gray matter regions. Within the targeted area, electrical currents depolarize cortical neurons [33] with a maximal effect on those with neuroaxis oriented parallel to the brain surface [34] (likely intracortical interneurons). Additionally, the delivery of long TMS trains made by multiple pulses enables the induction of longer modulatory effects on brain excitability, outlasting the duration of the patterns. Such TMS modality, known as repetitive TMS (rTMS) refers to any combination of pulses delivered at a given frequency (at least 1 Hz) with the ability to produce different effects than those of their isolated pulses or pairs of pulses. It encompasses a myriad of patterns combining the delivery of short trains of at least 3–5 pulses at high frequency (10–20 Hz, i.e. with a time interval between pulses around 50 ms) and also longer periods of rTMS stimulation (generally 10 to 30 min at a specific frequency, at 1, 3, 5, 10 or 20 Hz) either continuously or interleaved by stimulation-free intervals.

In most subjects, high frequency (HF) stimulation (>5 Hz, but mainly 10 and 20 Hz 1–2 s bursts interleaved by TMS-free intervals, for at least 15 min) induces excitatory effects on cortical activity correlates (motor evoked potentials, phosphene thresholds, in some instances also,

specific cognitive tasks). In contrast, low frequency (LF) stimulation (0.5 to 1 Hz delivered continuously for at least 15 min) has shown consistent inhibitory or suppressive effects on similar correlates [35]. More recently, the so-called Theta Burst Stimulation (TBS) consisting of 50 Hz triplets repeated every 200 ms (hence at 5 Hz) delivered in continuous (cTBS) or intermittent (iTBS) patterns of 600 to 900 TMS pulses during 40 to 190 s (in blocks of 8 s ON- and 8 s OFF-stimulation) has shown an ability to drive lastingly decreases and increases, respectively of cortico-spinal excitability.

Importantly, the effects of stimulation do not remain local, but exert a widespread network impact though white matter connectivity, linking different regions across the same cerebral circuits, which depends of the strength of the anatomical connectivity between the cortical targeted region and cortical or subcortical nodes of the same networks [36–38].

Lasting effects are considered to occur via use-dependent plasticity mechanisms including synapse modification, i.e. long-term potentiation-like (LTP) and long-term depression-like (LTD) mechanisms [39]. LTP-like effects can be induced either by applying pure high frequency rTMS (such as for example 5, 10 or 20 Hz) or by delivering composite theta-gamma (50 Hz/5 Hz) bursts of patterned stimulation via iTBS patterns. Similarly, it is possible to induce transient LTD-like effects on cortical excitability by applying either low frequency rTMS (1 Hz) or cTBS [40].

Commercial rTMS approved devices are able to deliver single or paired TMS pulses, from low to high-frequency (up to 50 Hz) short bursts, long repetitive patterns of repetitive TMS (rTMS) at single (1 Hz, 5 Hz, 10 Hz or 20 Hz) or patterned rTMS (Theta-burst TMS, iTBS, cTBS) frequencies [41]. Different TMS coil shapes are used for stimulation serving different purposes. The flat circular coil has a high penetration power, but lacks spatial selectivity [42] (>4–5 cm^2). The figure-of-eight shaped coil is more focal (1.5–2 cm^2) producing by summation maximal current at the intersection of the two flaps, but results in weaker magnetic fields [43]. TMS efficacy is limited to superficial brain areas due to the dramatic drop of electric field strength as a function of cortical depth. The figure-of-8 coil induces a highly focal supra-threshold fields under the coil's central segment, at depths of up to 1.5 cm [44,45]. Nonetheless, new coil designs such as the H-coil (aka *Hesed coil*) enables effective stimulation of deeper brain cortical regions (as for example the anterior cingulate cortex) or functional sites located close or at the fundus of a sulcus, limiting the influence of lateral spreading and strong fields in more superficial cortical regions. A crucial issue for a correct use of TMS is the accuracy of coil's placement, which should ensure the shortest path for the magnetic field to cross the skull and attain the targeted hotspot, and at the same time, minimize power loss and unwanted stimulation of adjacent regions. Targeting precision is enhanced by MRI based frameless stereotaxic neuronavigation equipment capable to use individual 3D brain reconstructions and track in real time TMS coil's position on participant's heads and brains [46,47]..

3.1.2. Clinical applications

Randomized clinical trials using rTMS in recently detoxified AUD patients are summarized in Table 1.

Mishra et al. were the first authors to report in 45 right-handed male patients with a severe form of alcohol dependence, a reduction of basal alcohol craving following 10 sessions of 10 Hz rTMS over the right DLPFC, which persisted for a month. Administered in ~50% of the former patients ($n = 23/45$) in association with anti-craving medication (naltrexone, acamprosate, disulfiram, carbamazepine fluoxetine) no difference on relapse rate at 4 weeks was observed after the end of TMS sessions [48].

In contrast with the former, Höppner et al. (2011) failed to find effects for 10 sessions of 20 Hz rTMS over the left DLPFC in basal craving nor on depressive mood in a cohort of 19 alcohol-dependent females. Nonetheless, significant increases in attention blink paradigm, towards alcohol-related pictures were found after active rTMS sessions [49]. Herremans et al. (2012) reported null effects of a single high frequency

Table 1
Deep brain stimulation in alcohol use disorder.

