

Gamma Transcranial Alternating Current Stimulation Improves Craving and Cognition in Patients with Alcohol Use Disorder: An Open Label Pilot Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Alcohol use disorder (AUD) is one of the most common psychiatric disorders worldwide. It often shows a chronic course, and pharmacological treatment is rather ineffective for maintaining abstinence. New non-invasive brain stimulation techniques could help to improve AUD symptoms by rebalancing and synchronizing the disturbed prefrontal brain function and thus reduce craving. This study aims at evaluating the use of gamma transcranial alternating current stimulation to improve clinical and neuropsychological symptoms in patients with AUD.

Methods: In this small open label study, six patients suffering from AUD for several years underwent treatment with prefrontal gamma transcranial alternating current stimulation for 10 min twice daily respectively 20 min once per day for 10 days. Clinical and neuropsychological tests as well as craving were assessed over the course of treatment.

Results: Scores of the Alcohol Craving Questionnaire decreased in all patients and cognitive functions assessed by word fluency and computer-based n-back test improved.

Conclusions: This new non-invasive brain stimulation technique could be of interest in treating craving symptoms and in maintaining abstinence.

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1. INTRODUCTION

World Health Organization estimates more than 280 million people worldwide suffering from alcoholism in 2010 [1]. Alcohol use disorder (AUD), which is defined as disruption of control over alcohol use, continued alcohol use, and continued use despite apparent problems, is one of the most common psychiatric disorders, and still undertreated despite effective therapies being available [2]. There are established and efficacious treatment regimens for acute withdrawal like benzodiazepines, and long-term maintenance of abstinence respectively reduction of craving symptoms like disulfiram, nalmefene, naltrexone, and acamprosate. However, benzodiazepines are not recommended for long-term use for dependency reasons and medications to maintain abstinence show moderate effect sizes, e.g. naltrexone and acamprosate, and incidentally result in considerable side effects like peripheral neuropathy that lowers patients' compliance [3].

Moreover, patients with AUD often carry the burden of stigmatization and social decline, and have relevant psychiatric comorbidities, e.g. depressive symptoms and cognitive impairment [4,5].

Currently, non-invasive brain stimulation (NIBS) therapies including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are widely investigated for the treatment of psychiatric disorders like major depression, schizophrenia, and substance abuse disorders [6]. There is some body of evidence that treatment with tDCS could reduce craving and relapses in AUD inpatients [7,8] In addition, improvement of mood and depressive symptoms have been observed [9]. Also, for repetitive transcranial magnetic stimulation (rTMS), beneficial effects in substance use disorders have been reported [10]. Although there is a solid background of evidence for the application of tDCS in psychiatric disorders [6], data for the use of tACS, another NIBS method distinct from tDCS, is almost lacking, as shown in a recent review article with 13 studies included in the synthesis [11], albeit tACS is investigated in neurophysiological and neuropsychological studies for two decades. However, due to its specific electrical characteristics, tACS could be

useful in psychiatric disorders and could be even superior to tDCS. Contrarily to the unidirectional deflection of the resting membrane potential during tDCS, the rapidly changing polarity during tACS application probably prevents neurons from counter-regulation against deflection of neural activity and resting membrane potentials [12,13].

Thus, contrarily to the static electric field of direct current (DC) application with unidirectional current flow, alternating current uses sinusoidal oscillating currents in various frequencies with phase shifts. Changes in neural function or induction of neuroplasticity are supposed to be generated by entrainment or inference of tACS frequencies with local neural or cortical network activity [12]. The underlying mechanism for sustained changes is long term potentiation (LTP) with supra-threshold activation of neurons, followed by signal propagation into interconnected and remote areas [14]. It is suggested that tACS has differential effects on reaction time, attention, and cognition, depending on area of stimulation, frequency, phase shift, and duration of stimulation [15,12]. Most clinical and neurophysiological studies investigated alpha and beta frequencies to modulate either psychiatric disorders [11], or cognitive and perception tasks [15]. However, there is some neurophysiological evidence that gamma frequency could be a biomarker for psychiatric disorders, e.g., major depression [16], and that substance use disorders are linked to changes of cortical gamma frequency [17]. Thus, tACS in gamma frequency could be used to modulate symptoms of substance use disorders. Recent studies showed that tACS at 40 Hz (gamma frequency) leads to an improvement of memory performance in healthy volunteers [18], to mood and cognitive improvement in patients with major depression [19,20], and to improvement of negative symptoms in patients with negative symptoms in schizophrenia [21]. However, meaning of gamma tACS for the improvement of cognition is still unclear as recent results on cognition in healthy volunteers and depressed patients are diverging [22]. It is hypothesized that the neuromodulatory effects of tACS may involve synchronization in frontal and prefrontal brain regions, however, its mechanisms of action are still unclear [19]. In alcohol-dependent persons or persons at high risk, frontal and parietal gamma activity was found to be reduced during cognitive tasks [23,24]. This reduced gamma power leads to altered brain connectivity in persons with

