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THE CURRENT PERSPECTIVE OF NEUROMODULATION TECHNIQUES IN THE TREATMENT OF ALCOHOL ADDICTION: A SYSTEMATIC REVIEW

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SUMMARY

Background: *Alcohol dependency can be considered as a chronic mental disorder characterized by frequent relapses even when treated with appropriate medical or psychotherapeutic interventions. Here, the efficacy of different neuromodulation techniques in alcohol addiction, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), vagal nerve stimulation (VNS) and electroconvulsive therapy (ECT) is critically evaluated.*

Methods: *A broad literature search on electronic databases such as NCBI PubMed, the Web of Knowledge, the Cochrane Library was conducted. Additionally, we searched recent handbooks on neuromodulation and/or addiction.*

Results: *Studies investigating these neuromodulation techniques in alcohol addiction remain to date rather limited and especially tDCS and rTMS applications have been investigated. Overall, the clinical effects seem modest. The use of VNS and ECT has yet to be investigated in alcohol dependent patients.*

Conclusions: *Neuromodulation techniques have only recently been subject to investigation in alcohol addiction and methodological differences between the few studies restrict clear-cut conclusions. Nevertheless, the scarce results encourage further investigation in alcohol addiction.*

Key words: *neuromodulation – neurostimulation – addiction - alcohol*

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INTRODUCTION

Alcohol abuse and alcohol dependence are major health issues. Both have an important impact on mortality and disability adjusted life years (DALY's), resulting in 2.5 million deaths per year worldwide. Alcohol is consumed by two billion people aged over 15 years old. Not surprisingly, alcohol consumption is the fifth largest risk factor for disease and disability (Johnson 2008). The misuse of alcohol has been linked to several neuropsychiatric disorders, gastrointestinal diseases, cancer, cardiovascular diseases, fetal alcohol syndrome, pre-term birth complications and diabetes mellitus. Alcohol abuse and alcohol-related disorders are more prominent in males then in females (WHO 2011). Harmful alcohol uses, such as binge drinking, seem to increase in minors and young adults (WHO 2011).

Genetic, biological and environmental factors could influence the development of alcohol addiction (Hillemacher & Bleich 2008). Once addicted this disease tends to become chronic (Feltenstein & See 2008). Furthermore, this disorder is difficult to treat and relapse rates are high, even when successful detoxification is followed by pharmacotherapeutic or psychotherapeutic interventions (Johnson 2008, Heinz et al. 2009). Currently, three pharmacotherapeutic agents are approved by the U.S. Food and Drug Administration for the treatment of alcohol addiction and craving: acamprosate, naltrexone and disulfiram (Fox et al. 2012). Other effective agents in alcohol addiction are baclofen and topiramate. All act on alcohol craving and consumption by influencing directly or indirectly the brain reward system (Johnson 2008, Arbaizar et al. 2012, Addolorato et al. 2006, De Mulder & Dom 2012). However, therapeutic effect sizes are usually small, even when products with different mechanisms of action are combined (Johnson 2008). Although complete abstinence remains the ultimate goal, it is equally important to try to limit the number of heavy drinking episodes in order to improve quality of life (Johnson 2008).

Albeit subjective alcohol craving is clinically difficult to measure, it contributes substantially to relapse (Wrase et al. 2008, Koob & Volkow 2010). In addition, physiological reactions to alcoholic cues are known to be related to relapse (Sinha et al. 2009) and conscious drug craving may only be apparent when the automatic process of drug intake is interrupted (Tiffany 1990). Koob (2011) describes an 'Addiction Cycle' in alcohol-dependent patients, which consists of three phases, namely the binge/intoxication phase, the withdrawal/negative affect phase and the preoccupation/anticipation phase. Further, before becoming dependent, this cycle is usually repeated multiple times. Although other neurotransmitter systems can be involved as well, the dopaminergic system is the key player in all phases (Charlet et al., in press). Alcohol addicted patients display a deregulated dopaminergic system, which results in stronger alcohol orientation and loss in interest for natural rewards. Because of this malfunctioning dopaminergic system alcoholic patients encounter

difficulties in learning new reward associated stimuli and they lack motivation to seek new rewarding stimuli (Heinz et al. 2009).