First author, year	Brain localisation of the implants	N°	Follow-up (years)	Age (years)	Gender	Main outcome
Muller, 2009 & Muller, 2016, Vosges, 2012	Bilateral NAc	5	>6	36	Male	Prolonged abstinence: Yes, after 8Y AUQ: from 29 to 8 at M12 OCDS: from 11/18 to 0 at M6 and M12
				37	Male	Prolonged abstinence: Yes, after 6 years AUQ: from 53 to 8 at M12 OCDS: from 18/19 to 0 at M6 and M12
				40	Male	Prolonged abstinence: Not completely after 2 M AUQ: from 37 to 8 at M12 OCDS: from 11/20 to 0 at M12
				51	Male	Prolonged abstinence: Yes, at M12 but not after M15 AUQ: from 20 to 8 at M12 OCDS: data not shown
				55	Male	Prolonged abstinence: Not completely over 20 M OCDS: data not shown AUQ: from 14 to 8 at M12
Kuhn, 2011	Bilateral NAc	1	>1	69	Male	Prolonged abstinence: Yes, at M12 ADS: from 17 to <8 at M12 CBQ: from 70 to <8 at M12 OCDS-G: from 20 to <8 at M12 AUDIT: from 25 to 15 at M12
Heldmann, 2012	Bilateral NAc BNST VP	1	NC	38	Male	Prolonged abstinence: Yes, the patient has been alcohol abstinent and reports a virtually complete reduction of his sensitivity to alcohol related cues. SCL: data not shown OCDS: data not shown AUQ: data not shown
De Ridder, 2016	dACC	1	>1.5	38	Male	Prolonged abstinence: Yes after 2.5Y VAS: from 10 to 1 at M12

N° = number of patients, AUQ = alcohol urge questionnaire, OCDS = obsessive-compulsive drinking scale, CBQ = craving believe questionnaire, SCL = symptom check list, AUDIT = alcohol use disorders identification Test, VAS = visual analog scale, NAc = nucleus acumbens, VP = ventral pallidum, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex.
OCDS scores dropped down to zero but periodically increased to values ranging from 5 to 10 (drinking thoughts) and from 9 to 15 (drinking behavior) in context of relapses.

rTMS sessions delivered to the right DLPFC on alcohol craving, immediately following stimulation, and also after alcohol exposure following a week-end at home [50]. In 2013, these same authors reported no effect of either 20 Hz-rTMS session over the right DLPFC on response inhibition (number of commission errors) but a stabilization of performance in a cognitive control task in $n = 50$ recently detoxified alcohol-dependent patients without cognitive impairment [51]. In a single blind uncontrolled trial, Mishra et al. [52] did not observe any difference in craving for $n = 20$ severe dependent patients after 10 sessions of 10 Hz TMS over right vs left DLFPC.

In alcohol-dependent patients with comorbid dysthymic disorder, Girardi et al. [53] carried out the first attempt to use the so called 'H coil' (aka H1 Hesed coil) producing a strong deep field able to reach medial and lateral prefrontal regions, including the orbitofrontal cortex, with a preference for the left hemisphere. Five rTMS sessions proved sufficient to significantly decrease basal craving and depressive symptoms, an effect that remained stable across 15 sessions, and lasted for a month.

Finally, Herremans et al. (2015) studied the impact of rTMS over the DLPFC on fMRI resting-state and after a block of event-related cue-reactivity paradigm in recently detoxified dependent patients. After alcohol-related cue-exposure, 15 rTMS sessions over the right DLPFC positively influenced craving, by the 4th consecutive session. Additionally, rTMS showed an impact on extended reward circuitry and modulated saliency and attention (Central Executive Network). Finally, Del Felice et al. observed an improvement in response-inhibition and selective attention tasks after 4 sessions of 10 Hz rTMS over the left DLPFC, an effect that persisted for a month. In contrast, basal alcohol craving and alcohol intake remained both unchanged [54].

3.1.3. Interim discussion on rTMS applications

In agreement with international guidelines and European expert recommendations [55], the tolerance and safety of high frequency rTMS have been confirmed in recent detoxified alcohol-dependent patients after benzodiazepine disruption. The main reported side-effects during the stimulation have been pain, anxiety, transient headache and less frequently, seizure, nightmare and middle insomnia [48,51,52]. Notwithstanding, due to a lack of supportive data, a potential impact on dependence severity remains to be demonstrated. Similarly, no significant conclusion can be drawn from rTMS efficacy on alcohol craving. Moreover, different questions, such as determining the most suited target between left or right hemisphere's DLPFC require further work. Indeed, Mishra et al. 2015 and Boggio et al. 2008 did not report any difference on craving reduction comparing rTMS stimulation of the left vs. the right DLPFC. Neuroimaging studies with PET or fMRI showed that the DLPFC in both hemispheres was involved in cue-induced alcohol craving [56]. Finally, the large heterogeneity in stimulation parameters shown by studies targeting the right or the left DLPFC preclude contrasting their outcomes to reliably isolate this variable. Moreover, craving reduction and relapse prevention seem to require several TMS sessions (5 positive studies used at least 10 sessions), whereas TMS effect lasts only a few weeks [48,53,54].

Given the promise set by TMS stimulation over the DLPFC and the high focality of this technique, further optimization of anatomical targets within the left or right prefrontal cortex remains a crucial question. The popular and widely used "5-cm approach" (5 cm anterior to the TMS primary motor cortex hotspot of the hand muscle along the para-sagittal line) provides a simple 'rule of thumb' for DLPFC localization. Nonetheless, this method has also been criticized for not precisely capturing interindividual differences in head and brain morphology [57]. The use of MRI-based frameless neuronavigation systems specifically targeting the DLPFC appears to enhance response to rTMS in treatment-resistant depression, hence should also potentiate outcomes in AUD applications.