chronic alcohol consumption and is likely to attribute to the impaired cognitive function in severe AUD [17], whereas during alcohol withdrawal, gamma activity was found to be increased, pointing to a hyperexcitability [25]. Therefore, tACS entrainment or interference with endogenous EEG oscillations could also be used to modulate disturbed cognitive function by rebalancing disturbed EEG patterns [26]. For the use of gamma tACS in AUD, there is one study comparing different stimulation modes in a population of people with different substance abuse disorders. Compared to alpha tACS, single session gamma tACS did not evoke relevant improvements in a go-no-go-task [27], but it is likely that single session tACS might not have been sufficient to provoke sustained results. Thus, a dosage-effect relationship could be responsible for negative results as also shown by Palm et al. [22]. Clinical NIBS application to provoke sustained changes in psychopathology and clinical symptoms usually requires 1-2 weeks of repeated stimulation, i.e., at least 5-10 stimulations. Therefore, a negative result from a single NIBS session in a neurophysiological or neuropsychological trial is not predictive for a clinical null result. Considering the potential meaning of modulation of gamma oscillations in substance abuse disorders, the investigation of repeated gamma tACS in substance abuse disorder seems promising. Here we provide first clinical data on the use of a gamma tACS stimulation series in patients with AUD. In this study, two different stimulation protocols (20 min once per day versus 10 min twice per day) were used. 20 min stimulation is a widely used duration in tDCS studies [6] and was applied in tACS studies on cognition [15, 22], and in neurophysiological [28] and clinical application [29]. Stimulation of 10 min duration is following findings on the improvement of prefrontal control over addiction behavior after prefrontal 10 Hz tACS [30], and a variety of neurophysiological [31-33] and neuropsychological studies [34,35, 15], however with different frequencies. The application of twice-daily stimulation has brought beneficial effects in clinical tDCS application and was found to accelerate clinical improvement [36,37]. Furthermore, there is evidence of a differential outcome of neurophysiological aftereffects after repeated and spaced tDCS, suggesting an enhancing effect of a second stimulation within the neuroplasticity window opened by the first stimulation [38,39]. In sum, there is a variety of results in neurophysiological

and neuropsychological studies suggesting that tACS in gamma frequency and others could be helpful to improve symptoms of craving and disturbed cognition in patients with substance abuse disorder. Albeit AUD being the most frequent substance abuse disorder, clinical investigation of tACS in this disorder is still lacking. Therefore, this study aims at gathering primary data on the application of gamma tACS in AUD.

2. MATERIALS AND METHODS

2.1 Study Design

This study was designed as an open-label interventional study with tACS add-on to standard psychiatric care in a sample of patients with AUD after completed withdrawal. Thus, primary aims of this study were feasibility and impact of tACS on clinical and neuropsychological outcome. Following the given results on single versus repeated stimulation, two different protocols with one respectively two stimulations per day were applied.

2.2 General Procedures

The study was approved by the local ethics committee and was according to the Declaration of Helsinki. Written and oral informed consent was obtained from each patient. Five male and one female patient (mean age: 50.0 ± 10.9 , range 38-66 years, all right-handed), diagnosed with AUD for several years (mean 16.8 ± 9.4 years) were included after completed alcohol withdrawal. They were recruited at the Psychiatric Hospital of the University of Munich, center for addiction disorders, day hospital and inpatient ward, respectively. Exclusion criteria were history of severe neurologic (e.g., stroke, epilepsy) or internal disease (e.g., cancer, metabolic disorders), metal implants or current skin diseases. All patients were randomly assigned to two groups following a computerized random generator, receiving either 20 gamma tACS sessions for 10 min twice daily within two weeks (group 1) or 10 gamma tACS sessions for 20 min once per day within two weeks (group 2) (see CONSORT Flowchart in Fig. 1). All sessions were performed after clinical and neuropsychological baseline testing and were followed up with the same rating instruments after last session.