Once 'addiction' is established, the cycle is characterized by impulsivity and compulsivity (Koob & Volkow 2010). Impulsivity is characterized by non-planned reactions to external and internal stimuli and it is associated with positive reinforcement (Zhang et al. 2012). Impulsivity is a multidimensional construct, consisting in impulsive action (behavioral component) and impulsive decision making (cognitive component) (Jacubczyk et al. 2012, Courtney et al., in press). The underlying neurobiology of impulsivity in alcohol dependency is complex (Courtney et al., in press). The prefrontal cortical network, and in particular the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) play an important role in inhibitory control mechanisms when patients are confronted with seductive options (Courtney et al., in press, Bechara 2005). Increasing activity of the PFC and thus cognitive control could decrease automatic impulses and therefore drinking behavior (Houben et al. 2011). Compulsivity, on the other hand, is associated with negative reinforcement. Negative emotional states are major motivational factors in relapse. Here, next to the deregulation of the dopaminergic system, the hypothalamus-pituitary-adrenal (HPA) axis is dysfunctional (Koob & Volkow 2010, Sinha et al. 2011).

Recently, modulation techniques, such as non-invasive transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and more invasive techniques such as deep brain stimulation (DBS) are applied to these kinds of patients. However, to date no clear guidelines in alcohol addiction are at hand to determine when such interventions can be applied. Therefore, the purpose of this review is to critically evaluate the efficacy of the current different neuromodulating techniques in the treatment of alcohol addiction.

MATERIAL AND METHODS

We conducted a broad search on electronic databases such as NCBI PubMed, the Web of Science, and the Cochrane Library. Additionally, we searched recent handbooks on neuromodulation and/or addiction.

The used PubMed search terms were alcohol abuse (mesh), craving, addiction, transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, vagal nerve stimulation and electroconvulsive therapy. Only articles written in English were taken into account. For the Web of knowledge-search we used following search terms: transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation, vagal nerve stimulation, electroconvulsive therapy, alcohol, addiction and craving. This search was refined with 'article' and 'English'. A total of 269 articles were found. Ten articles were included in this review. No articles that evaluated the effect of vagal nerve stimulation in alcohol-dependent animals or patients were found. For an overview see Table 1.

RESULTS

Transcranial direct current stimulation (tDCS) in the treatment of alcohol dependence

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that uses a continuous weak electric current via electrodes, placed on the scalp of a subject, in order to modulate brain activity. The DLPFC is the preferred place of stimulation. tDCS is beneficial in different neuropsychiatric disorders, including substance disorders (George & Aston-Jones 2010, Boggio et al. 2009, Boggio et al. 2008). Anodal stimulation is excitatory, while cathodal stimulation is inhibitory (Fregni et al. 2008). Only mild adverse events have been observed (Brunoni et al. 2011). tDCS can modify cognitive processing by changing neuronal activity, and thus also impulsive behavior (Fecteau et al. 2010). It is believed that tDCS can alter decision-making processes, which are important in addiction (Fecteau et al. 2010).

There are no animal studies investigating tDCS and alcohol dependency. Only one study was performed in alcohol-dependent patients by Boggio et al (2008). This research group included 13 patients in a randomized, double-blind, sham-controlled, crossover study. Patients received one sham, one anodal left/cathodal right and one anodal right/cathodal left stimulation of the DLPFC. To avoid carry-over effects the inter-session interval was 48 hours. Before and after stimulation patients were confronted with a cue exposure (movie of people drinking) and craving was measured with VAS. Both active stimulation sessions diminished craving measurements.

The use of multiple sessions has not yet been investigated in alcohol addiction.

Conclusion

Although only one study investigated the effect of tDCS in alcohol dependence, anodal stimulation of either left or right DLPFC was found to reduce alcohol craving temporarily. The most important limitation here was the small sample size and the absence of a neutral cue exposure. Although promising, tDCS parameters still need to be optimized and studies using multiple sessions need to be conducted too before tDCS can be considered as a treatment option in alcohol dependency. Also long-term follow-up still needs to be evaluated. Furthermore, the underlying neurobiological mechanisms as to how tDCS can alter neurocircuitries still have to be clarified.