3.2. Transcranial Direct Current Stimulation (tDCS)

3.2.1. Basic principles and preclinical studies

Transcranial Direct Current Stimulation (tDCS) is a painless non-invasive tool able to modulate cortical excitability in animals and humans [58]. It delivers very low electric constant current (1–2 mA) between at least 2 electrodes (normally of 25 to 35 cm^2 total surface) placed on the scalp, polarizing large cortical areas below the active lead (either the anode or the cathode) relative to a return lead, placed on a neutral distant cephalic or body region such as the neck or the shoulder. tDCS is able to modulate membrane resting potential, rendering neurons more or less prone to reach its firing thresholds and discharge action potentials in response to a physiological input. It has been shown that during and for a limited period of time also following tDCS exposure, motor cortical excitability is increased under the anode and decreased under the cathode [59]. In contrast to DBS or TMS, the primary effect of tDCS is a shift of resting membrane potential towards depolarization (anodal stimulation) or hyperpolarization (cathodal stimulation), depending on current flow direction and the relative orientation of neuron's neuroaxes (dendrites to axon) in gyry and sulci. **Transcranial direct current stimulation** has shown to induce transiently modulate local excitability as a function of electrode montage, stimulation polarity, current intensity and density and duration, whereas the cumulation of consecutive daily sessions may lead to longer lasting plasticity effects than isolated interventions [60].

As for low and high frequency rTMS, the facilitatory and inhibitory effects of tDCS on cortical excitability could be mediated by GABAergic vs. glutamatergic mechanisms [61], leading to long-term depression and long-term potentiation-like mechanisms, respectively. These effects on the gabaergic and glutamatergic receptors have also been demonstrated with treatments such as gabapentin, pregabalin, oxcarbazepine [62]. However, from a larger perspective, tDCS may also exert an impact on brain function and behavior by acting on resting state connectivity and notably via modulations of the default mode (self-referential) network and fronto-parietal systems [63]. tDCS has been proven highly safe and well tolerated, and only discomfort, itching, headache, mood changes, mild redness on the scalp stimulation site have been occasionally reported [64–66]. Due to its very safe risk profile, ease of use, low cost and high portability, tDCS has rapidly expanded as promising tool in clinical neuropsychiatric application for which DBS might prove unnecessarily invasive. Also, it can eventually replace rTMS solutions which are often expensive, cumbersome and none-exempt of epileptogenic risk. International guidelines of tDCS clinical uses [67] and ensuring safety [60] regulating its uses are periodically discussed and renewed.

3.2.2. Clinical applications

Randomized clinical trials of tDCS in recently detoxified AUD patients are summarized in Table 2.

In 2008, Boggio et al. [64] were the first to report the extinction of alcohol exposure-induced craving after bilateral anodal tDCS simultaneously on the left and right DLPFC in severely affected patients. In contrast, in 2012, Nakamura-Palacios et al. did not observe any effect of anodal tDCS on the left DLPFC on basal craving, even if such treatment significantly improved cognitive performance [68]. Extending their experience in this subgroup of patients, Da Silva et al. reported following 5 sessions of right anodal and left cathodal tDCS over the DLPFC, a decrease in the basal craving score with an eventual gain in executive performance. However, this protocol also resulted in a trend towards a higher number of relapses [62]. Klauss et al. [66] were the first to apply a bilateral stimulation protocol (i.e., dual tDCS stimulation) with 5 daily sessions of anodal right plus cathodal left tDCS over the DLPFC of each hemisphere. The study was designed to focus its primary outcome measure on AUD relapse rate and hypothesized large effect sizes. Unfortunately, no effect on craving, mood or pre-frontal function was observed following the tDCS sessions. Nonetheless a three-fold lower rate in alcohol consumption relapse was reported by the study. In a

Table 2
Repetitive transcranial magnetic stimulation in alcohol use disorder.