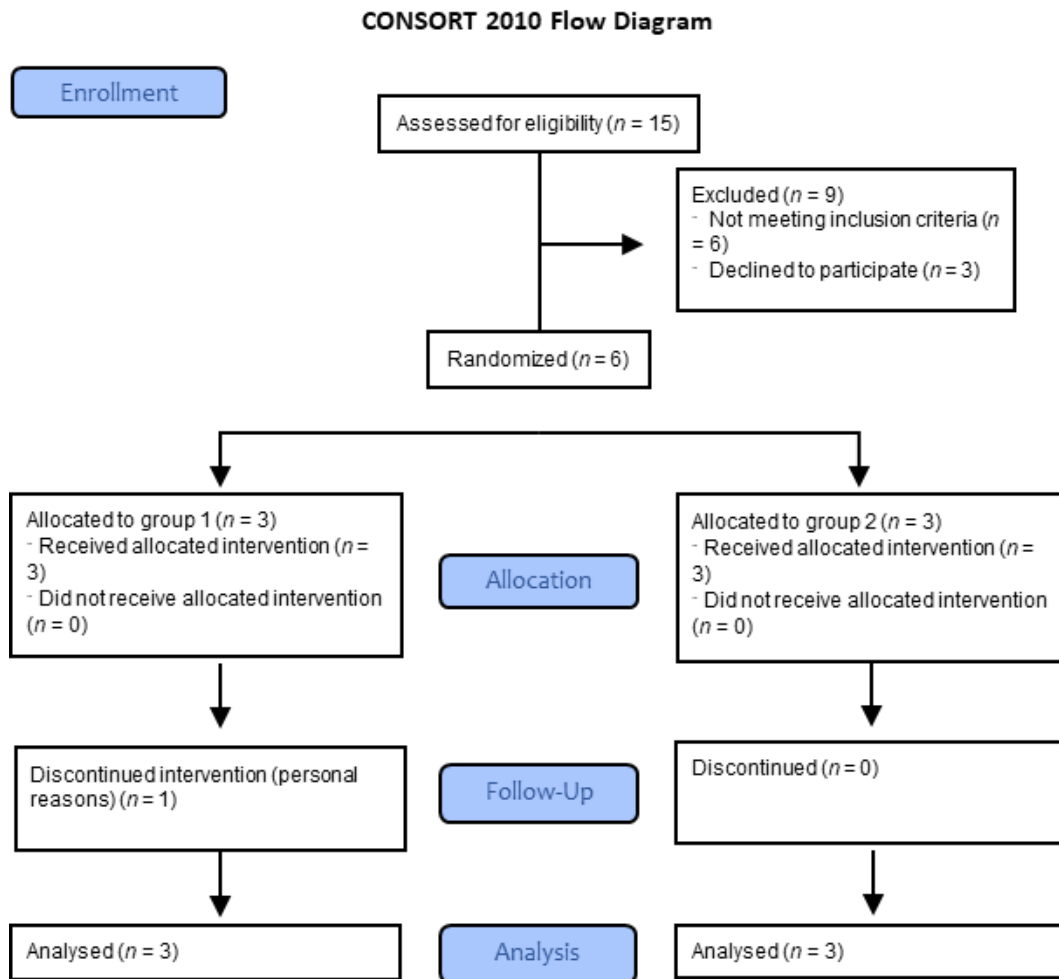


Fig. 1. Consort flowchart

2.3 Stimulation Procedures

For gamma tACS, a CE-certified neuroConn Eldith® DC-stimulator was used. Stimulation parameters were set to a current of 2 mA (amplitude -1 mA to +1 mA, peak-to-peak) at 40 Hz (0° phase shift, i.e., in-phase stimulation). In total, 48.000 cycles of tACS were applied per day over ten workdays sparing the weekend. Saline-soaked sponge electrodes (35 cm²) were placed over left and right dorsolateral prefrontal cortices (DLPFC), i.e., F3 and F4, according to the international 10-20-EEG system, and fixed with rubber bands to the skull. Stimulations were performed in the morning (20 min), respectively in the morning and within an interval of three hours (2x10 min).