Table 1. Overview of human studies on the effect of brain stimulation in alcohol dependence

Study	Substance use status	N of subjects	Stimulation technique and parameters	Assessment	Findings
Roper et al. 1966	Active drinking period	1 alcohol dependent patient	ECT	interview	Complete abstinence after several months
Boggio et al. 2007	After detoxification	13	tDCS - randomized sham-controlled cross-over (sham - anodal right / cathodal left - anodal left/cathodal right) - DLPFC	VAS	↓ craving by anodal right/cathodal left and anodal left/cathodal right stimulation
Kuhn et al. 2007	Active drinking period	1 male	DBS - nucleus accumbens - primary disorder: agora-phobia and panic attacks	AUDIT - interview	No effect on primary disorder ↓ alcohol consumption
Heinze et al. 2009	Active drinking period	3 cases	DBS - nucleus accumbens	interview	Complete alcohol-stop and absence of craving in two patients - ↓ alcohol consumption and craving in the other patient
Mishra et al. 2009	After detoxification	55	HF-rTMS (10Hz) - 10 daily sessions - 110% MT - 980 p/session - randomized sham-controlled - right DLPFC	ACQ-NOW	↓ immediate craving = craving after 4 weeks
Höppner et al. 2011	14 days after detoxification	19 females	HF-rTMS (20Hz) - 10 daily sessions - 90% MT - 1000 p/session – sham-controlled) - left DLPFC	OCDS AB	= craving ↑ AB for alcohol related pictures
Herremans et al. 2012	After detoxification	36	HF-rTMS (20Hz)- 1 session - 110% MT- 1560 p/session - randomized, sham-controlled - right DLPFC	OCDS	No effect on immediate and long term craving measurements
De Ridder et al. 2012	Active drinking period	1 female	LF-rTMS (1Hz) -double coil - MFC - 50% tonic mode - daily sessions during 5 weeks (30 min)	VAS	↓ immediate craving Relapse after 3 months with ↑ craving after 3 months

Legend: ECT: electroconvulsive therapy; tDCS: transcranial direct current stimulation; DBS: deep brain stimulation; HF-rTMS: high-frequency repetitive transcranial magnetic stimulation; LF-rTMS: low-frequency repetitive transcranial magnetic stimulation; DLPFC: dorsolateral prefrontal cortex; MFC: medial frontal cortex; VAS: visual analogue scale, p/session: pulses/ session; ACQ-NOW: Alcohol craving Questionnaire; OCDS: obsessive compulsive drinking scale; AB: attentional blink; AUDIT: alcohol use disorders identification test.

Repetitive transcranial magnetic stimulation (rTMS) in the treatment of alcohol dependence

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique and has been used to treat a variety of major neuropsychiatric illnesses (George et al. 2002). rTMS can alter cortical excitability, and hence induce changes in neuronal circuits (Fitzgerald et al. 2009, Cho & Strafella 2009). rTMS is also able to influence the HPA-axis (Baeken et al. 2011). The use of rTMS is considered to be safe when the existing safety guidelines are respected (Rossi et al. 2009).

Also with this technique, the DLPFC is the preferred stimulation place for the rTMS application in alcohol dependency (Bechara 2005, Mishra et al. 2010). rTMS has the capacity to modulate decision-making in healthy individuals (van 't Wout et al. 2005) and it is hypothesized that this neuromodulation technique can change impulsivity in addicted individuals (Fecteau et al. 2010). Animal studies are nonexistent.

SINGLE STIMULATION SESSIONS

Herremans et al. (2012) stimulated thirty-six recently detoxified alcohol-dependent patients with one sham-controlled high-frequency (HF)-rTMS session delivered on the right DLPFC. Alcohol craving was evaluated and measured with the Obsessive Compulsive Drinking Scale (OCDS). Immediate effects were registered in the lab setting without cue exposure, while long-term effects were evaluated in patients' natural environment. The lack of effect in subjective craving measurements was explained by the absence of cue-reactivity and because not all alcoholic patients do

experience craving when confronted with alcohol cues (Ooteman et al. 2006). This was the first study that evaluated alcohol-dependent patients in their natural environment and it was also the first study that localized the DLPFC with 3D-MRI.

MULTIPLE STIMULATION SESSIONS

In a case report, a 48-year-old woman with a treatment-resistant alcohol dependence problem was stimulated with low-frequency (LF)-rTMS during an active drinking period (De Ridder et al. 2011). The frontal cortex was stimulated with a double cone coil. A double cone coil is able to modulate both dorsal and subcallosal ACC, both important in craving. The patient was stimulated during 5 weeks. During the treatment craving measurements - measured with VAS during a cue exposure - were suppressed and remained so until three months after stimulation. At that moment patient relapsed.