First author, year	Inclusion criteria	Design	N°	Brain target	Stimulation parameters	Main evaluation criteria	Main outcome
Mishra, 2010	Age: 18–60 years CIWA-Ar scores ≤10	randomized single-blind control: sham stimulation - follow-up: 1 month	45	R DLPFC	10 Hz, 110% MT 10 daily sessions	ACQ-NOW	ACQ-Now at M1 (active/sham): from 245 ± 23.47/244.53 ± 28.72 to 44.25 ± 73.76/89.93 ± 103.80
						Relapse	Relapse (active/sham): 13.8%/ 33.33%
Hoppner, 2011	Gender: Female 14 days after detoxification	randomized control: sham stimulation - follow-up: 10 days	19	L DLPFC	20 Hz, 90% MT 10 daily sessions	OCDS HDRS BDI AB	OCDS at D10: from 6/5 to 4/2 HDRS at D10: from 8/8 to 1/1 BDI at D10: from 15/13 to 4/3 AB: improvement/improvement
Herremans, 2012	Age: 18–65 years After complete detoxification	randomized single-blind control: sham stimulation	31	R DLPFC	20 Hz single session	OCDS	OCDS (before and after HF-rTMS): No effect on basal craving post TMS No effect on basal craving after week-end at home
Herremans, 2013	Age: 18–65 years	randomized single-blind control: sham stimulation	50	R DLPFC	20 Hz, 110% MT single session	OCDS	OCDS (active/sham) before and after rTMS: from 9,45/12,79 to 8,62/11,55
Mishra, 2015	Age: 18–60 years. Gender: Male CIWA-Ar scores ≤10	randomized single-blind follow-up: 10 days	20	R vs L DLPFC	10 Hz, 110% MT 10 daily sessions	ACQ-NOW	ACQ-NOW after sessions of rTMS at D10: Right: from 268.106 (21.52) to 144.506 (36.98) Left: from 269.606 (30.48) to 142.806 (37.16)
Girardi, 2015	16–65 years >5-year duration of illness	open label add-on compared to standard treatment follow-up: 6 M	20	medial and lateral PFC	20 Hz, 120% MT 5 daily sessions in a week over 4 weeks	OCDS	OCDS: dTMS-add on: from 24.8 to 6.8 at M6 standard treatment: from 23.7 to 9.7 at M6
						HDRS	HDRS: dTMS-add on: from 19.1 to 9.1 at M6 standard treatment: from 19.7 to 8.7 at M6
						CGI	CGI: dTMS-add on: from 6.0 to ≈1.2 at M6 standard treatment: from 6.0 to ≈1.7 at M6
Ceccanti, 2015	Gender: Male- 10 days after residential withdrawal	randomized double-blind control: sham stimulation - follow-up: 6 months	18	medial PFC	20 Hz, 120% MT 10 sessions (5 per week)	Average number of drinks consumed daily	Daily alcohol consumption: Active group: from 18.6 ± 4.9 drinks/day to 0.7 ± 0.7 drinks/day at M3. Sham group: from 10.1 ± 2.8 drinks/day to 5.3 ± 1.8 drinks/day at M3.
						DMAI	DMAI: Active group: from 23.4 ± 7.1 to 0.7 ± 0.7 drinks/DMAI at M3. Sham group: from 13.7 ± 5.0 to 5.3 ± 1.8 drinks/DMAI at M3.
						VAS	VAS: Active group: from 26.7 ± 7.3 mm to 15.5 ± 12.4 at M2 Sham group: from 43.9 ± 12.9 mm to 49.5 ± 29.5 at M2 Drop out: Active group: 7 subjects dropped out at M6 Sham group: 9 subjects dropped out at M6
Herremans, 2015	Age: 18–65 years	open label	23	R DLPFC	15 Hz, 110% MT 15 sessions over 4 days	TLS	TLS: from 1.0 (1.8) to 1.1 (2.0) after the third block cue-exposure
						AUQ	AUQ: from 16.85 (11.53) to 7.98 (7.98) at D4
						OCDS	OCDS: from 3.95 (9.90) to 2.43 (2.56) at D4
Herremans, 2016	Age: 18–65 years	open label	19	R DLPFC	20 Hz, 110% MT 15 sessions over 4 days	Relapse rate	13/23 (68%) relapse at M1
Del Felice, 2016	Age: 18–65 years	randomized single blind control: sham stimulation	23	L DLPFC	10 Hz, 100% MT 2 weekly sessions over two weeks	Alcohol intake	Alcohol intake: No significant modifications over time or group
						Craving (VAS)	Craving (VAS): No significant modifications over time or group

(*continued on next page*)

Table 2 (*continued*)

First author, year	Inclusion criteria	Design	N°	Brain target	Stimulation parameters	Main evaluation criteria	Main outcome
						Numeric Stroop task Go/No-Go task	Numeric Stroop task: from 0.311 to 0.901 at M1 Go/No-Go task: 0.450 to 0.966 at M1

CIWA-Ar = clinical institute withdrawal assessment for alcohol, MT = motor threshold, ACQ-NOW = Alcohol Craving Questionnaire, DMAI = the number of alcoholic drinks/day of maximum alcohol intake, Attentional blink (AB), TLS = ten-point Likert scales, HDRS = Hamilton Depression rating scale, Beck Depression Inventory (BDI).

population of 40 young heavy drinkers, Den Uyl et al. (2015) compared tDCS stimulation of the left DLPFC with that of the right inferior frontal gyrus (IFG). Results showed that tDCS on the left DLPFC improved valence categorization speed of attribute words in the Implicit Association Test (IAT) and reduced craving. In contrast IFG stimulation did not impact craving, but induced an impact on motor inhibitory control systems [69].

The work of Wietchorke et al. (2016) [70] was second in using a bilateral DLPFC stimulation protocol (anodal right/cathodal left versus sham) in right handed AUD patients with comorbid affective disorders. These authors assessed participant's own selection of alcohol relevant pictures and subjective craving, using a Positive and Negative Affective Schedule (PNAS) scores. Nonetheless, no significant results were observed. Den Uyl et al. carried out the first randomized and controlled large-scale trial to assess the efficacy of an in-patient treatment comparing right anodal or left cathodal tDCS to sham stimulation over the DLPFC for 3 months. Patients were also randomized between active and sham tDCS with or without cognitive training. No significant effect on residential abstinence at hospital discharge (3 months) was found. The trial did not observe any enhancing effect of tDCS on cognitive training either. Nonetheless, logistic regression at 12 months post treatment revealed a trend towards lower relapse rate for actively stimulated participants, only when tDCS was combined with cognitive training.

3.2.3. Interim discussion on tDCS applications

Evidence summarized in the present review supports an impact for unilateral DLPFC stimulation on alcohol craving in AUD patients [71]. The efficacy of dual or bifrontal DLPFC stimulation (i.e., right anodal tDCS combined with left cathodal tDCS) on craving control has been granted a level of evidence of 'grade B' [67]. However, outcome data on alcohol craving remain inconclusive [66,72]. Finally, lower relapse rate observed after 5 stimulation sessions in severe forms of alcohol dependence cannot be yet confirmed and require further studies.