2.4 Rating Instruments

Patients were assessed with objective and subjective rating instruments at three time points:

At baseline (BL), after 5th stimulation (D5), and after the 10th stimulation (D10). Patients were assessed at all three time points by:

- a) Alcohol Craving Questionnaire-short form-revised (ACQ-SF-R) [40]: This specific rating instrument for assessment of craving consists in 12 questions with proposed answers scoring from 1 to 7. Sum score of the 12 items indicates craving severity, subgroups indicate the four factors 'compulsivity, expectancy, purposefulness, emotionality'.
- b) Regensburg Word Fluency Test (RWT) [41]: This German language test for semantic word fluency, attention, and cognition requires the participant to cite as many words with a given capital letter as possible within one minute. The number of correct words is summarized.
- c) Trail Making Test A and B (TMT-A/B) [42]: This test for attention and cognition is

widely used and comprises two parts: in part A, participants must link numbers 1-25 as quick as possible. In part B, a number-letter sequence must be linked. Outcome parameters are time and errors.

- d) Positive and Negative Affect Schedule (PANAS) [43]: This scale for assessing a subject's emotional state uses 20 adjectives with a 5-point Likert scale for refusal or agreement. Mean values indicate a mood profile over the past week.
- e) Clinical Global Impression (CGI) [44]: This two-part scale focuses on illness severity and clinical improvement. Although being a raw scale, it is widely used and helps to depict clinical courses. In this study, only the first part was used.
- f) Computer-based n-back test (3-back test), calculated with a d-prime value (sensitive index d') [45]: On a standard computer screen, participants are presented with a letter from an 8-letter set, randomly selected from the alphabet [A to Z] for 500 ms in a pseudo-randomized order. In three consecutive experimental blocks with increasing cognitive load, participants must press a button when the presented letter matched the letter one (1-back, 121 trials), two (2-back, 122 trials) or three (3-back, 123 trials) items before.

At the end of each week of stimulation, patients filled-in the Comfort Rating Questionnaire (CRQ) [46] for assessing side effects of the stimulation. This Likert-scaled questionnaire assesses side effects of electrical stimulation during and after stimulation, as well as general comfort, and light flashes (phosphenes) and sleep disturbances as a dichotomous question. At baseline (BL), the following tests were performed additionally:

- a) Multiple-choice vocabulary intelligence test (MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest) [47]: This test measures semantic intelligence by presenting 37 lines with 5 words each in German language. Only one word per line is correct and needs to be recognized. Sum scores point to different intelligence levels.
- b) Alcohol Use Disorders Identification Test (AUDIT) [48]: The Audit is one of the most popular screening instruments of Alcohol dependency and has been translated in

different languages. Questions sum up to a score between 0 and 40 points, indicating severity of alcohol abuse. Cutoff for critical use is ≥ 8 points.

- c) Fagerström test for nicotine dependence (FTND) [49]: FTND is a standard rating instrument to assess the severity of nicotine dependence. To score the FTND, yes/no items are scored from 0 to 1 and multiple-choice items are scored from 0 to 3. The items are summed to a total score of 0-10. The higher the total Fagerström score, the more intense is the patient's physical dependence on nicotine.
- d) Edinburgh Handedness Test (EHT) [50]: This 14-item questionnaire delivers a percentage value between -100 and +100 for indicating left- respectively right-handed persons and their dominant hemispheres.

Craving for alcohol was assessed at each day of stimulation with a custom-made visual analogue scale (VAS), consisting of smiley icons that were collated to integral numbers between 1 (no craving at all) and 10 (maximum craving).

2.5 Statistics

Due to the small number of participants in this pilot study, no analysis tools to proof significance levels were used. For the computer-based n-back test (3-back test), d-prime value (sensitive index d') was calculated with a standard scheme [51].

3. RESULTS

3.1 Demographic Results

Five patients completed the study; one male patient (group 1) withdrew his consent for personal reasons after 8th stimulation. His results were included in analysis up to D5. Patients were all right-handed. Further clinical characteristics, i.e., duration of illness, number of hospitalisations and other are shown in Table 1. Clinical outcomes, craving measures, and cognitive outcomes are shown in Fig. 2a, 2b, and Fig. 3a, 3b. Most patients received anti-craving drugs (i.e., acamprosate in several cases; Table 1) which were kept stable for at least one week before enrolment and throughout stimulation series.