Mishra et al. (2010) performed a sham-controlled study with ten daily sessions of HF-rTMS on the right DLPFC in forty-five alcohol-dependent patients. Craving was evaluated before the first and after the last stimulation session with the Alcohol Craving Questionnaire (ACQ-NOW). Real rTMS was significantly superior in decreasing craving measurements compared to sham stimulation. Craving measurements were evaluated until 4 weeks after stimulation. After four weeks however, there were no significant differences between the active and the sham group, which might imply that the effects are waning after a couple of weeks.

Höppner et al. (2011) stimulated nineteen detoxified alcohol-dependent female patients at the left DLPFC during 10 days with HF-rTMS in a sham-controlled design. Although no differences were found in craving measurements with the OCDS, they found an alteration in the attentional blink (AB) paradigm. The AB was increased after rTMS exclusively for the alcohol related pictures, but not for the neutral, positive and negative pictures. This means that the physiological inhibition of the second target stimuli (the alcoholic picture) was elevated by HF-rTMS at the left DLPFC. It has been shown that the DLPFC inhibits the limbic system, which includes the amygdala, which is as said above important in addiction. The amygdala is important in emotion regulation. Since rTMS only elevated AB for the alcoholic pictures the authors hypothesize that rTMS inhibits the amygdala by stimulating the DLPFC. According to the authors this alteration in the AB could be a physiological parable for craving reduction. However, patients did not acknowledge a decrease in subjective craving.

Conclusion

Research on rTMS is still relatively scarce and over the different studies there is a considerable variability in methodology. Therefore it is difficult to draw firm conclusions. Stimulation parameters, such as frequency, % MT, train duration, intertrain interval and laterality of stimulation differ significantly among studies. Until now, there are no fixed stimulation protocols in alcohol addiction. Research on the effect of rTMS on impulsivity is inconclusive and as to which hemisphere needs to be stimulated remains to be determined.

A single stimulation session does not seem to result in a decrease on subjective craving measurements. The use of multiple sessions may prove to be more effective in decreasing craving. It also could be that subjective craving assessment is not that reliable (Höppner et al. 2011).

Based on these findings we suggest the evaluation of multiple rTMS sessions in larger, randomized, sham-controlled population samples. Low-frequency rTMS has, until this day, not been investigated in a randomized controlled design. Studies should be done to evaluate whether patients need stimulation with high or low frequency.

Deep brain stimulation (DBS) in the treatment of alcohol dependence

Deep brain stimulation (DBS) has mainly been used in medication-refractory movement disorders, such as Parkinson's disease and essential tremor, in treatment-resistant obsessive compulsive disorder and depression (Knapp et al. 2009). Animal studies and some recent case reports show a potential beneficial effect in substance use disorders (Knapp et al. 2009, Henderson et al. 2010, Kuhn et al. 2007, Heinze et al. 2009). Although invasive, this technique is reversible, unlike neurosurgery. Its mechanism of action is poorly understood, but mimics ablation of the targeted area (Stephen et al., in press). The preferred stimulation place is the nucleus accumbens, playing a key role in the reward system. It is hypothesized that DBS here normalizes dopaminergic and glutamergic neurotransmitter systems (Kuhn et al. 2007).

Two animal studies have been published that evaluated the effect of DBS in alcohol-dependent rats. Henderson et al. (2010) used a sham-controlled design where a decrease in alcohol consumption was observed after real stimulation. Knapp et al (2009) found that stimulating both the core and the shell of the nucleus accumbens could decrease alcohol consumption in alcohol-dependent rats. The authors concluded that apparently both regions are important in mediating alcohol consumption. All published articles concerning humans are case reports. The nucleus accumbens was the chosen stimulation location.

Kuhn et al. (2007) reported on the case of a 54-year-old man receiving DBS of the nucleus accumbens for a treatment-resistant agoraphobia with panic attacks. Just before the stereotactic intervention patient consumed at least 10 alcohol units daily. Although almost no effect on patient's primary disorder was found, a drastic decrease in alcohol consumption was observed one month after stimulation. One year later, the patient only sporadically consumed alcohol.

Heinze et al. (2009) describes three cases. Two of the patients remained abstinent and had no subjective craving. The other patient experienced only short periods of relapse and reported a reduction in craving. Next to craving and consumption of alcohol, these investigators evaluated incentive salience with an incentive salience task, namely a visual search task. These researchers found that the left nucleus accumbens and ventral striatum are activated automatically when patients are confronted with drug related stimuli.