In sum, tDCS outcomes turn out to be strongly dependent on current intensity, stimulation duration and electrode size and position [65,73], whereas longer-lasting effects of tDCS must be further confirmed. These could be achieved by increasing the duration of stimulation sessions, enhancing tDCS intensity and most and foremost, by accruing daily tDCS sessions (less than 24 h inter-session interval) along several weeks of treatment, options that could be hampered by safety limitations, such as skin rashes or scalp pain by an excess of dissipated heat. Indeed, tDCS has been shown to induce cumulative effects only when applied daily for long periods of time [74]. Since in AUD, repetitive tDCS sessions were more effective on craving [75] than promoting sustained abstinence [66], it remains unclear whether such a repetition rate (generally a session per day), is optimally suited to stabilize long-lastingly, tDCS-induced adaptive plasticity. Overall, it is also challenging to draw solid conclusions, since tDCS protocols might have likely involved multifactorial effects of variables such as clinical severity, number of consecutive sessions and stimulation cortical sites, the specific influence of which have not been yet well-isolated.

3.3. Deep brain stimulation (DBS)

3.3.1. Basic principles and preclinical studies

DBS is a neurosurgical procedure that involves the stereotactic implantation of unilateral or bilateral electrodes connected permanently to a programmable pulse generator stimulator device implanted subcutaneously below the clavicle [11]. Stimulation parameters such as train frequency, pulse width and shape and mono vs. bipolar stimulation montages can be wirelessly selected to maximize the efficacy on each patient and reduce potential side effects.

Intracranial electric brain stimulation was born in 1950 with the discovery by Olds and Milner [12] of the reward neural circuit in the rodent brain. Sometime later, in 1963, Bishop et al. [13], published the first report of deep brain stimulation in humans for neuropsychiatric disorders, pain and movement disorders. The modern era of DBS began in 1987, with the pioneering work of Benabid et al. [14] who reported tremor cessation in parkinsonians during high-frequency stimulation (25–100 Hz) of the thalamic nuclei.

Deep brain stimulation (DBS) is considered safe, well tolerated and effective. Accordingly, it has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of essential tremor (in the thalamus), Parkinson's disease and primary dystonia (in the Globus Pallidus and the Subthalamic Nuclei). Investigational studies using DBS have been conducted for refractory epilepsy, obesity, chronic pain, tardive dyskinesia, Tourette syndrome, and other movement disorders; yet none of them has paved the way for FDA approval in these pathologies. DBS has been approved by the FDA under a Humanitarian Device Exemption (HDE) for treatment-resistant obsessive-compulsive disorder [15].

The use of DBS in AUD was translated to human patients on the basis of the first Knapp report [16] on male rats showing a reduction of alcohol intake after DBS stimulation of the NAc shell (160 Hz, 50–150 μA, 200 μs). However, in alcohol-preferring rats, a more robust animal model of AUD, bilateral stimulation of the NAc shell (140–150 Hz, 200 μA, 60 μs) failed to alter free-choice baseline drinking but did reduce alcohol intake after a period of forced abstinence and reduced incidence of alcohol relapse [17]. More recently, Wilden et al. [18] reported that unilateral left NAc shell stimulation with 100-200 μA reduced alcohol intake by 47% in chronically drinking rats (1.5 g/Kg/day).

3.3.2. Clinical applications

Clinical evidence for the impact of DBS on alcohol-dependence came from collateral serendipitous findings in patients implanted for others indication. Kuhn et al. [19] reported the case of a 54 years-old patient who received bilateral DBS in the NAc to treat a severe panic disorder and depression. Before implantation surgery, the patient developed alcohol dependence spanning across more than 10 years. The patient showed at best, a slight reduction of anxiety and depressive mood, however unexpectedly, he experienced a drastic reduction of alcohol consumption during a 12-months follow-up period in absence of any other specific motivation. The patient claimed to have lost the desire to drink and felt no longer a pressing need to consume alcohol.

A second case report published by Levin et al. [20] involved a 69-year-old man with severe essential tremor resistant to

pharmacological treatment, implanted bilaterally and stimulated with DBS electrodes in the *nucleus ventralis intermedius* of the thalamus (130 Hz, 60 μs). Eight months later, he was tremor-free and unexpectedly, he was able to abstain from alcohol consumption he previously abused of to alleviate his symptoms.

Further studies reported cases of DBS treatment in severe forms of AUD in which other treatment options had failed. All published clinical data exploring DBS in patients suffering from AUD are the case reports, summarized in Table 3. Müller et al. (2009) [21] characterized the long term impact of DBS in 5 males between 36 and 65 years of age (3 with family history of alcohol dependence) implanted bilaterally in the NAc. Kühn et al. [22] informed on an additional case with a drastic reduction of alcohol consumption after a 13 months follow-up. All these patients showed abolition of alcohol craving following initial treatment. Nonetheless, 2 patients achieved longer term abstinence lasting for more than 6 years; 3 patients showed a marked reduction of alcohol consumption triggered by stress and induced by intermittent relapses; whereas 2 of them died after a 7-year follow-up, very likely, consequence of their alcohol dependence.