Table 1. Clinical and demographic characteristics at baseline. EHT = Edinburgh Handedness Test; FTND = Fagerström Test for Nicotine Dependence; MWT-B = multiple-choice vocabulary intelligence test

	Patient number	gender	age	Age of onset	Duration of illness (months)	Concomitant medication	Number of hospitalisations	Total duration of hospitalisations (weeks)	Course of illness	EHT	FTND	MWT-B
Group 1	1	m	52	44	96	oxazepam 40mg mirtazapine 7.5mg	3	6	episodic	100	3	28
	2	m	42	34	96	quetiapine 25 mg	20	40	episodic	100	0	35
	3	m	40	23	17	acamprosate 666mg	2	4	continuous	71.4	4	27
Group 2	4	m	66	30	360	acamprosate 666mg	6	78	episodic	100	0	34
	5	f	38	23	180	acamprosate 666mg	2	6	continuous	100	3	30
	6	m	62	45	17	naltrexone 50mg acamprosate 666mg	4	50	episodic	100	4	27

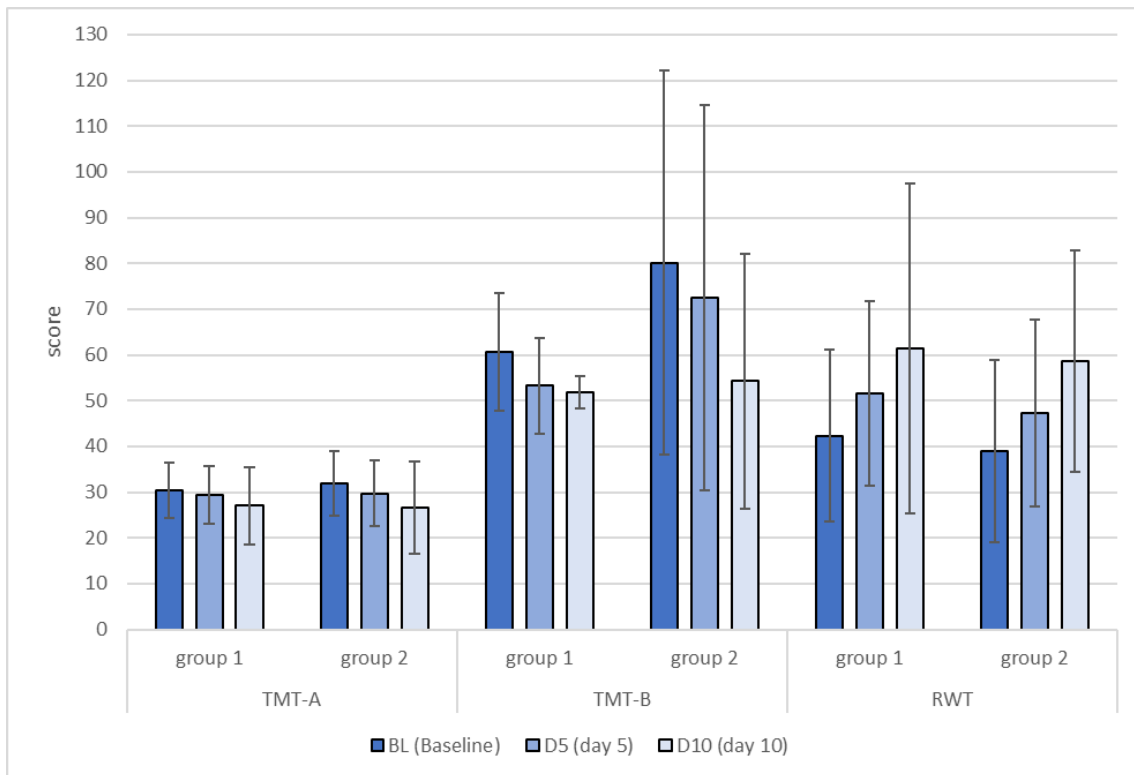


Fig. 2a. Clinical Results. Performance (y-axis: score, x-axis: Rating Scales) in the Trail Making Test A and B (TMT-A/B) and Regensburg Word Fluency Test (RWT) at Baseline (BL), day 5 (D5), and day 10 (D10). Clinical scores are given in mean values and standard deviation