Conclusion

DBS seems to have therapeutic effects in the treatment of resistant alcohol addiction. However, in humans only case reports exist, which makes it difficult to extrapolate the findings. Although DBS is considered a reversible substitute of neurosurgery it remains an invasive procedure. In addition, the optimal stimulation place and parameters need further investigation.

Electroconvulsive therapy (ECT) in the treatment of alcohol dependence

Electroconvulsive therapy (ECT) is a technique where an epileptic seizure is induced by administering an electric current using electrodes placed on the scalp of a patient. The objective is to treat severe psychiatric diseases such as psychotic depression, treatment-resistant unipolar and bipolar depression, mania, schizophrenia and catatonia (Eitan et al. 2008). The most important side effect is transient cognitive impairment (Sienaert 2011).

Only one dated study related to the use of ECT in the treatment of addiction was found. Roper et al. (1966) described six cases of substance-dependent patients, whereof only one was alcohol-dependent. Patients were treated with the combination of ECT and chlorpromazine, a typical antipsychotic. For several months four out of six patients, including the alcohol-dependent patient, remained abstinent. Notwithstanding, the only review, written by Quitkin et al. (1972), stated that ECT was poor treatment in alcohol addicted phobic patients.

Conclusions

It is unclear why no further ECT studies have been published after 1972. This could in part be explained by the fact that ECT became in disuse during the 1950's until the 1970's due to the negative attention in the media and the development of antidepressant and antipsychotic medication (Sienaert 2011). In the 1980's, an increase in the use of ECT was observed after the National Institute of Mental Health and the National institutes of health came to a consensus that ECT was efficient in several severe psychiatric conditions. The American Psychiatric Association composed clear ECT indications, leaving out addiction (1978). Why addiction was left out was not explained. Furthermore, the indication for double diagnosis remains to be answered.

Vagal Nerve stimulaton (VNS) in the treatment of alcohol dependence

Our survey did not yield a single study of vagal nerve stimulation (VNS) applied in alcohol dependency. Only one animal study has been published (Liu et al. 2011). These researchers performed a sham-controlled study that evaluated the effect of VNS on heroin-seeking behavior in rats. A decline in heroin consumption was observed.

DISCUSSION

It is only recently that neuromodulation techniques have been subject to investigation in alcohol addiction. Due to the limited number of conducted studies and the methodological differences even within the same applications, it is nearly impossible to currently draw firm conclusions. It is obvious that additional research is needed.

Because of the tolerability and safety of these procedures, future research studies might do well to evaluate the use of tDCS and rTMS in the early stages of the addiction cycle. To date, when confronted with recently alcohol-addicted patients none of the discussed techniques have been thoroughly investigated. Nevertheless, this treatment approach would be in line with the use of these applications in other psychiatric disorders, such as major depression, where it is advocated to apply it more acutely and not during chronic episodes (George & Post 2011). Evidently, without clear-cut evidence, the more invasive procedures such as DBS and VNS have currently no place in these types of patients.

In chronic alcohol-addiction, the evidence that rTMS and tDCS could have beneficial effects on alcohol craving and consumption is still limited. On one hand, single rTMS sessions do not seem to decrease craving measurements significantly. On the other hand however, the application of only one tDCS session tends to decrease craving. Because in other psychiatric illnesses only daily sessions spread over a couple of weeks have been proven to be successful, for future research we advocate to evaluate multiple rTMS sessions. Additionally, the clinical effect of multiple tDCS stimulation sessions has still to be investigated in alcohol dependency. Furthermore, rTMS and tDCS long-term treatment effects are currently not available. At present, there is no clear-cut evidence that VNS and ECT treatment are indicated in these kinds of patients. Concerning DBS, only case reports in treatment-resistant alcohol-dependent patients have been reported with a reduction in relapse frequency, together with a positive effect on craving measurements. Because of the invasive character, the use of DBS in this form of pathology might be warranted in those severe treatment resistance alcohol-dependent patients.

Although clinical effects of these neuromodulation techniques still have to be established, at present no data

are available to appreciate its use as add-on therapy to other interventions such as anti-craving medication or psychotherapy. Further, it remains unclear as to how these applications, in particular tDCS and rTMS, affect the three phases in the Addiction cycle and/or for instance impulsivity and compulsivity.

CONCLUSION

Research concerning neuromodulation techniques has only recently set off and indicates to be promising. However, before these applications can enter daily clinical practice a substantial increase in research studies are needed to substantiate such an approach.

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