Two other studies assessed cognitive performance after bilateral DBS stimulation of the NAc. Kuhn et al. [22] reported improvement of psychometric scores and electrophysiological measures of cognitive control 12 months post DBS, whereas, Heldmann et al. [23] suggested that DBS of the NAc operated in part by improving behavioral control processes. In the latter study, PET/CT-Scan imaging performed 18 months after DBS implantation revealed a role for brain regions involved in action

Table 3
transcranial direct current stimulation in alcohol use disorder.

First author, year	Inclusion criteria	Design	N°	Brain target (T) Number of sessions (N)	Main evaluation criteria	Main outcome
Boggio, 2008	Age: 30–55 years Gender: F & M After detoxification >10D	randomized: yes double-blind control: sham stimulation cross-over	13	T = L & R DLPFC (anodal vs cathodal tDCS) *N* = 1 for each stimulation mode	AUQ	AUQ from baseline to post-tDCS and post second cue exposure: Sham tDCS: from 37.9 (15.0) to 32.5 (15.8) Anodal left/cathodal right tDCS: from 35.2 (17.0) to 38.7 (14.9) Anodal right/cathodal left tDCS: from 37.3 (16.1) to 40.0 (13.0)
Nakamura, 2012	Age: 18–75 years Gender: F & M After detoxification >7D	randomized: yes double-blind control: sham stimulation cross-over	49	T = L DLPFC (anodal tDCS) *N* = 1 for each stimulation mode (active and sham)	OCDS	OCDS before and after the session: no statistically significant difference in the mean scores among different types of alcoholics
da Silva, 2013	Age: 18–75 years Gender: F & M After detoxification >7D	randomized: yes double-blind control: sham stimulation	13	T = L DLPFC (anodal tDCS) *N* = 1 session per week during 5 weeks	Relapse OCDS	Relapse: 4 patients suffering from AUD from the tDCS group (66.7%)/only one subject in the sham-tDCS group (14.3%) OCDS: the difference between initial and final scores was of −8.0 (±SD 4.6) for active tDCS and of −0.9 (±SD 2.3) for sham tDCS.
Klauss, 2014	Age: 18–75 years Gender: F & M After detoxification >7D	randomized: yes double-blind control: sham stimulation	33	T = bilateral tDCS *N* = 2 sessions per day for a total of 5 days	Relapse OCDS	Relapse at M6: 15 of 17 subjects from the sham-tDCS and 8 of 16 from the tDCS group relapsed OCDS (sham/tdcs): Initial 8.4 (3.6)/7.3 (4.3) Final 3.3 (3.1)/2.8 (3.1)
den Uyl, 2015	Age: not defined Gender: F & M AUDIT >8	randomized: yes blinding: NC control: sham stimulation	41	T = L DLPFC (anodal tDCS) or IFG *N* = 1 session	IAT Craving (AAAQ)	No effects of tDCS on the IAT were found. Craving decreased after L DLPFC stimulation compared to sham stimulation ($t = -1.88$, $p = 0.034$,1) Craving did not change significantly after IFG stimulation compared to sham stimulation ($t = 0.79$, $p = 0.43$).
Wietschorke, 2016	Age: 18–60 years Gender: F & M After detoxification >7D	randomized: yes double-blind control: sham stimulation	30	T = L cathodal/R anodal tDCS *N* = 1 session per day during 4 weeks	Craving (VAS) PANAS	VAS: tendency for reduced craving in the subscales "intention to drink" ($t = 1.50$, $p = 0.10$) and "desire" ($t = 1.39$, $p = 0.10$) after verum stimulation. PANAS: Post-hoc test revealed that the sham group reported a significant decrease in negative affect ($t = 2.2$, $p = 0.05$), while the verum group do not show any significant changes from beginning to the end of the experiment ($t = -0.6$, $p = 0.58$)
Den Uyl, 2016	Age: 18–60 years Gender: F & M	randomized: yes double-blind control: sham stimulation	100	T = L DLPFC (anodal tDCS) with or without CBM *N* = 4 sessions	Craving (PACS) Relapse at M3 and M12	Craving: Craving decreased over time ($F = 7.98$, $p < 0.01$) Relapse at M3: no significant difference between groups in the primary outcome time to relapse ($\chi2 = 3.53$, $p = 0.77$) Relapse at M12: The median of the logistic regression showed a trend-level significant effect of treatment condition ($\chi2 = 5.37$, $p = 0.07$)
Trojak, 2016	Age: >18 years Gender: F & M Non abstinent	randomized: yes double-blind control: sham stimulation	340	T = R DLPFC (anodal tDCS) *N* = 2 sessions per day for a total of 5 days	TAC VAS Proportion of subjects with a significant categorical shift in risk levels of drinking (OCDS)	Not available yet

IAT = implicit association test, AAAQ = approach and avoidance of alcohol questionnaire, PANAS = the positive and affective affect schedule, PACS = penn alcohol craving scale, CBM: cognitive brain modification, TAC = total alcohol consumption.

monitoring and behavioral control, notably, the paracingulate cortex, the temporal poles, the precuneus and the hippocamp. Also, noteworthy, such PET/CT-Scan results could not be fully replicated four months later.

Finally, De Ridder et al., published in 2016 [24] the case of a 38-years old man with intractable alcohol dependence secondary to a co-morbid anxious disorder, who improved of his alcohol craving, anxiety and negative mood, over 2–3 days. The patient endured high frequency DBS applied bilaterally to the dorsal anterior cingulate cortices for up to 18 months. Interestingly, the rational for such DBS target was supported upon short-lasting *offline* effects induced by deep rTMS on alcohol craving and monitored by fMRI recordings.