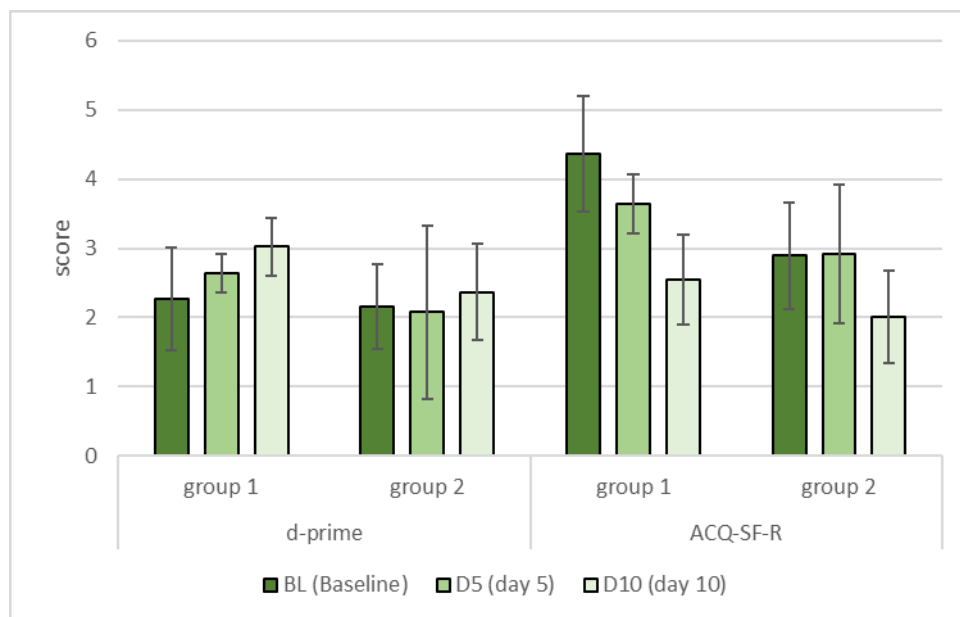


Fig. 2b. Clinical Results. Performance (y-axis: score, x-axis: Rating Scales) in the d-prime value (n-back) and the Alcohol Craving Questionnaire-short form-revised (ACQ-SF-R) at Baseline (BL), day 5 (D5), and day 10 (D10). Clinical scores are given in mean values and standard deviation

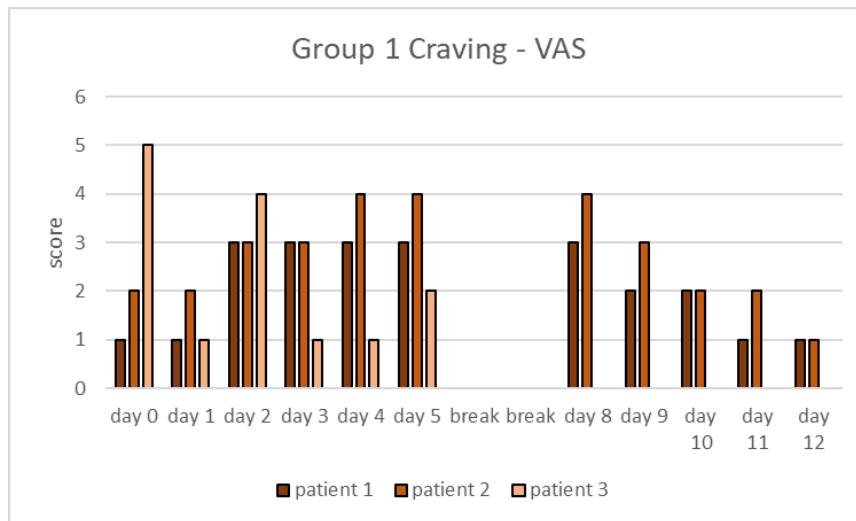


Fig. 3a. Craving for alcohol Visual analogue scale (VAS; score 1-10), daily measure during course of treatment for group 1 (2x10 min/day)