Unfortunately, studies in comorbid populations cannot easily rule out whether the beneficial effects of DBS stimulation on craving result from a direct impact on the systems sub-serving this function or explained indirectly by a reduction of anxiety.

All these reports, show that DBS is in general well tolerated. The main side effect reported by authors has been hypomania, a symptom that usually remits after adaptation to stimulation parameters [23,25,26]. However, the implantation of DBS electrodes carries intra- and perio-perative risks such as mortality rates for up to 1.8%, and morbidity from 0.4 to 4.6%, both mainly caused by intracranial bleeding [27]. It can be also associated to infections (1.7%), seizures (1.5%) and transient states of confusion (15.6%) [28].

3.3.3. *Interim discussion*

DBS in the NAc and ACC has shown to exert efficient, rapid and long lasting (up to 8 years) effects on cue-induced craving and alcohol consumption in severe forms of intractable AUD. Thus, invasive stimulation is considered a “rescue” option and an acceptable alternative to surgical bilateral NAc ablation, a previously practiced intervention which according to a study failed preventing opioid relapse in 48% of patients at 5 years [29]. Nonetheless, despite its apparent efficacy, DBS outcomes in AUD raise several worth-discussing concerns.

First, DBS to the NAc does not necessarily protect from stress. Even if it has been reported that stimulation of such target reduces cue-induced craving and improves cognitive control [22,23], in some cases, this intervention failed to protect patients from stress-induced relapse [26], whereas in case of comorbid anxiety disorder, NAc stimulation only reduced craving [19]. Second, with regards to the NAc target, the only available parameter reference is based on DBS uses in patients suffering from resistant depression or OCD [30].

Third, the benefit/risk ratio of DBS interventions has to be carefully weighted. Indeed, DBS is an invasive procedure non-exempt of surgical risks, which can produce irreversible physical and psychosocial sequels. As previously stated [25], choosing the right time for surgery remains the biggest challenge. This treatment option should be anticipated and eventually implemented well before a stage of irreversible brain atrophy exposing patients to an inexorable path towards severe disability and premature death is reached.

Finally, a trans-disciplinary approach integrating critical input from neurosurgeons, hepatologists, addiction specialists and bio-ethicists is required to evaluate the suitability of this technique in AUD cases that underwent liver transplantation, given that 10% of such cases relapse into harmful alcohol dependence.

4. General discussion

The aim of this systematic critical review was to cover current scientific evidence concerning uses of non-invasive (rTMS and tDCS) and invasive (DBS) neurostimulation. We aimed at better understand and treat alcohol use disorders (AUD) and identify specific aspects to improve the quality of future studies in this field. Several large-scope reviews have previously addressed and covered uses of brain stimulation techniques in substance use disorders (SUD), including tobacco (nicotine), alcohol, stimulants and opiates. Nonetheless, to the best of our knowledge this review is the first to focus specifically on the use of non-invasive and invasive brain neuromodulation to investigate and treat AUD.

As show by several case reports in patients undergoing DBS to treat severe forms of substance dependence, a significant reduction of alcohol craving and long-lasting alcohol abstinence (8 years) have been achieved following bilateral stimulation of the NAc, a central component of the reward circuit [26]. Nevertheless, despite proven clinical efficacy in AUD, NAc stimulation remains an invasive and costly neurosurgical procedure, potentially associated to short-term surgical risks (e.g. brain hemorrhage) and severe long-term adverse effects (e.g. surgical wound infection, seizures and stimulation-induced psychiatric perturbations). Moreover, AUD patients frequently present with impaired liver function and abnormal prothrombin and thrombocytopenia, hence posing a risk of intracranial hemorrhage, which massively outweighs the benefits of DBS. Accordingly, DBS is generally reserved for the most severe life-threatening cases of AUD resistant to pharmacotherapy.

Studies investigating the effects of tDCS on alcohol dependence, targeted the DLPFC with low intensity (2 mA) anodal tDCS and yielded rather inconsistent results on alcohol craving. More specifically, outcomes differed, from significantly reduced cue-induced alcohol craving by active tDCS to non-significant differences of the latter compared to sham tDCS. Concerning stimulation parameters, multi-session protocols have been shown more effective than single-sessions in reducing alcohol craving and consumption. Moreover, studies investigating tDCS across diverse SUDs demonstrated that longer stimulation sessions (>10 min) yielded most promising results than brief interventions. Furthermore, in a meta-analysis concerning non-invasive brain stimulation, Jansen et al. (2013) [71] suggested that right DLPFC neurostimulation may be the most effective target for craving suppression. In spite of these limitations, tDCS devices are relatively inexpensive, convenient for double-blind controlled studies and safe and simple to apply concurrently with behavioral tasks in clinical settings. Therefore, their efficiency in reducing alcohol craving and consumption in AUD deserves further investigation.