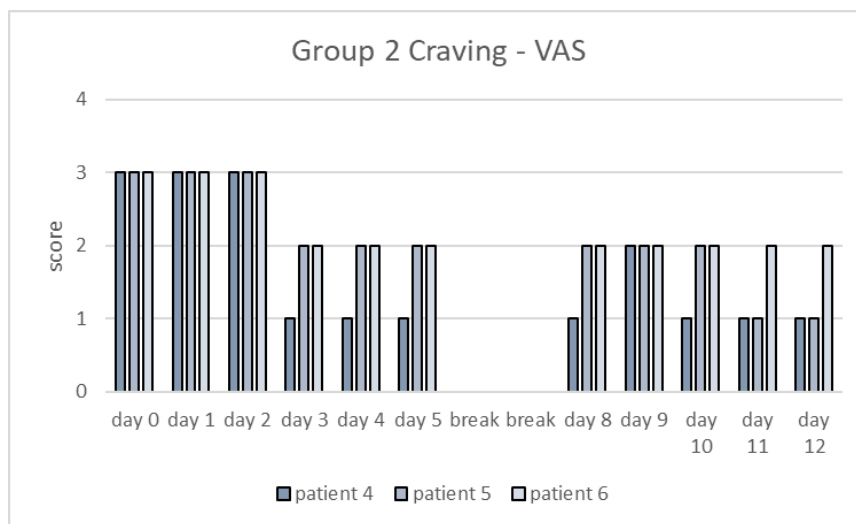


Fig. 3b. Craving for alcohol Visual analogue scale (VAS; score 1-10), daily measure during course of treatment for group 2 (1x20 min/day)

Baseline measurements (MWT-B, AUDIT, and FTND) showed no obvious differences between both groups. The MWT-B was 30.2 ± 3.2 points, the FTND was 2.3 ± 1.7 points (three of five were smokers). The AUDIT score, reflecting drinking behaviour and amount, was 32.3 ± 3.9 points. Patients' history of previous inpatient treatment ranged from 2 to 20 periods.

3.2 Clinical Results

At baseline, group 1 (2x10 min/day) presented a mean ACQ-SF-R score of 4.4 ± 0.8 , and RWT with 42.3 ± 18.8 words. TMT-A was performed in 30.5 ± 6.0 sec, and TMT-B in 60.6 ± 12.8 sec

respectively. The Positive Affect Schedule showed 2.8 ± 0.4 , and 2.6 ± 1.1 respectively in the Negative Affect Score. CGI was 4.3 ± 0.6 . The baseline d-prime of the virtual n-back was 2.3 ± 0.7 .

After the 5th stimulation, group 1 showed a mean ACQ-SF-R Score with 3.6 ± 0.4 , and RWT with 51.7 ± 20.1 words. TMT-A was performed in 29.4 ± 6.4 sec, and TMT-B in 53.3 ± 10.4 sec respectively. The Positive Affect Schedule showed 3.1 ± 0.6 , and 1.9 ± 0.7 respectively in the Negative Affect Score. CGI was 4.0 ± 0.0 . The average d-prime of the virtual n-back was 2.6 ± 0.3 .

After the 10th stimulation, group 1 showed a mean ACQ-SF-R Score of 2.5 ± 0.7 , and RWT with 61.5 ± 36.1 words. TMT-A was performed in 27.1 ± 8.4 sec, and TMT-B in 51.8 ± 3.6 sec respectively. The Positive Affect Schedule showed 3.0 ± 1.3 , and 2.1 ± 0.7 respectively in the Negative Affect Score. CGI was 2.5 ± 0.7 . The d-prime of the virtual n-back was 3.0 ± 0.4 . Craving for alcohol with a visual analogue scale (VAS) showed scores between 1 and 5 at start of treatment, and an improvement to a score of 2 (2 remaining patients in group 1) at the end of treatment.

Group 2 (1x20 min/day) presented a mean ACQ-SF-R Score of 2.9 ± 0.8 at baseline, and RWT with 39.0 ± 19.9 words. TMT-A was performed in 31.9 ± 7.1 sec, and TMT-B in 80.2 ± 41.9 sec respectively. The Positive Affect Schedule showed 2.8 ± 0.7 , the Negative Affect Score showed 2.5 ± 0.8 . CGI was 4.3 ± 1.2 . The baseline d-prime of the virtual n-back was 2.2 ± 0.6 .

At D5, group 2 presented a mean ACQ-SF-R Score of 2.9 ± 1.0 , and RWT with 47.3 ± 29.5 words. TMT-A was performed in 29.8 ± 7.3 sec, and TMT-B in 72.5 ± 42.1 sec respectively. The Positive Affect Schedule showed 2.9 ± 0.7 , the Negative Affect Score showed 1.9 ± 0.5 . CGI was 4.0 ± 1.0 . The average d-prime of the virtual n-back was 2.1 ± 1.3 .

At D10, group 2 presented a mean ACQ-SF-R Score of 2.0 ± 0.7 , and RWT with 58.7 ± 24.2 words. TMT-A was performed in 26.7 ± 10.2 sec, and TMT-B in 54.3 ± 27.9 sec respectively. The Positive Affect Schedule showed 3.9 ± 0.4 , the Negative Affect Score showed 1.2 ± 0.1 . CGI was 2.3 ± 0.6 . The d-prime of the virtual n-back was 2.4 ± 0.7 .

In group 2, initial VAS scores were on a lower level (3 points) compared to group 1 and improved to 2 respectively 1 point.

3.3 Safety and Side Effects

Gamma tACS was safe and well tolerated. This overall impression was supported by the CRQ scores after the 5th (group 1: 30.0 ± 12.5 ; group 2: 31.0 ± 7.2) and the 10th stimulation (group 1: 19.0 ± 2.8 ; group 2: 23.0 ± 3.6). Five patients reported phosphenes during stimulation, but no one reported disturbed sleep. Two of the smokers spontaneously reported less craving for tobacco.

4. DISCUSSION

This small open label pilot study provides first clinical evidence that gamma tACS may exert therapeutic effects in patients with AUD. Although improvement in the main outcome measures was observed in both groups, group 1 showed a slightly superior outcome on a descriptive level, however group 2 showed higher changes in the total scores. Theoretically, tACS for 10 min twice daily may represent a treatment protocol with effects distinct from those after a single 20 min stimulation per day as similarly shown in an early motor cortex tDCS study comparing different stimulation periods [52,38,39]. For tDCS in AUD, Klauss et al. [7] observed a reduction of craving through multiple sessions of tDCS stimulation. Analogously, repeated gamma tACS sessions seem to have a positive effect on AUD symptoms as well as cognitive measures. Such effects on cognition may be explained by modulation of prefrontal neural activity, as shown in a recent study for tACS in healthy volunteers [18]. Similarly, tACS may drive synchronization of disturbed alpha activity of frontal and prefrontal brain regions, resulting in an improvement of processing complex tasks like TMT, RWT, or n-back test.

Concerning placement of electrodes, there is some evidence from tDCS studies suggesting clinical improvement of craving symptoms when placing the anode over the left dorsolateral prefrontal cortex, whereas bilateral montage or reverse stimulation does not seem to have the same effect [53]. To date, studies stimulating the right [54, 7] respectively the left DLPFC (e.g., den Uyl et al., 2018) with anodal current report improvement of craving symptoms and cognition, blurring a clear recommendation for electrode positioning. This polarity effect, however, is a characteristic of the unidirectional current flow during tDCS but is not relevant for tACS. Thus, tACS could overcome this shortcoming of tDCS application.

Finally, it should be mentioned that gamma tACS was well tolerated and there were no serious adverse effects. Side effects were mild, not exceeding typical side effects of tDCS.

Limitations of this pilot study are the small sample size and the lack of a control group. Therefore, deflecting a hypothesis from these results for building a randomized placebo-controlled trial could result in biased study design and power analysis [55,56]. Most patients were

treated with anti-craving drugs like acamprosate, which could have influenced craving measures even when medication was kept stable one week before and throughout the treatment.

For the moment, this small-scale study does not allow to specifically attribute the observed changes to gamma tACS treatment. It is a well-known fact that there can be a strong bias by nonspecific effects of care and patients' expectations raised by the procedure of stimulation itself [57]. This also could have driven the results of this study. Therefore, future studies should present a more rigorous design [58].

5. CONCLUSION

In sum, treatment with 40 Hz tACS treatment was safe and showed preliminary efficacy in this small open label pilot study with six patients suffering from AUD.

Gamma tACS is a novel and promising NIBS technique in AUD and merits further investigation as it is low cost, easy to use and nearly free of side effects. Randomized controlled trials including neurobiological measures are needed for assessing its efficacy and to develop a deeper mechanistic understanding of gamma tACS action.

CONSENT

All authors declare that written informed consent was obtained from all patients.

ETHICAL APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Ludwig-Maximilian University, Munich, Germany (protocol code 603-16; date of approval: 14 Nov 2016).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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