Studies investigating the effect of TMS in alcohol-dependent patients have examined alcohol-related craving as the main outcome measure. In fact, such published reports using both, rTMS and tDCS, have highlighted analogies concerning their stimulation strategy. For example, nearly all non-invasive stimulation trials in AUD targeted either the left or the right DLFPC. As for tDCS, the stimulation of the right DLPFC showed a pattern towards greater craving suppression, which unfortunately, failed to reach statistical significance [71]. Furthermore, rTMS studies have employed the conventional figure-of-8 coil to target the DLPFC and also the ‘H-coil’ able to reach deeper regions of the prefrontal cortex such as the medial PFC or the dorsal ACC, hardly accessible with conventional TMS coils or with tDCS approaches. Thus, regarding other brain region of interest in the treatment of AUD, two ‘deep TMS’ studies used ‘H-coils’ to target profound subcortical structures such as the mPFC [53] whereas a double cone coil [76] (aka bell's shape coil) was used to target the dACC. All these three studies significantly reduced alcohol-related craving after periodical stimulation sessions, showing that targeting brain regions related to the reward pathways and/or executive control networks yields the most efficient outcomes on alcohol craving and consumption. Moreover, the effect of several stimulation parameters (e.g. number of sessions, frequency or polarity, intensity and cortical target/targets) on alcohol craving varied significantly across rTMS studies. Importantly, reports involving a single or a few rTMS sessions showed a lack of efficacy on alcohol-related cravings, whereas studies accruing ten [50] or twenty [52] stimulation sessions yielded significant long-lasting effects on both, alcohol craving and consumption. A large majority of studies in AUD employed high frequency stimulation (at least 10 Hz and up to 20 Hz), whereas rTMS studies on SUD have shown that high frequency rTMS was more effective than low-frequency ones [77].

In recent papers, it has been proven that addiction reflects

progressive dopamine system dysregulation and the sensitization of corticotropin-releasing factor and dynorphin brain stress systems, which interact, are subjectively experienced as hypohedonia, and support craving from a negative reinforcement perspective [78]. It has been then hypothesized that a neuromodulatory approach can restore these alterations, thus reversing the allostatic load of hedonic dysregulation. Following this observation, the authors suggested that dorsolateral prefrontal cortex stimulation with rTMS possibly produces a "craving downregulated" therapeutic interval, during which compulsivity phenomena (craving driven by hypohedonia) do not interfere with progress in rehabilitation programs.

Despite the potential influence of methodological discrepancies, effects of high frequency rTMS did not reach clinical significance on craving reduction [54]. Similarly, few studies have provided a long-term follow-up (3–6 months) after stimulation treatment to determine whether stimulation offered or not a sustained neuromodulatory effect on alcohol craving and consumption. This is a weakness since for chronic relapsing brain diseases such as AUD, therapeutic durability is paramount. Additionally, suboptimal sham-controlled study designs and blinding strategies (or the lack thereof) limits the clinical relevance of rTMS studies performed to date in AUD. Last but not least, psychiatric conditions (i.e. depression, moodiness, anxiety and schizophrenia) which co-occur with AUD may influence the efficacy of brain stimulation regimes. Hence, further studies are warranted to uncover the differential effects of brain stimulation in co-occurring disorders.

In sum, the absence of data concerning AUD severity, the use of multiple questionnaires for the assessment of craving and the lack of long follow up periods after discontinuing neurostimulation curtail the scope of the research being published in the field of AUD. In this scenario, further progress will only be made if additional controlled and randomized double-blind clinical trial in large patient cohorts (if possible multicentric) assessing long-term abstinence are carried out.

5. Future directions to guide future studies

Both non-invasive (rTMS and tDCS) and Invasive (DBS) brain stimulation approaches targeting respectively basal ganglia systems or prefrontal cortical regions are safe and well tolerated, showing promise in the clinical management of alcohol consumption and craving. Invasive DBS should remain the treatment of choice for very severe forms of life-threatening AUD, whereas non-invasive brain stimulation approaches could be used as treatment in less severe AUD cases. Nonetheless, a winning strategy aiming to make efficient use of brain stimulation techniques in the field of AUD addictions needs be able to implement in future studies and clinical trials several improvements.

First, a detailed characterization of patient populations in terms of clinical features such as consumption and craving severity levels is crucial to allow reliable comparability across studies. Second, precise primary and secondary outcome measures and a pre-hoc choice of evaluation criteria needs to be clearly defined to warrant transposable data. To this regard, alcohol craving should remain the main criteria to assess efficacy. Third, a solid and reliable assessment of craving at baseline and following treatment is paramount to be able to compare across studies. To this end, we would strongly recommend the implementation of ecological cue- or sensory driven strategies which have been shown to be well-correlated with short-term relapse [78]. Fourth and last, an adequate selection of appropriate targets (e.g. left, right or bilateral DLPFC, NAc, STN, dorsal striatum, lateral habenula, mPFC or hypothalamus [79]) remains one of the main challenges of neuromodulation studies. To this regard, clinical studies often collide with the choice of stimulation technology (rTMS vs tDCS) and the selection of cortical target/targets, which is based on incomplete physiopathological theories of addiction. An informed choice of stimulation strategy (single, dual or multi-site with either rTMS or tDCS), stimulation parameters (number of pulses, frequency or polarity, duration and intensity) and multiday stimulation regime (number of sessions), all three based on the best available evidence and a well-thought plan of follow-up evaluations is crucial for success.

6. Conclusions

In conclusion, non-invasive and invasive brain stimulation technologies are safe and well-tolerated, and remain promising approaches to contribute to the clinical management of AUD. Invasive DBS must be the neurostimulation treatment of choice for episodes of life-threatening AUD, whereas non-invasive brain stimulation (rTMS or tDCS) could have a role as long-term therapy in less severe AUD cases. Importantly, the optimization of current neuromodulation strategies needs to resolve uncertainties tied to the physiopathological basis of alcohol addiction and craving, and clarify the mechanisms and establish the parameters by which brain stimulation might provide relief. On such basis, well-designed, controlled, randomized double-blind trials in large patient cohorts will have the mission to further assess clinical efficacy, which to date remains uncertain.

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Declaration of Competing Interest

No competing interest.

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